

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
2 August 2007 (02.08.2007)

PCT

(10) International Publication Number
WO 2007/085087 A1

(51) International Patent Classification:

C40B 40/06 (2006.01) **C07K 14/575** (2006.01)
A61K 31/00 (2006.01) **C12N 15/16** (2006.01)
A61K 38/00 (2006.01) **C12Q 1/00** (2006.01)
A61K 38/22 (2006.01) **C12Q 1/68** (2006.01)
A61P 29/00 (2006.01) **C40B 30/00** (2006.01)
C07H 21/00 (2006.01) **C12P 19/34** (2006.01)

(21) International Application Number:

PCT/CA2007/000111

(22) International Filing Date: 24 January 2007 (24.01.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/761,328 24 January 2006 (24.01.2006) US
60/795,157 27 April 2006 (27.04.2006) US

(71) Applicant (for all designated States except US): **THE UNIVERSITY OF BRITISH COLUMBIA** [CA/CA];
University-Industry Liaison Office, 103-6190 Agronomy
Road, Vancouver, British Columbia V6T 1Z3 (CA).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **RUSSELL, James A.** [CA/CA]; 1963 West 35th Avenue, Vancouver, British
Columbia V6M 1H8 (CA). **WALLEY, Keith R.** [CA/CA];

4172 Coventry Way, North Vancouver, British Columbia V7N 4M9 (CA). **WELLMAN, Hugh F.** [CA/CA];
104-522 Moberly Road, Vancouver, British Columbia V5Z 4G4 (CA). **MARKWARD, Nathan J.** [US/US]; 616
Spanish Town Road, Baton Rouge, Louisiana 70802 (US).

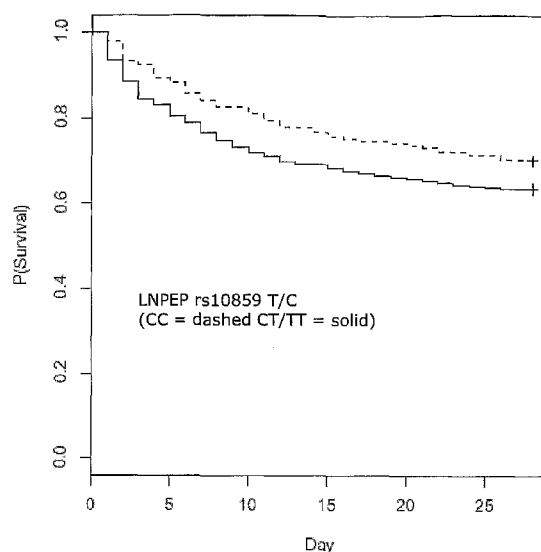
(74) Agent: **SMART & BIGGAR**; Box 11560, Vancouver
Centre, Suite 2200, 650 West Georgia Street, Vancouver,
British Columbia V6B 4N8 (CA).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS,
LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY,
MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS,
RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,

[Continued on next page]

(54) Title: VASOPRESSIN PATHWAY POLYMORPHISMS AS INDICATORS OF SUBJECT OUTCOME IN CRITICALLY ILL SUBJECTS



(57) Abstract: The invention provides methods, nucleic acids, compositions and kits for predicting a subject's response to treatment with one or more vasopressin receptor agonists to identify subjects having a greater benefit from treatment with vasopressin receptor agonist(s). The method generally comprises determining a vasopressin pathway associated gene polymorphism genotype(s) of a subject for one or more polymorphisms in the these genes, comparing the determined genotype with known genotypes for the polymorphism that correspond with an improved response genotype to identify potential subjects having an inflammatory condition who are more likely to benefit from treatment with a vasopressin receptor agonist and subsequent to treatment recover from the inflammatory condition. The invention also provides for methods of treating such subjects with vasopressin receptor agonists based on the subject's genotype.

WO 2007/085087 A1



RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

**Vasopressin Pathway Polymorphisms
as Indicators of Subject Outcome in Critically Ill Subjects**

FIELD OF THE INVENTION

- 5 The field of the invention relates to the assessment and/or treatment of subjects with an inflammatory condition.

BACKGROUND OF THE INVENTION

- 10 Arginine vasopressin (AVP) has both vasoconstrictor and anti-diuretic properties. AVP is synthesized in the hypothalamus and secreted from posterior pituitary gland, secreted into the circulation and binds to several receptors. AVP binds to vasopressin-specific membrane bound receptor AVPR1A on vascular smooth muscle (MOUILLAC B. *et al.* J Biol Chem (1995) 270: 25771-25777), AVPR2 in the distal convoluted tubule and collecting ducts in the kidney and AVPR1B pituitary receptors that modify adrenocorticotropin hormone (ACTH) production
- 15 (ORLOFF J. and HANDLER J. Am J Med (1967) 42: 757-768). Binding to AVPR1A induces vasoconstriction. AVP has a very short half-life and is metabolized by leucyl/cystinyl aminopeptidase (LNPEP).

- Under normal physiological conditions, AVP does not contribute much to the maintenance of
- 20 blood pressure (GROLLMAN J Pharm Exper Therap (1932) 46:447-460; GRAYBIEL Am Heart J (1941) 21:481-489; and WAGNER, J Clin Invest (1956) 35:1412-1418). However, when blood pressure falls, AVP is fundamental to the response to hypotension as AVP is released from the posterior pituitary and causes arterial smooth muscle to contract (vasoconstriction) (WAGNER, J Clin Invest (1956) 35:1412-1418; AISENBREY J Clin Invest (1981) 67:961-968; and
- 25 SCHWARTZ Endocrinology (1981) 108:1778-1780). If AVP is not secreted by the posterior pituitary in response to hypotension, then blood pressure remains low or falls further as a result of inappropriate vasodilation.

- Critically ill subjects with septic shock have been shown to have low serum AVP levels
- 30 (LANDRY Circ. (1997) 95:1122-1125). Although AVP levels are initially high in septic shock, they fall within hours (GOETZ Proc. Exp. Biol. Med. (1974) 145(1):277-80; WILSON Surg. Gynecol. Obstet. (1981) 153(6):869-72; (MORALES D. *et al.* Circulation (1999) 100(3): 226-9); and ERRINGTON J Physiol (1971) 217(1): 43P-45P). Indeed, septic shock develops in part because there is a defect in the baro-receptor-mediated increase in AVP secretion (LANDRY Circ.

(1997) 95:1122-1125). AVP can be administered to subjects who have septic shock who are not responding adequately. It has been reported that AVP increases blood pressure, decreases need for vasopressors such as norepinephrine, and increases urine output (LANDRY DW *et al.* *Circulation*. (1997) 95:1122-1125; HOLMES CL *et al.* *Int. Care Med.* (2001) 27:1416-1421). In a small, proof
5 of concept randomized controlled trial of norepinephrine (NE) versus AVP in subjects with severe septic shock, it has been shown that AVP spared NE use, maintained mean arterial pressure and cardiac index, and improved measures of renal function including increased urine output and creatinine clearance (PATEL BM *et al.* *Anesthesiology* (2002) 96:576-582). Blood AVP levels were also found to be very low (1.3 +/- 0.9pg/ml) (HOLMES CL *et al.* *Int. Care Med.* (2001)
10 27:1416-1421; and PATEL BM *et al.* *Anesthesiology* (2002) 96:576-582). Several other studies have also shown that AVP increases blood pressure in septic shock (LANDRY DW *et al.* *Circulation* (1997) 95:1122-5; MALAY MB *et al.* *J Trauma* (1999) 47(4): 699-703; GOLD JA *et al.* *Crit. Care Med.* (2000) 28(1): 249-52; and MORALES DL. *et al.* *Ann Thorac Surg.* (2000) 69(1): 102-6).

15 Vasopressin is commonly used after cardiac surgery as studies have shown that AVP levels are lower after cardiac surgery compared to baseline. In addition, AVP infusion has been demonstrated to increase blood pressure after cardiac surgery (ARGENZIANO J *Circulation* (1997) 96(9 Suppl):II-286-90; ARGENZIANO J *Thorac. Cardiovasc Surg.* (1998) 116(6):973-80;
20 CHEN *Circulation* (1999) 100(19 Suppl):II244-6; and ROSENZWEIG *Circulation* (1999) 100(19 Suppl):II182-6).

Arginine vasopressin (also known as antidiuretic hormone or ADH) is encoded by the AVP - neurophysin II gene (AVP) which contains three exons and maps to chromosome 20p13. AVP is
25 synthesized in the hypothalamus as a precursor polypeptide (prepro-AVP-NP11) and undergoes post-translational processing to yield three functional peptides: AVP, NP11, and copeptin (Entrez Gene; <http://www.ncbi.nlm.nih.gov/entrez>). The AVP-NP11 complex is transported along nerve axons to the posterior pituitary where it is secreted into the bloodstream or directly into the brain. In addition to its vasoconstrictor properties, AVP acts to maintain fluid homeostasis by signaling
30 through AVPR2 receptors in the collecting ducts of the kidney (BIRNBAUMER M *Trends Endocrinol Metab* (2000) 10:406-10) and plays a role in pH regulation (TASHIMA Y *et al.* *Plufgers Arch* (2001) 442(5):652-61. Furthermore, AVP is thought to be involved in cognition, tolerance, adaptation as well as complex sexual and maternal behavior (YOUNG WS *et al.* *Neurosci* (2006) 143(4):1031-9).

A representative human AVP mRNA sequence is listed in GenBank under accession numbers NM_00490 (633 bp). NM 00490 contains AVP rs1410713 but not rs857242.

- 5 Human arginine vasopressin receptor 1A (AVPR1A) is also known as the V1a vasopressin receptor (V1aR); SCCL vasopressin subtype 1a receptor; V1-vascular vasopressin receptor; antidiuretic hormone receptor 1A; and vascular/hepatic-type arginine vasopressin receptor. AVPR1A maps to chromosomal region 12q14-q15. The protein encoded by this gene acts as receptor for arginine vasopressin (AVP). This receptor belongs to the subfamily of G-protein
 10 coupled receptors which also includes AVPR1B, AVPR2 and OXTR. AVPR1A agonist binding increases intracellular calcium concentrations by signaling through the phospholipase C cascade (OMIM: 600821). The downstream effects of this signaling cascade include cell contraction and proliferation, platelet aggregation, release of coagulation factors and glycogenolysis. AVPR1A has been investigated for associations with social behaviors, including affiliation and attachment
 15 (YOUNG LJ *et al* Nature (1999) 400(6746):766-8) as well as essential hypertension (THIBONNIER M *et al* J Mol Cell Cardiol (2000) 32(4):557-564).

- A representative human AVPR1A mRNA sequence is listed in GenBank under accession number NM_000706 (4154 bp). The NM_000706 sequence contains AVPR1A SNP rs3803107 (and
 20 rs1042615), but not rs1495027 or rs10877970.

- Homo sapiens leucyl/cystinyl aminopeptidase (LNPEP) is also known as AT (4) receptor; angiotensin IV receptor; insulin-regulated aminopeptidase; insulin-responsive aminopeptidase; otase; oxytocinase; placental leucine aminopeptidase; and vasopressinase. LNPEP maps to
 25 chromosomal region 5q15. The LNPEP gene encodes a metalloproteinase that cleaves polypeptides such as vasopressin, oxytocin, lys-bradykinin, met-enkephalin and dynorphin A (Entrez Gene: www.ncbi.nlm.nih.gov/entrez). LNPEP also catalyzes the conversion of angiotensinogen to angiotensin IV (AT4) and is thought to play a role in memory processing by acting as a receptor for AT4 (LEW RA *et al* J Neurochem (2003) 86(2):344-50. LNPEP also plays
 30 a role in the maintenance of pregnancy (NORMURA S *et al* Biochim Biophys Acta (2005) 1751(1):19-25).

A representative human LNPEP mRNA sequence is listed in GenBank under accession number NM_005575 (4470 bp). The NM_005575 sequence does not contain the LNPEP SNP rs18059.

Homo sapiens leukocyte-derived arginine aminopeptidase (LRAP) is also known as endoplasmic reticulum aminopeptidase 2; (ERAP2). LRAP maps to chromosomal region 5q15, immediately upstream of LNPEP. The longest annotated transcript of LRAP (NM 022350) has 18 exons and is predicted to encode a protein of 915 amino acids (aa). LRAP is localized to the endoplasmic reticulum (ER) of the cell where it functions to cleave antigenic peptides greater than nine aa for presentation to major histocompatibility complex 1 (MHC-1) molecules (TANIOKA T *et al* J Biol Chem (2003) 278(34):32275-83).

A representative human LRAP mRNA sequence is listed in GenBank under accession number NM_022350 (3356 bp).

Genotype has been shown to play a role in the prediction of subject outcome in inflammatory and infectious diseases (MCGUIRE W. *et al. Nature* (1994) 371:508-10; NADEL S. *et al. Journal of Infectious Diseases* (1996) 174:878-80; MIRA JP. *et al. JAMA* (1999) 282:561-8; MAJETSCHAK M. *et al. Ann Surg* (1999) 230:207-14; STUBER F. *et al. Crit Care Med* (1996) 24:381-4; STUBER F. *et al. Journal of Inflammation* (1996) 46:42-50; and WEITKAMP JH. *et al. Infection* (2000) 28:92-6). Furthermore, genotype can alter response to therapeutic interventions.

Genentech's HERCEPTIN® was not effective in its overall Phase III trial but was shown to be effective in a genetic subset of subjects with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer. Similarly, Novartis' GLEEVEC® is only indicated for the subset of chronic myeloid leukemia subjects who carry a reciprocal translocation between chromosomes 9 and 22.

SUMMARY OF THE INVENTION

This invention is based in part on the surprising discovery that vasopressin pathway SNPs from AVP, AVPR1A, LNPEP and LRAP are predictive or indicative of subject outcome, wherein subject outcome is the ability of the subject to recover from an inflammatory condition based on having a particular AVP, AVPR1A, LNPEP or LRAP genotype as compared to a subject not having that genotype.

This invention is also based in part on the surprising discovery of vasopressin pathway SNPs having an association with improved prognosis or subject outcome, in subjects with an inflammatory condition. Furthermore, various vasopressin pathway SNPs are provided which are

useful for subject screening, as an indication of subject outcome, or for prognosis for recovery from an inflammatory condition.

This invention is also based in part on the identification that the particular nucleotide (allele) or genotype at the site of a given SNP may be associated with a decreased likelihood of recovery from an inflammatory condition ('risk genotype') or an increased likelihood of recovery from an inflammatory condition ('decreased risk genotype'). Furthermore, this invention is in part based on the discovery that the genotype or allele may be predictive of increased responsiveness to the treatment of the inflammatory condition with vasopressin receptor agonist (i.e. "adverse response genotype" (ARG) or "improved response genotype" (IRG)). The vasopressin receptor agonist may be vasopressin. The inflammatory condition may be SIRS, sepsis or septic shock.

This invention is also based in part on the surprising discovery that AVP, AVPR1A LNPEP and LRAP SNPs alone or in combination are useful in predicting the response a subject with an inflammatory condition will have to vasopressin receptor agonist treatment or vasopressin treatment. Whereby the subjects having an improved response genotype are more likely to benefit from and have an improved response to vasopressin receptor agonist treatment and subjects having a non-improved response genotype are less likely to benefit from the same treatment.

Furthermore, there are provided herein AVP, AVPR1A LNPEP and LRAP SNPs and SNPs in linkage disequilibrium (LD) thereto, which are also useful in predicting the response a subject with an inflammatory condition will have to vasopressin receptor agonist treatment or vasopressin treatment.

In accordance with one aspect of the invention, methods are provided for obtaining a prognosis for a subject having, or at risk of developing, an inflammatory condition, the method including determining a genotype of said subject which includes one or more polymorphic sites in the subject's vasopressin pathway gene sequences or a combination thereof, wherein said genotype is indicative of an ability of the subject to recover from the inflammatory condition.

In accordance with a further aspect of the invention, methods are provided for identifying a polymorphism in a vasopressin pathway gene sequence that correlates with prognosis of recovery from an inflammatory condition, the method including: obtaining vasopressin pathway gene sequence information from a group of subjects having an inflammatory condition; identifying at least one polymorphic nucleotide position in the vasopressin pathway gene sequence in the subjects; determining a genotypes at the polymorphic site for individual subjects in the group;

determining recovery capabilities of individual subjects in the group from the inflammatory condition; and correlating the genotypes determined in step (c) with the recovery capabilities determined in step (d) thereby identifying said vasopressin pathway gene sequence polymorphisms that correlate with recovery.

5
10
15
In accordance with a further aspect of the invention, a kit is provided for determining a genotype at a defined nucleotide position within a polymorphic site in vasopressin pathway gene sequence in a subject to provide a prognosis of the subject's ability to recover from an inflammatory condition, the kit including: a restriction enzyme capable of distinguishing alternate nucleotides at the polymorphic site; or a labeled oligonucleotide having sufficient complementary to the polymorphic site so as to be capable of hybridizing distinctively to said alternate. The kit may further include an oligonucleotide or a set of oligonucleotides operable to amplify a region including the polymorphic site. The kit may further include a polymerization agent. The kit may further include instructions for using the kit to determine genotype.

20
In accordance with a further aspect of the invention, methods are provided for treating an inflammatory condition in a subject in need thereof, the method including administering to the subject a vasopressin receptor agonist, wherein said subject has an improved response genotype in their vasopressin pathway associated gene sequence.

25
In accordance with a further aspect of the invention, methods are provided for treating an inflammatory condition in a subject in need thereof, the method including: selecting a subject having an improved response genotype in their vasopressin pathway associated gene sequence; and administering to said subject one or more vasopressin receptor agonist(s).

30
In accordance with a further aspect of the invention, methods are provided for treating a subject with an inflammatory condition by administering a vasopressin receptor agonist, the method including administering the vasopressin receptor agonist to subjects that have an improved response genotype in their vasopressin pathway associated gene sequence, wherein the improved response genotype is predictive of increased responsiveness to the treatment of the inflammatory condition with a vasopressin receptor agonist.

In accordance with a further aspect of the invention, methods are provided for identifying a subject with increased responsiveness to treatment of an inflammatory condition with a vasopressin receptor agonist, including the step of screening a population of subjects to identify those subjects that have an improved response genotype in their vasopressin pathway associated gene sequence, wherein the identification of a subject with an improved response genotype in their vasopressin pathway associated gene sequence is predictive of increased responsiveness to the treatment of the inflammatory condition with the vasopressin receptor agonist.

In accordance with a further aspect of the invention, methods are provided for selecting a subject for the treatment of an inflammatory condition with a vasopressin receptor agonist, including the step of identifying a subject having an improved response genotype in their vasopressin pathway associated gene sequence, wherein the identification of a subject with the improved response genotype is predictive of increased responsiveness to the treatment of the inflammatory condition with the vasopressin receptor agonist.

In accordance with a further aspect of the invention, methods are provided for treating an inflammatory condition in a subject, the method including administering a vasopressin receptor agonist to the subject, wherein said subject has an improved response genotype in their vasopressin pathway associated gene sequence.

In accordance with a further aspect of the invention, methods are provided for treating an inflammatory condition in a subject, the method including: identifying a subject having an improved response genotype in their vasopressin pathway associated gene sequence; and administering a vasopressin receptor agonist to the subject.

In accordance with a further aspect of the invention, methods are provided for administering one or more vasopressin receptor agonist(s) to a subject in need thereof, said subject having an improved response genotype in their vasopressin pathway associated gene sequence.

In accordance with a further aspect of the invention, methods are provided for treating an inflammatory condition in a subject, the method including: identifying a subject having an adverse response genotype in their vasopressin pathway associated gene sequence; and selectively not administering a vasopressin receptor agonist to the subject.

In accordance with a further aspect of the invention, methods are provided for selectively not administering one or more vasopressin receptor agonist(s) to a subject, wherein said subject has an adverse response genotype in their vasopressin pathway associated gene sequence.

5 In accordance with another aspect of the invention, there is provided a use of a vasopressin receptor agonist in the manufacture of a medicament for the treatment of an inflammatory condition, wherein the subjects treated have an improved response polymorphism in their vasopressin pathway associated gene sequence.

10 In accordance with another aspect of the invention, there is provided a use of a vasopressin receptor agonist in the manufacture of a medicament for the treatment of an inflammatory condition, wherein the subjects treated do not have an adverse response polymorphism in their vasopressin pathway associated gene sequence.

15 In accordance with another aspect of the invention, there is provided a use of a vasopressin receptor agonist in the manufacture of a medicament for the treatment of an inflammatory condition in a subset of subjects, wherein the subset of subjects have an improved response polymorphism in their vasopressin pathway associated gene sequence.

20 In accordance with another aspect of the invention, there is provided a use of a vasopressin receptor agonist in the manufacture of a medicament for the treatment of an inflammatory condition in a subset of subjects, wherein the subset of subjects do not have an adverse response polymorphism in their vasopressin pathway associated gene sequence.

25 In accordance with another aspect of the invention, there is provided a commercial package containing, as active pharmaceutical ingredient, use of a vasopressin receptor agonist, or a pharmaceutically acceptable salt thereof, together with instructions for its use for the curative or prophylactic treatment of an inflammatory condition in a subject, wherein the subject treated has an improved response polymorphism in their vasopressin pathway associated gene sequence.

30

In accordance with another aspect of the invention, there is provided a commercial package containing, as active pharmaceutical ingredient, use of a vasopressin receptor agonist, or a pharmaceutically acceptable salt thereof, together with instructions for its use for the curative or prophylactic treatment of an inflammatory condition in a subject, wherein the subject treated does

not have an adverse response polymorphism in their vasopressin pathway associated gene sequence.

The method or use may further include determining the subject's APACHE II score as an assessment of subject risk. The method or use may further include determining the number of organ system failures for the subject as an assessment of subject risk. The subject's APACHE II score may be indicative of an increased risk when ≥ 25 . 2 or more organ system failures may be indicative of increased subject risk.

10 The improved response genotype may be found at one or more of the following polymorphic sites: rs18059; rs27711; rs10051637; rs1410713; rs857240; rs857242; and rs1495027; or a polymorphic site in linkage disequilibrium thereto. The polymorphic site in linkage disequilibrium is selected from one or more of the following: rs2762; rs10051637; rs1477364; rs7731592; rs7736466; rs1363974; rs2351010; rs1423357; rs1544777; rs2161548; rs38032; rs38034; rs38041; rs27436; 15 rs27306; rs27307; rs27397; rs27659; rs27711; rs27290; rs38030; rs27294; rs27747; rs39602; rs248215; rs27302; rs2278018; rs1559355; rs3734015; rs4869315; rs2247650; rs2549781; rs2549782; rs2161657; rs251339; rs187265; rs2548527; rs1056893; rs2548523; rs2255546; rs2255637; rs1019503; rs251344; rs1981846; rs10071975; rs7700332; rs38042; rs18059; rs9127; rs7972829; rs10784339; rs3803107; rs11836346; rs7308008; rs11835545; rs7959001; 20 rs11832877; rs10877977; rs2201895; rs7302323; rs10877986; rs2030106 and rs18059; rs27296; rs27300; rs27613; rs27711; rs38033; rs38035; rs38036; rs38041; rs38043; rs716848; rs1216565; rs1230358; rs1363907; rs1974871; rs2042385; rs2113050; rs2113189; rs2161658; rs2255633; rs2255634; rs2287988; rs2548524; rs2548529; rs2548530; rs2548532; rs2548533; rs2548536; rs2548538; rs2548539; rs2548540; rs2549783; rs2549784; rs2549790; rs2549791; rs2549794; 25 rs2549795; rs2549796; rs2549797; rs2617447; rs2910686; rs2927609 rs3797796; rs3849749; rs3849750; rs4360063; rs4869314; rs4869316; rs6556942; rs7713127; rs7716222; rs7719705; rs10044354; rs10051637; rs10058476; rs12516666; and rs12716486.

The improved response genotype may be selected from one or more of the following: rs18059CT; 30 rs18059TT; rs27711GG; rs10051637GA; rs10051637AA; rs1410713AC; rs1410713AA; rs857240CC; rs857242CC; rs1495027CC; and rs1495027CT; or a polymorphic site in linkage disequilibrium thereto. The adverse response genotype which may be selected from one or more of the following: rs18059CC; rs27711AA; rs10051637GG; rs1410713CC; rs857240CT; rs857242AC; and rs1495027TT; or a polymorphic site in linkage disequilibrium thereto. The

genotype of the polymorphic site in linkage disequilibrium may be selected from one or more of the polymorphic sites and corresponding genotypes set out in TABLES 1B and 1D.

The subject having one or more improved response genotypes may be selectively administered the vasopressin receptor agonist. The subject having one or more adverse response genotypes may be selectively not administered the vasopressin receptor agonist.

In accordance with a further aspect of the invention, methods are provided for selecting a group of subjects for determining the efficacy of a candidate drug known or suspected of being useful for the treatment of an inflammatory condition, the method including determining a genotype at one or more polymorphic sites in a vasopressin pathway gene sequence for each subject, wherein said genotype is indicative of the subject's ability to recover from the inflammatory condition and sorting subjects based on their genotype. The method may further include, administering the candidate drug to the subjects or a subset of subjects and determining each subject's ability to recover from the inflammatory condition. The method may further include comparing subject response to the candidate drug based on genotype of the subject.

The polymorphic site may be selected from one or more of the following: rs18059; rs27711; rs38041; rs10051637; rs1410713; rs857240; rs857242; rs10877970; rs3803107; and rs1495027; or a polymorphic site in linkage disequilibrium thereto. The method of claim 2, wherein the polymorphic site in linkage disequilibrium may be selected from one or more of the following: rs2762; rs10051637; rs1477364; rs7731592; rs7736466; rs1363974; rs2351010; rs1423357; rs1544777; rs2161548; rs38032; rs38034; rs38041; rs27436; rs27306; rs27307; rs27397; rs27659; rs27711; rs27290; rs38030; rs27294; rs27747; rs39602; rs248215; rs27302; rs2278018; rs1559355; rs3734015; rs4869315; rs2247650; rs2549781; rs2549782; rs2161657; rs251339; rs187265; rs2548527; rs1056893; rs2548523; rs2255546; rs2255637; rs1019503; rs251344; rs1981846; rs10071975; rs7700332; rs38042; rs18059; rs9127; rs7972829; rs10784339; rs3803107; rs11836346; rs7308008; rs11835545; rs7959001; rs11832877; rs10877977; rs2201895; rs7302323; rs10877986; rs2030106; rs1495027; rs10877962; rs1042615; rs16856; rs18059; rs27296; rs27300; rs27613; rs27711; rs38033; rs38035; rs38036; rs38041; rs38043; rs716848; rs1216565; rs1230358; rs1363907; rs1974871; rs2042385; rs2113050; rs2113189; rs2161658; rs2255633; rs2255634; rs2287988; rs2548524; rs2548529; rs2548530; rs2548532; rs2548533; rs2548536; rs2548538; rs2548539; rs2548540; rs2549783; rs2549784; rs2549790; rs2549791; rs2549794; rs2549795; rs2549796; rs2549797; rs2617447; rs2910686; rs2927609

rs3797796; rs3849749; rs3849750; rs4360063; rs4869314; rs4869316; rs6556942; rs7713127;
rs7716222; rs7719705; rs10044354; rs10051637; rs10058476; rs12516666; and rs12716486.

The method may further include comparing the genotype determined with known genotypes,
5 which are known to be indicative of a prognosis for recovery from the subject's type of
inflammatory condition, or another inflammatory condition.

The method may further include obtaining vasopressin pathway gene sequence information for the
subject. The genotype may be determined using a nucleic acid sample from the subject. The
method may further include obtaining the nucleic acid sample from the subject. The genotype may
10 be determined using one or more of the following techniques: restriction fragment length analysis;
sequencing; micro-sequencing assay; hybridization; invader assay; gene chip hybridization assays;
oligonucleotide ligation assay; ligation rolling circle amplification; 5' nuclease assay; polymerase
proofreading methods; allele specific PCR; matrix assisted laser desorption ionization time of
flight (MALDI-TOF) mass spectroscopy; ligase chain reaction assay; enzyme-amplified electronic
15 transduction; single base pair extension assay; and reading sequence data. The genotype of the
subject may be indicative of increased risk of death or organ dysfunction from the inflammatory
condition. The subject may be critically ill and the genotype is indicative of a prognosis of severe
cardiovascular or respiratory dysfunction.

20 The genotype may include at least one of the following risk genotypes: rs18059CT; rs18059TT;
rs27711GA; rs27711GG; rs38041GA; rs38041GG; rs10051637GA; rs10051637GG;
rs1410713AA; rs857240CC; rs857242CC; rs10877970CC; rs3803107TT; and rs1495027TT; or a
polymorphic site in linkage disequilibrium thereto. The genotype may include at least one of the
following risk alleles: rs3803107T; and rs10877970C; or a polymorphic site in linkage
25 disequilibrium thereto.

The genotype of the subject may be indicative of decreased risk of death or organ dysfunction
from the inflammatory condition. The subject may be critically ill and the genotype is indicative
of a prognosis of mild cardiovascular or respiratory dysfunction. The genotype may include at
30 least one of the following reduced risk genotypes: rs18059CC; rs27711AA; rs38041AA;
rs10051637AA; rs1410713CC; rs1410713AC; rs857240TT; rs857240CT; rs857242AA;
rs857242AC; rs10877970TT; rs10877970CT; rs3803107CC; rs3803107CT; rs1495027CC and
rs1495027CT; or a polymorphic site in linkage disequilibrium thereto. The genotype may include

at least one of the following reduced risk alleles: rs3803107C; and rs10877970T; or a polymorphic site in linkage disequilibrium thereto.

Alternatively, the genotype of the polymorphic site in linkage disequilibrium may be selected from one or more of the polymorphic sites and corresponding genotypes set out in TABLES 1B and 1D.

The inflammatory condition may be selected from the group consisting of: sepsis, septicemia, pneumonia, septic shock, systemic inflammatory response syndrome (SIRS), Acute Respiratory Distress Syndrome (ARDS), acute lung injury, aspiration pneumonitis, infection, pancreatitis, bacteremia, peritonitis, abdominal abscess, inflammation due to trauma, inflammation due to surgery, chronic inflammatory disease, ischemia, ischemia-reperfusion injury of an organ or tissue, tissue damage due to disease, tissue damage due to chemotherapy or radiotherapy, and reactions to ingested, inhaled, infused, injected, or delivered substances, glomerulonephritis, bowel infection, opportunistic infections, and for subjects undergoing major surgery or dialysis, subjects who are immunocompromised, subjects on immunosuppressive agents, subjects with HIV/AIDS, subjects with suspected endocarditis, subjects with fever, subjects with fever of unknown origin, subjects with cystic fibrosis, subjects with diabetes mellitus, subjects with chronic renal failure, subjects with acute renal failure, oliguria, subjects with acute renal dysfunction, glomerulo-nephritis, interstitial-nephritis, acute tubular necrosis (ATN), subjects, subjects with bronchiectasis, subjects with chronic obstructive lung disease, chronic bronchitis, emphysema, or asthma, subjects with febrile neutropenia, subjects with meningitis, subjects with septic arthritis, subjects with urinary tract infection, subjects with necrotizing fasciitis, subjects with other suspected Group A streptococcus infection, subjects who have had a splenectomy, subjects with recurrent or suspected enterococcus infection, other medical and surgical conditions associated with increased risk of infection, Gram positive sepsis, Gram negative sepsis, culture negative sepsis, fungal sepsis, meningococemia, post-pump syndrome, cardiac stun syndrome, myocardial infarction, stroke, congestive heart failure, hepatitis, epiglottitis, E. coli 0157:H7, malaria, gas gangrene, toxic shock syndrome, pre-eclampsia, eclampsia, HELLP syndrome, mycobacterial tuberculosis, Pneumocystis carinii, pneumonia, Leishmaniasis, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, Dengue hemorrhagic fever, pelvic inflammatory disease, Legionella, Lyme disease, Influenza A, Epstein-Barr virus, encephalitis, inflammatory diseases and autoimmunity including Rheumatoid arthritis, osteoarthritis, progressive systemic sclerosis, systemic lupus erythematosus, inflammatory bowel disease, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, systemic vasculitis, Wegener's granulomatosis, transplants including heart, liver,

lung kidney bone marrow, graft-versus-host disease, transplant rejection, sickle cell anemia, nephrotic syndrome, toxicity of agents such as OKT3, cytokine therapy, and cirrhosis. The inflammatory condition may be SIRS. The inflammatory condition may be sepsis. The inflammatory condition may be septic shock.

5

The vasopressin receptor agonist may be vasopressin.

In accordance with another aspect of the invention, there are provided two or more oligonucleotides or peptide nucleic acids of about 10 to about 400 nucleotides that hybridize specifically to a sequence contained in a human target sequence consisting of a subject's vasopressin pathway associated gene sequence, a complementary sequence of the target sequence or RNA equivalent of the target sequence and wherein the oligonucleotides or peptide nucleic acids are operable in determining the presence or absence of two or more polymorphism(s) or in their vasopressin pathway associated gene sequence selected from of the following polymorphic sites: rs18059; rs27711; rs38041; rs10051637; rs1410713; rs857240; rs857242; rs10877970; rs3803107; and rs1495027; or one or more polymorphic sites in linkage disequilibrium thereto.

In accordance with another aspect of the invention, there are provided two or more oligonucleotides or peptide nucleic acids selected from the group including of: (a) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:1 having a T at position 201 but not to a nucleic acid molecule including SEQ ID NO:1 having a C at position 201; (b) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:1 having a C at position 201 but not to a nucleic acid molecule including SEQ ID NO:1 having a T at position 201; (c) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:2 having a G at position 201 but not to a nucleic acid molecule including SEQ ID NO:2 having a A at position 201; (d) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:2 having an A at position 201 but not to a nucleic acid molecule including SEQ ID NO:2 having a G at position 201; (e) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:3 having an A at position 201 but not to a nucleic acid molecule including SEQ ID NO:3 having a G at position 201; (f) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule

including SEQ ID NO:3 having a G at position 201 but not to a nucleic acid molecule including SEQ ID NO:3 having an A at position 201; (g) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:4 having a G at position 201 but not to a nucleic acid molecule including SEQ ID NO:4 having an A at position 201; (h) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:4 having an A at position 201 but not to a nucleic acid molecule including SEQ ID NO:4 having a G at position 201; (i) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:5 having an A at position 201 but not to a nucleic acid molecule including SEQ ID NO:5 having a C at position 201; (j) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:5 having a C at position 201 but not to a nucleic acid molecule including SEQ ID NO:5 having an A at position 201; (k) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:6 having an T at position 201 but not to a nucleic acid molecule including SEQ ID NO:6 having a C at position 201; (l) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:6 having a C at position 201 but not to a nucleic acid molecule including SEQ ID NO:6 having an T at position 201; (m) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:7 having an A at position 201 but not to a nucleic acid molecule including SEQ ID NO:7 having a C at position 201; (n) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:7 having a C at position 201 but not to a nucleic acid molecule including SEQ ID NO:7 having an A at position 201; (o) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:8 having a T at position 201 but not to a nucleic acid molecule including SEQ ID NO:8 having a C at position 201; (p) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:8 having a C at position 201 but not to a nucleic acid molecule including SEQ ID NO:8 having a T at position 201; (q) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:9 having a C at position 201 but not to a nucleic acid molecule including SEQ ID NO:9 having a T at position 201; (r) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:9 having a T at position 201 but not to a nucleic acid molecule including SEQ ID NO:9 having a C at position 201;

(s) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including SEQ ID NO:10 having a T at position 201 but not to a nucleic acid molecule including SEQ ID NO:10 having a C at position 201; (t) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule including
5 SEQ ID NO:10 having a C at position 201 but not to a nucleic acid molecule including SEQ ID NO:10 having a T at position 201; (u) an oligonucleotide or peptide nucleic acid capable of hybridizing under high stringency conditions to a nucleic acid molecule including a first allele for a given polymorphism selected from the polymorphisms listed in TABLE 1D but not capable of hybridizing under high stringency conditions to a nucleic acid molecule including a second allele
10 for the given polymorphism selected from the polymorphisms listed in TABLE 1D; and (v) an oligonucleotide or peptide nucleic acid capable of hybridizing under high stringency conditions to a nucleic acid molecule including the second allele for a given polymorphism selected from the polymorphisms listed in TABLE 1D but not capable of hybridizing under high stringency conditions to a nucleic acid molecule including the first allele for the given polymorphism selected
15 from the polymorphisms listed in TABLE 1D.

In accordance with another aspect of the invention, there is provided an array of oligonucleotides or peptide nucleic acids attached to a solid support, the array including two or more of the oligonucleotides or peptide nucleic acids as set out herein.

20

In accordance with another aspect of the invention, there is provided a composition including an addressable collection of two or more oligonucleotides or peptide nucleic acids, the two or more oligonucleotides or peptide nucleic acids selected from the oligonucleotides or peptide nucleic acids as set out herein.

25

In accordance with another aspect of the invention, there is provided a composition including an addressable collection of two or more oligonucleotides or peptide nucleic acids, the two or more oligonucleotides or peptide nucleic acids consisting essentially of two or more nucleic acid molecules set out in SEQ ID NO:1-264 or compliments, fragments, variants, or analogs thereof.

30

In accordance with another aspect of the invention, there is provided a composition including an addressable collection of two or more oligonucleotides or peptide nucleic acids, the two or more oligonucleotides or peptide nucleic acids consisting essentially of two or more nucleic acid molecules set out in TABLES 1C and 1D or compliments, fragments, variants, or analogs thereof.

The oligonucleotides or peptide nucleic acids described herein may further include one or more of the following: a detectable label; a quencher; a mobility modifier; a contiguous non-target sequence situated 5' or 3' to the target sequence or 5' and 3' to the target sequence.

5

In accordance with another aspect of the invention, there is provided a computer readable medium including a plurality of digitally encoded genotype correlations selected from the vasopressin pathway associated gene SNP correlations in TABLE 1E, wherein each correlation of the plurality has a value representing an ability to recover from an inflammatory condition and a value
10 representing an indication of responsiveness to treatment with a vasopressin receptor agonist.

The oligonucleotides or peptide nucleic acids may further include one or more of the following: a detectable label; a quencher; a mobility modifier; a contiguous non-target sequence situated 5' or 3' to the target sequence or 5' and 3' to the target sequence. The oligonucleotides or peptide nucleic
15 acids may alternatively be of about 10 to about 400 nucleotides, about 15 to about 300 nucleotides. The oligonucleotides or peptide nucleic acids may alternatively be of about 20 to about 200 nucleotides, about 25 to about 100 nucleotides. The oligonucleotides or peptide nucleic acids may alternatively be of about 20 to about 80 nucleotides, about 25 to about 50 nucleotides. The genotype may be determined using a nucleic acid sample from the subject. Genotype may be
20 determined using one or more of the following techniques: restriction fragment length analysis; sequencing; micro-sequencing assay; hybridization; invader assay; gene chip hybridization assays; oligonucleotide ligation assay; ligation rolling circle amplification; 5' nuclease assay; polymerase proofreading methods; allele specific PCR; matrix assisted laser desorption ionization time of flight (MALDI-TOF) mass spectroscopy; ligase chain reaction assay; enzyme-amplified electronic
25 transduction; single base pair extension assay; and reading sequence data. A determination of whether a site is in linkage disequilibrium (LD) with another site may be determined based on an absolute r^2 value or D' value. When evaluating loci for LD those sites within a given population having a high degree of linkage disequilibrium (for example an absolute value for D' of ≥ 0.5 or $r^2 \geq 0.5$) are potentially useful in predicting the identity of an allele of interest (for example
30 associated with the condition of interest). A high degree of linkage disequilibrium may be represented by an absolute value for D' of ≥ 0.6 or $r^2 \geq 0.6$. Alternatively, a higher degree of linkage disequilibrium may be represented by an absolute value for D' of ≥ 0.7 or $r^2 \geq 0.7$ or by an absolute value for D' of ≥ 0.8 or $r^2 \geq 0.8$. Additionally, a high degree of linkage disequilibrium may be represented by an absolute value for D' of ≥ 0.85 or $r^2 \geq 0.85$ or by an absolute value for D'

of ≥ 0.9 or $r^2 \geq 0.9$. Two or more oligonucleotides or peptide nucleic acids may include 3 or more; 4 or more; 5 or more; 6 or more; 7 or more; 8 or more; 9 or more; 10 or more; 11 or more; 12 or more; 13 or more; 14 or more; 15 or more; 16 or more; 17 or more; 18 or more; 19 or more; or 20 or more.

5

Sequence variations may be assigned to a gene if mapped within 2 kb or more of an mRNA sequence feature. In particular, such a sequence may extend many kilobases (kb) from a vasopressin pathway gene and into neighbouring genes, where the LD within a region is strong.

10 BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows a Kaplan-Meier curve for a cohort of Caucasian Subjects with systematic inflammatory response syndrome by genotype of Leucyl aminopeptidase (LNPEP) rs18059 (CC = dashed CT/TT = solid).

15 FIGURE 2 shows Kaplan-Meier survival curves for a cohort of Caucasian Subjects with systematic inflammatory response syndrome by genotype of Arginine Vasopressin (AVP) rs1410713 (AA = dashed CC/AC = solid).

FIGURE 3 shows Kaplan-Meier survival curves for a cohort of Caucasian Subjects with sepsis by genotype of Arginine Vasopressin (AVP) rs1410713 (AA = dashed CC/AC = solid).

20 FIGURE 4 shows Kaplan-Meier survival curves for a cohort of Caucasian Subjects with septic shock by genotype of Arginine Vasopressin (AVP) rs1410713 (AA = dashed CC/AC = solid).

FIGURE 5 shows Kaplan-Meier survival curves for a cohort of Caucasian Subjects with systematic inflammatory response syndrome by genotype of Arginine Vasopressin (AVP) rs857242 (AC/AA = solid vs. CC = dashed).

25 FIGURE 6 shows Kaplan-Meier survival curves for a cohort of Caucasian Subjects with sepsis by genotype of Arginine Vasopressin (AVP) rs857242 (AC/AA = solid vs. CC = dashed).

FIGURE 7 shows Kaplan-Meier survival curves for a cohort of Caucasian Subjects with septic shock by genotype of Arginine Vasopressin (AVP) rs857242 (AC/AA = solid vs. CC = dashed).

30 FIGURE 8 shows Kaplan-Meier survival curves for a cohort of Caucasian Subjects with systematic inflammatory response syndrome by genotype of arginine vasopressin receptor (AVPR1A) rs3803107 (CC/CT = solid vs. TT = dashed).

FIGURE 9 shows a Kaplan Meier survival curve over 28 days for a cohort of Asian Subjects with systematic inflammatory response syndrome by allele of arginine vasopressin receptor (AVPR1A) rs3803107 (C = solid vs. T = dashed).

FIGURE 10 shows a Kaplan Meier survival curve over 28 days for a cohort of Asian Subjects with systematic inflammatory response syndrome by allele of arginine vasopressin receptor (AVPR1A) rs10877970 (T = dashed vs. C = solid).

DETAILED DESCRIPTION OF THE INVENTION

1. Definitions

In the description that follows, a number of terms are used extensively, the following definitions are provided to facilitate understanding of the invention.

“Vasopressin Receptor Agonist” as used herein includes any vasopressin molecule, vasopressin derivative, vasopressin variant, vasopressin analogue, non-peptidyl analogues and any prodrug thereof, metabolite thereof, isomer thereof, combination of isomers thereof, or pharmaceutical composition of any of the preceding. Such agonists may be capable of binding to or interacting with a vasopressin receptor and initiating one or more of the types of responses typically produced by the binding of an endogenous vasopressin molecule to a vasopressin receptor (for example, AVPR1A, AVPR1B, AVPR2 and OXTR). Such activity may be present at the time of or following, administration to a subject. Vasopressin receptor agonists may be used alone or in combination with other vasopressin receptor agonists or other medications. Vasopressin receptor agonists may be synthesized or purified. Examples of vasopressin receptor agonists capable of increasing blood pressure, include, but are not limited to, arginine vasopressin (AVP), lysine vasopressin (LVP), triglycyl-lysine vasopressin (also known as Terlipressin or Glycopressin), Octapressin, Ornipressin, Desmopressin, Desmopressin acetate, Lypressin, Felypressin, and Argipressin. Vasopressin analogues may be 1 – 3 amino acids such as Ala-AVP, Ser-Ala-AVP, Thr-Ser-Ala-AVP (KALISZAN R. *et al.* Pharmacol Res Commun (1988) 20(5):377-381) or 3-beta- (2-thienyl)-L-alanine)-8-lysine-vasopressin and other similar analogues (Smith CW. Acta Pharmacol Toxicol (Copenhag) (1978) 43(3):190-195). Examples of derivatives, variants, analogues or compositions etc. may found in US patent applications: 20050075328; 20040229798; 20030134845; 20030021792; 20030018024; 20030008863; 20030004159; 20020198196; 20020198191; 20020049194; 20050075328; 20040229798; 20030018024; and 20020198191 and issued US patents: 6,903,091; 6,831,079; 6,642,223; 6,620,807; 6,511,974; 6,344,451; 6,335,327; 6,297,234; 6,268,360; 6,235,900; 6,204,260; 6,194,407; 6,096,736; 6,096,735; 6,090,803;

4,908,475; 4,810,778; 4,760,052; 4,711,877; 6,903,091; 6,620,807; 6,344,451; 6,297,234; and 6,268,360.

“Vasopressin” as used herein includes: Antidiuretic hormone; Argiprestocin; Arginine

- 5 Vasopressin; Arginine oxytocin; Pitressin tannate; Arginine vasotocin; Vasotocin; Vasopressin, isoleucyl; 3-Isoleucyl vasopressin; 1-[[19-amino-13-butan-2-yl-10-(2-carbamoylethyl)-7-(carbamoylmethyl)-16-[(4-hydroxyphenyl)methyl]-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentazacycloicos-4-yl]carbonyl]-N-[1-(carbamoylmethylcarbamoyl)-4-guanidino-butyl]-pyrrolidine-2-carboxamide (IUPAC name). Vasopressin is a nine amino acid peptide (Cys-Tyr-
- 10 Ile-Gln-Asn-Cys-Pro-Arg-Gly, cyclic 1-6 disulfide) secreted from the posterior pituitary and binds to receptors in blood vessels, the brain and distal or collecting tubules of the kidney to promote vasoconstriction or reabsorption of water back into the circulation. Vasopressin receptor targets, include AVPR1A, AVPR1B, AVPR2 and OXTR. Vasopressin, for example, is sold as PRESSYN AR™ by Ferring Inc., and also sold in various formulations as VASOPRESSIN by Ferring Inc.,
- 15 Sandoz Canada Inc. and Pharmaceutical Partners of Canada Inc. Similarly, PITRESSIN™ is sold by Warner-Lambert Company, Parke-Davis Division, as a synthetic injectable vasopressin (8-Arginine vasopressin). It is substantially free from the oxytocic principle and is standardized to contain 20 pressor units/mL. The solution contains 0.5% Chlorobutanol (chloroform derivative) as a preservative. Also, DIAPID™ is sold as a nasal spray by Sandoz Inc. The current published
- 20 indications for vasopressin (from the label of Ferring's PRESSYN AR™) are “Vasopressin is intended for use in the prevention of treatment of post-operative abdominal distension, dispelling of gas shadows in abdominal roentgenography and symptomatic control of diabetes insipidus.”

- 25 "Genetic material" includes any nucleic acid and can be a deoxyribonucleotide or ribonucleotide polymer in either single or double-stranded form.

- A “purine” is a heterocyclic organic compound containing fused pyrimidine and imidazole rings, and acts as the parent compound for purine bases, adenine (A) and guanine (G). A “Nucleotide” is generally a purine (R) or pyrimidine (Y) base covalently linked to a pentose, usually ribose or
- 30 deoxyribose, where the sugar carries one or more phosphate groups. Nucleic acids are generally a polymer of nucleotides joined by 3'-5' phosphodiester linkages. As used herein “purine” is used to refer to the purine bases, A and G, and more broadly to include the nucleotide monomers, deoxyadenosine-5'-phosphate and deoxyguanosine-5'-phosphate, as components of a polynucleotide chain.

A “pyrimidine” is a single-ringed, organic base that forms nucleotide bases, cytosine (C), thymine (T) and uracil (U). As used herein “pyrimidine” is used to refer to the pyrimidine bases, C, T and U, and more broadly to include the pyrimidine nucleotide monomers that along with purine nucleotides are the components of a polynucleotide chain.

A nucleotide represented by the symbol M may be either an A or C, a nucleotide represented by the symbol W may be either an T/U or A, a nucleotide represented by the symbol Y may be either an C or T/U, a nucleotide represented by the symbol S may be either an G or C, while a nucleotide represented by the symbol R may be either an G or A, and a nucleotide represented by the symbol K may be either an G or T/U. Similarly, a nucleotide represented by the symbol V may be either A or G or C, while a nucleotide represented by the symbol D may be either A or G or T, while a nucleotide represented by the symbol B may be either G or C or T, and a nucleotide represented by the symbol H may be either A or C or T.

A “polymorphic site” or “polymorphism site” or “polymorphism” or “single nucleotide polymorphism site” (SNP site) or single nucleotide polymorphism” (SNP) as used herein is the locus or position with in a given sequence at which divergence occurs. A “polymorphism” is the occurrence of two or more forms of a gene or position within a gene (allele), in a population, in such frequencies that the presence of the rarest of the forms cannot be explained by mutation alone. The implication is that polymorphic alleles confer some selective advantage on the host. Preferred polymorphic sites have at least two alleles, each occurring at frequency of greater than 1%, and more preferably greater than 10% or 20% of a selected population. Polymorphic sites may be at known positions within a nucleic acid sequence or may be determined to exist using the methods described herein. Polymorphisms may occur in both the coding regions and the noncoding regions (for example, promoters, introns or untranslated regions) of genes. Polymorphisms may occur at a single nucleotide site (SNPs) or may involve an insertion or deletion as described herein.

A “risk genotype” as used herein refers to an allelic variant (genotype) at one or more polymorphic sites within the vasopressin pathway gene (i.e. AVP, AVPR1A and LNPEP) sequences described herein as being indicative of a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome. The risk genotype may be determined for either the haploid genotype or diploid genotype, provided that at least one copy of a risk allele is present.

Risk genotype may be an indication of an increased risk of not recovering from an inflammatory condition. Subjects having one copy (heterozygotes) or two copies (homozygotes) of the risk allele (for example rs18059 CT, rs18059 TT) are considered to have the “risk genotype” even though the degree to which the subjects risk of not recovering from an inflammatory condition may increase, depending on whether the subject is a homozygote rather than a heterozygote. Such “risk alleles” or “risk genotypes” may be selected from the following: rs18059CT; rs18059TT; rs27711GA; rs27711GG; rs38041GA; rs38041GG; rs10051637GA; rs10051637GG; rs1410713AA; rs857240CC; rs857242CC; rs10877970TT; rs3803107TT; and rs1495027CC; or a polymorphic site in linkage disequilibrium thereto.

A “decreased risk genotype” as used herein refers to an allelic variant (genotype) at one or more polymorphic sites within the vasopressin pathway gene (i.e. AVP, AVPR1A and LNPEP) sequences described herein as being indicative of an increased likelihood of recovery from an inflammatory condition or a decreased risk of having a poor outcome. The decreased risk genotype may be determined for either the haploid genotype or diploid genotype, provided that at least one copy of a risk allele is present. Decreased risk genotype may be an indication of an increased likelihood of recovering from an inflammatory condition. Subjects having one copy (heterozygotes) or two copies (homozygotes) of the decreased risk allele (for example rs1410713 CC rs1410713 AC) are considered to have the “decreased risk genotype” even though the degree to which the subjects risk of not recovering from an inflammatory condition may increase, depending on whether the subject is a homozygote rather than a heterozygote. Such “decreased risk alleles” or “decreased risk genotypes” or “reduced risk genotypes” may be selected from the following: rs18059CC; rs27711AA; rs38041AA; rs10051637AA; rs1410713CC; rs1410713AC; rs857240TT; rs857240CT; rs857242AA; rs857242AC; rs10877970TT; rs10877970CT; rs3803107CC; rs3803107CT; rs1495027CC and rs1495027CT; or a polymorphic site in linkage disequilibrium thereto.

An “improved response genotype” (IRG) or improved response polymorphic variant (IRP) as used herein refers to an allelic variant or genotype at one or more polymorphic sites within the vasopressin pathway associated polymorphisms selected from arginine vasopressin (AVP), arginine vasopressin receptor 1A (AVPR1A) leucyl/cystinyl aminopeptidase (LNPEP) or leukocyte-derived aminopeptidase (LRAP) as described herein as being predictive of a subject’s improved survival in response to vasopressin receptor agonist treatment (for example rs18059TT, rs27711GG, rs10051637AA, rs1410713AA, rs857240CC, rs857242CC or rs1495027CC), or a

polymorphic site in linkage disequilibrium thereto.

An “adverse response genotype” (ARG) or adverse response polymorphic variant as used herein refers to an allelic variant or genotype at one or more polymorphic sites within the vasopressin pathway associated polymorphisms selected from arginine vasopressin (AVP), arginine vasopressin receptor 1A (AVPR1A), leucyl/cystinyl aminopeptidase (LNPEP) or leukocyte-derived aminopeptidase (LRAP) as described herein as being predictive of a subject’s decreased survival in response to vasopressin receptor agonist treatment (for example rs18059CC, rs27711AA, rs10051637GG, rs1410713CC, rs857240CT, rs857242AC or rs1495027TT), or a polymorphic site in linkage disequilibrium thereto. Subjects having a ARG are preferably selected for treatments not involving vasopressin receptor agonist administration.

A “clade” is a group of haplotypes that are closely related phylogenetically. For example, if haplotypes are displayed on a phylogenetic (evolutionary) tree a clade includes all haplotypes contained within the same branch.

The pattern of a set of markers along a chromosome is referred to as a “Haplotype”. Accordingly, groups of alleles on the same small chromosomal segment tend to be transmitted together. Haplotypes along a given segment of a chromosome are generally transmitted to progeny together unless there has been a recombination event. Absence of a recombination event, haplotypes can be treated as alleles at a single highly polymorphic locus for mapping.

As used herein “haplotype” is a set of alleles of closely linked loci on a chromosome that tend to be inherited together. Such allele sets occur in patterns, which are called haplotypes.

Accordingly, a specific SNP or other polymorphism allele at one SNP site is often associated with a specific SNP or other polymorphism allele at a nearby second SNP site or other polymorphism site. When this occurs, the two SNPs or other polymorphisms are said to be in LD because the two SNPs or other polymorphisms are not just randomly associated (i.e. in linkage equilibrium).

In general, the detection of nucleic acids in a sample depends on the technique of specific nucleic acid hybridization in which the oligonucleotide is annealed under conditions of “high stringency” to nucleic acids in the sample, and the successfully annealed oligonucleotides are subsequently detected (see for example Spiegelman, S., Scientific American, Vol. 210, p. 48 (1964)).

Hybridization under high stringency conditions primarily depends on the method used for

hybridization, the oligonucleotide length, base composition and position of mismatches (if any). High-stringency hybridization is relied upon for the success of numerous techniques routinely performed by molecular biologists, such as high-stringency PCR, DNA sequencing, single strand conformational polymorphism analysis, and in situ hybridization. In contrast to Northern and Southern hybridizations, these aforementioned techniques are usually performed with relatively short probes (e.g., usually about 16 nucleotides or longer for PCR or sequencing and about 40 nucleotides or longer for in situ hybridization). The high stringency conditions used in these techniques are well known to those skilled in the art of molecular biology, and examples of them can be found, for example, in Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons, New York, N.Y., 1998.

“Oligonucleotides” as used herein are variable length nucleic acids, which may be useful as probes, primers and in the manufacture of microarrays (arrays) for the detection and/or amplification of specific nucleic acids. Such DNA or RNA strands may be synthesized by the sequential addition (5'-3' or 3'-5') of activated monomers to a growing chain, which may be linked to an insoluble support. Numerous methods are known in the art for synthesizing oligonucleotides for subsequent individual use or as a part of the insoluble support, for example in arrays (BERNFELD MR. and ROTTMAN FM. J. Biol. Chem. (1967) 242(18):4134-43; SULSTON J. *et al.* PNAS (1968) 60(2):409-415; GILLAM S. *et al.* Nucleic Acid Res.(1975) 2(5):613-624; BONORA GM. *et al.* Nucleic Acid Res.(1990) 18(11):3155-9; LASHKARI DA. *et al.* Proc Nat Acad Sci (1995) 92(17):7912-5; MCGALL G. *et al.* PNAS (1996) 93(24):13555-60; ALBERT TJ. *et al.* Nucleic Acid Res.(2003) 31(7):e35; GAO X. *et al.* Biopolymers (2004) 73(5):579-96; and MOORCROFT MJ. *et al.* Nucleic Acid Res.(2005) 33(8):e75). In general, oligonucleotides are synthesized through the stepwise addition of activated and protected monomers under a variety of conditions depending on the method being used. Subsequently, specific protecting groups may be removed to allow for further elongation and subsequently and once synthesis is complete all the protecting groups may be removed and the oligonucleotides removed from their solid supports for purification of the complete chains if so desired.

“Peptide nucleic acids” (PNA) as used herein refer to modified nucleic acids in which the sugar phosphate skeleton of a nucleic acid has been converted to an N-(2-aminoethyl)-glycine skeleton. Although the sugar-phosphate skeletons of DNA/RNA are subjected to a negative charge under neutral conditions resulting in electrostatic repulsion between complementary chains, the backbone structure of PNA does not inherently have a charge. Therefore, there is no electrostatic repulsion.

Consequently, PNA has a higher ability to form double strands as compared with conventional nucleic acids, and has a high ability to recognize base sequences. Furthermore, PNAs are generally more robust than nucleic acids. PNAs may also be used in arrays and in other hybridization or other reactions as described above and herein for oligonucleotides.

5

An “addressable collection” as used herein is a combination of nucleic acid molecules or peptide nucleic acids capable of being detected by, for example, the use of hybridization techniques or by any other means of detection known to those of ordinary skill in the art. A DNA microarray would be considered an example of an “addressable collection”.

10

In general the term “linkage”, as used in population genetics, refers to the co-inheritance of two or more nonallelic genes or sequences due to the close proximity of the loci on the same chromosome, whereby after meiosis they remain associated more often than the 50% expected for unlinked genes. However, during meiosis, a physical crossing between individual chromatids may result in recombination. "Recombination" generally occurs between large segments of DNA, whereby contiguous stretches of DNA and genes are likely to be moved together in the recombination event (crossover). Conversely, regions of the DNA that are far apart on a given chromosome are more likely to become separated during the process of crossing-over than regions of the DNA that are close together. Polymorphic molecular markers, like SNPs, are often useful in tracking meiotic recombination events as positional markers on chromosomes.

15
20

Furthermore, the preferential occurrence of a disease gene in association with specific alleles of linked markers, such as SNPs or other polymorphisms, is called “Linkage Disequilibrium” (LD). This sort of disequilibrium generally implies that most of the disease chromosomes carry the same mutation and the markers being tested are relatively close to the disease gene(s).

25

For example, in SNP-based association analysis and LD mapping, SNPs can be useful in association studies for identifying polymorphisms, associated with a pathological condition, such as sepsis. Unlike linkage studies, association studies may be conducted within the general population and are not limited to studies performed on related individuals in affected families. In a SNP association study the frequency of a given allele (i.e. SNP allele) is determined in numerous subjects having the condition of interest and in an appropriate control group. Significant associations between particular SNPs or SNP haplotypes and phenotypic characteristics may then be determined by numerous statistical methods known in the art.

30

Association analysis can either be direct or LD based. In direct association analysis, potentially causative SNPs may be tested as candidates for the pathogenic sequence. In LD based SNP association analysis, SNPs may be chosen at random over a large genomic region or even genome wide, to be tested for SNPs in LD with a pathogenic sequence or pathogenic SNP. Alternatively, candidate sequences associated with a condition of interest may be targeted for SNP identification and association analysis. Such candidate sequences usually are implicated in the pathogenesis of the condition of interest. In identifying SNPs associated with inflammatory conditions, candidate sequences may be selected from those already implicated in the pathway of the condition or disease of interest. Once identified, SNPs found in or associated with such sequences, may then be tested for statistical association with an individual's prognosis or susceptibility to the condition.

For an LD based association analysis, high density SNP maps are useful in positioning random SNPs relative to an unknown pathogenic locus. Furthermore, SNPs tend to occur with great frequency and are often spaced uniformly throughout the genome. Accordingly, SNPs as compared with other types of polymorphisms are more likely to be found in close proximity to a genetic locus of interest. SNPs are also mutationally more stable than variable number tandem repeats (VNTRs) and short tandem repeats (STRs).

In population genetics linkage disequilibrium refers to the “preferential association of a particular allele, for example, a mutant allele for a disease with a specific allele at a nearby locus more frequently than expected by chance” and implies that alleles at separate loci are inherited as a single unit (Gelehrter, T.D., Collins, F.S. (1990). Principles of Medical Genetics. Baltimore: Williams & Wilkens). Accordingly, the alleles at these loci and the haplotypes constructed from their various combinations serve as useful markers of phenotypic variation due to their ability to mark clinically relevant variability at a particular position, such as position 201 of SEQ ID NO:1 (see Akey, J. *et al.* Eur J Hum Genet (2001) 9:291-300; and Zhang, K. *et al.* (2002). Am J Hum Genet. 71:1386-1394). This viewpoint is further substantiated by Khoury *et al.* ((1993). Fundamentals of Genetic Epidemiology. New York: Oxford University Press at p. 160) who state, “[w]henver the marker allele is closely linked to the true susceptibility allele and is in [linkage] disequilibrium with it, one can consider that the marker allele can serve as a proxy for the underlying susceptibility allele.”

As used herein “linkage disequilibrium” (LD) is the occurrence in a population of certain combinations of linked alleles in greater proportion than expected from the allele frequencies at the loci. For example, the preferential occurrence of a disease gene in association with specific alleles of linked markers, such as SNPs, or between specific alleles of linked markers, are considered to be in LD. This sort of disequilibrium generally implies that most of the disease chromosomes carry the same mutation and that the markers being tested are relatively close to the disease gene(s). Accordingly, if the genotype of a first locus is in LD with a second locus (or third locus etc.), the determination of the allele at only one locus would necessarily provide the identity of the allele at the other locus. When evaluating loci for LD those sites within a given population having a high degree of linkage disequilibrium (i.e. an absolute value for $r^2 \geq 0.5$) are potentially useful in predicting the identity of an allele of interest (i.e. associated with the condition of interest). A high degree of linkage disequilibrium may be represented by an absolute value for $r^2 \geq 0.6$.

Alternatively, a high degree of linkage disequilibrium may be represented by an absolute value for $r^2 \geq 0.7$ or by an absolute value for $r^2 \geq 0.8$. Additionally, a high degree of linkage disequilibrium may be represented by an absolute value for $r^2 \geq 0.85$ or by an absolute value for $r^2 \geq 0.9$.

Accordingly, two SNPs that have a high degree of LD may be equally useful in determining the identity of the allele of interest or disease allele. Therefore, we may assume that knowing the identity of the allele at one SNP may be representative of the allele identity at another SNP in LD. Accordingly, the determination of the genotype of a single locus can provide the identity of the genotype of any locus in LD therewith and the higher the degree of linkage disequilibrium the more likely that two SNPs may be used interchangeably. For example, in the population from which the tagged SNPs were identified from the SNP identified by rs18059 is in “linkage disequilibrium” with the SNP identified by rs2762, whereby when the genotype of rs18059 is T the genotype of rs2762 is G. Similarly, when the genotype of rs18059 is C the genotype of rs2762 is A. Accordingly, the determination of the genotype at rs18059 will provide the identity of the genotype at rs2762 or any other locus in “linkage disequilibrium” therewith. Particularly, where such a locus is has a high degree of linkage disequilibrium thereto.

LD is useful for genotype-phenotype association studies. For example, if a specific allele at one SNP site (e.g. “A”) is the cause of a specific clinical outcome (e.g. call this clinical outcome “B”) in a genetic association study then, by mathematical inference, any SNP (e.g. “C”) which is in significant LD with the first SNP, will show some degree of association with the clinical outcome. That is, if A is associated ($\sim$) with B, i.e. $A \sim B$ and $C \sim A$ then it follows that $C \sim B$. Of course, the SNP that will be most closely associated with the specific clinical outcome, B, is the causal SNP –

the genetic variation that is mechanistically responsible for the clinical outcome. Thus, the degree of association between any SNP, C, and clinical outcome will depend on LD between A and C.

Until the mechanism underlying the genetic contribution to a specific clinical outcome is fully understood, LD helps identify potential candidate causal SNPs and also helps identify a range of SNPs that may be clinically useful for prognosis of clinical outcome or of treatment effect. If one SNP within a gene is found to be associated with a specific clinical outcome, then other SNPs in LD will also have some degree of association and therefore some degree of prognostic usefulness.

By way of prophetic example, if multiple polymorphisms were tested for individual association with an improved response to vasopressin receptor agonist administration in our SIRS/sepsis/septic shock cohort of ICU subjects, wherein the multiple polymorphisms had a range of LD with LNPEP rs18059 and it was assumed that rs18059 was the causal polymorphism, and we were to order the polymorphisms by the degree of LD with rs18059, we would expect to find that polymorphisms with high degrees of LD with rs18059 would also have a high degree of association with this specific clinical outcome. As LD decreased, we would expect the degree of association of the polymorphism with an improved response vasopressin receptor agonist administration to also decrease. It follows that any polymorphism, whether already discovered or as yet undiscovered, that is in LD with one of the improved response genotypes described herein will likely be a predictor of the same clinical outcomes that rs18059 is a predictor of. The similarity in prediction between this known or unknown polymorphism and rs18059 would depend on the degree of LD between such a polymorphism and rs18059.

Numerous sites have been identified as polymorphic sites in the vasopressin pathway associated genes (see TABLE 1A). Furthermore, the polymorphisms in TABLE 1A are linked to (in LD with) numerous polymorphism as set out in TABLE 1B below and may also therefore be indicative of subject prognosis.

TABLE 1A. Polymorphisms in the vasopressin pathway associated genes genotyped in a cohort of critically ill Subjects with severe sepsis. Minor Allele Frequencies (MAFs) for Caucasians were taken from Hapmap.org (Thorisson GA. *et al.* The International HapMap Project Website. Genome Research (2005)15:1591-1593).

Polymorphism Name (Alleles)	Official Gene Name	rs#	Mar 2006 Chromo- somal position (Build 36)	Minor allele	Minor Allele Frequency
--------------------------------	-----------------------	-----	--	-----------------	------------------------------

Polymorphism Name (Alleles)	Official Gene Name	rs#	Mar 2006 Chromo- somal position (Build 36)	Minor allele	Minor Allele Frequency
LNPEP rs18059 (C/T)	leucyl/cystinyl aminopeptidase (LNPEP)	rs18059	96377824	T	0.39
LNPEP rs27711 (G/A)	leucyl/cystinyl aminopeptidase (LNPEP)	rs27711	96371495	A	0.49
LNPEP rs38041 (A/G)	leucyl/cystinyl aminopeptidase (LNPEP)	rs38041	96356058	G	0.48
LNPEP rs10051637 (A/G)	leucyl/cystinyl aminopeptidase (LNPEP)	rs10051637	96305246	G	0.49
AVP rs1410713 (A/C)	arginine vasopressin (AVP)	rs1410713	3008350	C	0.44
AVP rs857240 (C/T)	arginine vasopressin (AVP)	rs857240	3023629	T	0.09
AVP rs857242 (C/A)	arginine vasopressin (AVP)	rs857242	3029101	A	0.1
AVPR1A rs10877970 (T/C)	arginine vasopressin receptor 1A(AVPR1A)	rs10877970	61837421	C	0.09
AVPR1A rs3803107 (C/T)	arginine vasopressin receptor 1A(AVPR1A)	rs3803107	61827101	T	0.13
AVPR1A rs1495027 (C/T)	arginine vasopressin receptor 1A(AVPR1A)	rs1495027	61890334	T	0.42

TABLE 1B. Polymorphisms in linkage disequilibrium with those listed in TABLE 1A above, as identified using the Haploview program (BARRETT JC. *et al.* Bioinformatics (2005) 21(2):263-5 (<http://www.broad.mit.edu/mpg/haploview/>)) and the LD function in the Genetics Package in R (R

Core Development Group, 2005 - R Development Core Team (www.R-project.org). Linkage Disequilibrium between markers was defined using r^2 whereby all SNPs available on Hapmap.org (phase II) (cohort H), all SNPs genotyped internally using the Illumina Goldengate assay (cohort I) and all SNPs sequenced using the Sequenom Iplex Platform (cohort S) in our genes of interest were included. A minimum r^2 of 0.5 was used as the cutoff to identify LD SNPs. The genes are identified, along with the alleles, rs designation and the chromosomal position (March 2006 Build 36). An LD allele was only predicted for those cohorts that had sufficient power and NA designations indicate that the sample sizes were insufficient to make an allele designation with confidence at the time of filing. However, the assignment of allele designations for NA designated LD alleles is a routine procedure. A '*' indicates that there is more than one RSID assigned to a single SNP.

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
LNPEP	TC (T)	96377824	rs18059	H / I	C	96346251	rs10044354
				H / I	A	96305246	rs10051637
				H	T	96323283	rs10058476
				I	T	96345363	rs10476696
				S	NA	96238651	rs1230360
				S	NA	96240263	rs1230363
				S	NA	96240337	rs1230364
				S	NA	96240415	rs1230365
				H	G	96278559	rs1363907
				H / I	A	96319572	rs1363974
				H / I	T	96324514	rs1423357
				H	G	96310648	rs1477364
				H	A	96339986	rs1544777
				H	A	96259206	rs2113189
				H / I	G	96343901	rs2161548
				H / I	C	96319685	rs2351010
				H	A	96396635	rs248215
				I	A	96298789	rs2548225
				H	G	96265683	rs2548530
				H	A	96264334	rs2548532
				H	C	96257128	rs2549783
				H	A	96268198	rs2549791
				H	T	96270305	rs2549794
				S	NA	96239682	rs2617436
				H	T	96293411	rs2617447
				I	T	96372034	rs27289
				H / I	A	96375844	rs27290
				H	G	96383016	rs27294
				H	T	96387382	rs27296
				H	T	96389163	rs27300
				H	T	96360314	rs27306
				H	G	96364261	rs27307
				H	G	96366372	rs27397
				H / I	C	96356722	rs27436
				H	G	96365029	rs27613
				H / I	G	96299054	rs2762

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				H / I	G	96369308	rs27659
				H	G	96371495	rs27711
				H	G	96385668	rs27747
				H	T	96278345	rs2910686
				I	T	96302142	rs2910792
				H	C	96277835	rs2927609
				S	NA	96239688	rs35199417
				H / I	G	96342514	rs3797796
				H	T	96379440	rs38030
				H	T	96347643	rs38032
				H / I	A	96347892	rs38033
				H / I	C	96348175	rs38034
				H	C	96349036	rs38035
				H	A	96349259	rs38036
				H	G	96356058	rs38041
				H / I	G	96362547	rs38043
				H	T	96260289	rs3849749
				H	G	96390210	rs39602
				H	A	96318909	rs4360063
				H	G	96251952	rs6556942
				I	C	96307418	rs6871162
				H	G	96290756	rs716848
				I	G	96315986	rs7703341
				H	A	96313894	rs7713127
				H	C	96318762	rs7716222
				H	G	96312042	rs7719705
				H / I	G	96314716	rs7731592
				H	G	96315467	rs7736466
				I	T	96346342	rs9314181
LNEP	GA (G)	96371495	rs27711	S	NA	96346167	rs10038651
				H / I	C	96346251	rs10044354
				H / I	A	96305246	rs10051637
				H	T	96323283	rs10058476
				S	NA	96309577	rs10061936
				H / I	G	96326898	rs10071975
				H / I	G	96280573	rs1019503

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				S	NA	96251278	rs10434708
				I	G	96298936	rs1046395
				I	T	96345363	rs10476696
				S	NA	96276415	rs10537702
				S	NA	96276948	rs10546363
				H / I	T	96271195	rs1056893
				S	NA	96284454	rs10592692
				S	NA	96255974	rs10707238
				I	G	96247321	rs11135483
				I	G	96247645	rs11135484
				S	NA	96312725	rs11135485
				S	NA	96357847	rs11311774
				S	NA	96370825	rs11414909
				I	A	96247097	rs11750025
				H	C	96291635	rs1216565
				S	NA	96289812	rs1216566
				S	NA	96289595	rs1216567
				S	NA	96289402	rs1216568
				S	NA	96288290	rs1216569
				S	NA	96287473	rs1216570
				I	T	96246767	rs12189125
				H	G	96237497	rs1230358
				I	A	96279965	rs1230381
				H	T	96254538	rs12516666
				H	A	96333392	rs12716486
				I	C	96247776	rs13167902
				S	NA	96304809	rs13170029
				I	A	96248383	rs13189819
				S	NA	96321566	rs13358339
				H / I	G	96278559	rs1363907
				S	NA	96278860	rs1363908
				H / I	A	96319572	rs1363974
				S	NA	96274642	rs1363975
				S	NA	96274551	rs1363976
				I	A	96274463	rs1363977
				H / I	T	96324514	rs1423357

Gene	Tag SNP (IRP)	Tag Polymorp h-isms	Polymorph- ism RSID	Cohort	LD Allele	Polymorph- ism in LD	RSIDs of Polymorph- ism in LD
				I	A	96299523	rs1423566
				H	G	96310648	rs1477364
				H	A	96339986	rs1544777
				I	T	96329454	rs1559267
				I	G	96249877	rs1559354
				H / I	T	96252451	rs1559355
				S	NA	96252485	rs1559356
				S	NA	96252486	rs1559357
				S	NA	96268737	rs17087165
				H	T	96377824	rs18059
				S	NA	96278754	rs1820148
				S	NA	96332914	rs1820149
				H / I	G	96262870	rs187265
				H	C	96252291	rs1974871
				H / I	G	96294618	rs1981846
				S	NA	96260377	rs2042383
				H	G	96273749	rs2042385
				S	NA	40328876	rs210687
				H / I	A	96340258	rs2113050
				H	A	96259206	rs2113189
				I	A	96262074	rs2113190
				H / I	G	96343901	rs2161548
				H / I	T	96258562	rs2161657
				H / I	C	96265401	rs2161658
				H / I	A	96255506	rs2247650
				H	A	96274871	rs2255546
				H	T	96275079	rs2255633
				H	T	96275107	rs2255634
				H	G	96275134	rs2255637
				H / I	T	96250335	rs2278018
				I	A	96251008	rs2278019
				H / I	A	96263082	rs2287988
				S	NA	96247939	rs2303208
				I	T	96247941	rs2303209
				H / I	C	96319685	rs2351010
				S	NA	96277431	rs2351011

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				H	A	96396635	rs248215
				H / I	C	96260794	rs251339
				S	NA	96262168	rs251340
				S	NA	96283585	rs251343
				H	G	96284683	rs251344
				I	A	96298789	rs2548225
				I	G	96301169	rs2548516
				S	NA	96276759	rs2548520
				S	NA	96276684	rs2548521
				I	T	96276213	rs2548522
				H	A	96272696	rs2548523
				H / I	A	96272357	rs2548524
				H	G	96270341	rs2548527
				H / I	G	96265976	rs2548529
				H / I	G	96265683	rs2548530
				H	A	96264334	rs2548532
				H	C	96264157	rs2548533
				H	T	96258158	rs2548536
				H / I	T	96257898	rs2548538
				H	A	96257260	rs2548539
				H	T	96255934	rs2548540
				H	T	96255878	rs2549781
				H	T	96256756	rs2549782
				H / I	C	96257128	rs2549783
				H	T	96257276	rs2549784
				S	NA	96265593	rs2549787
				S	NA	96268026	rs2549789
				H	C	96268168	rs2549790
				H / I	A	96268198	rs2549791
				H / I	T	96270305	rs2549794
				H	G	96270394	rs2549795
				H / I	T	96271099	rs2549796
				H / I	G	96271274	rs2549797
				S	NA	96271659	rs2549798
				S	NA	96271666	rs2549799
				S	NA	96275390	rs2549800

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				I	A	96276020	rs2549801
				S	NA	96297394	rs2617434
				H / I	T	96293411	rs2617447
				I	T	96372034	rs27289
				H / I	A	96375844	rs27290
				S	NA	96376026	rs27291
				S	NA	96382934	rs27293
				H	G	96383016	rs27294
				H / I	T	96387382	rs27296
				S	NA	96388556	rs27298
				S	NA	96388807	rs27299
				H	T	96389163	rs27300
				I	A	96399506	rs27302
				S	NA	96359090	rs27305
				H / I	T	96360314	rs27306
				H / I	G	96364261	rs27307
				H	G	96366372	rs27397
				H / I	C	96356722	rs27436
				H	G	96365029	rs27613
				H / I	G	96299054	rs2762
				I	C	96387089	rs27621
				H / I	G	96369308	rs27659
				I	T	96389819	rs27712
				H	G	96385668	rs27747
				I	G	96381359	rs27993
				I	T	96365244	rs27997
				H / I	T	96278345	rs2910686
				S	NA	96277457	rs2910688
				I	C	96299979	rs2910787
				S	NA	96302151	rs2910789
				I	T	96302142	rs2910792
				H	C	96277835	rs2927609
				S	NA	96259970	rs3096167
				S	NA	96259968	rs3096168
				I	A	96382420	rs31398
				S	NA	96364859	rs3214461

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				S	NA	96322341	rs33918743
				S	NA	96268622	rs33934033
				S	NA	96243448	rs34037881
				S	NA	96353305	rs34323164
				S	NA	96354765	rs34340727
				S	NA	96258006	rs34701361
				S	NA	96306710	rs34815125
				S	NA	96314264	rs34962665
				S	NA	96344773	rs35304156
				S	NA	96357125	rs35475916
				S	NA	96371146	rs35562078
				S	NA	96301058	rs35929998
				S	NA	96314613	rs36019589
				H / I	T	96254184	rs3734015
				H / I	G	96342514	rs3797796
				I	G	96378979	rs38029
				H / I	T	96379440	rs38030
				S	NA	96381204	rs38031
				H / I	T	96347643	rs38032
				H / I	A	96347892	rs38033
				H / I	C	96348175	rs38034
				H / I	C	96349036	rs38035
				H	A	96349259	rs38036
				I	G	96353419	rs38040
				H	G	96356058	rs38041
				H / I	A	96361106	rs38042
				H / I	G	96362547	rs38043
				S	NA	96363546	rs38044
				H	T	96260289	rs3849749
				H / I	A	96260334	rs3849750
				S	NA	96320877	rs3909451
				H / I	G	96390210	rs39602
				S	NA	96260693	rs3985004/rs3912722*
				S	NA	96260692 or 96260693	rs3985004 or rs33912722*
				S	NA	96363405	rs42983

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				S	NA	96357127	rs430827
				H	A	96318909	rs4360063
				H / I	T	96254981	rs4869314
				H	A	96255028	rs4869315
				S	NA	96259011	rs5869737
				S	NA	96278700	rs5869740
				H / I	G	96251952	rs6556942
				S	NA	96260062	rs6859160
				S	NA	96260071	rs6859168
				S	NA	96249932	rs6868302
				I	C	96307418	rs6871162
				S	NA	96260108	rs6873441
				S	NA	96260131	rs6874656
				S	NA	96345686	rs6879678
				I	G	96303477	rs6887500
				H	G	96290756	rs716848
				H	G	96333368	rs7700332
				I	G	96315986	rs7703341
				H / I	A	96313894	rs7713127
				H	C	96318762	rs7716222
				H	G	96312042	rs7719705
				I	T	96345247	rs7722694
				S	NA	96306799	rs7726445
				H / I	G	96314716	rs7731592
				I	C	96311577	rs7733312
				H	G	96315467	rs7736466
				I	A	96397921	rs9127
				I	T	96346342	rs9314181
LNPEP	AG (G)	96356058	rs38041	S	NA	96346167	rs10038651
				H / I	C	96346251	rs10044354
				H / I	A	96305246	rs10051637
				H	T	96323283	rs10058476
				S	NA	96309577	rs10061936
				I	G	96310559	rs10069361
				H / I	G	96326898	rs10071975
				H / I	G	96280573	rs1019503

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				S	NA	96251278	rs10434708
				I	C	96251530	rs10434709
				I	T	96345363	rs10476696
				S	NA	96276415	rs10537702
				S	NA	96276948	rs10546363
				H / I	T	96271195	rs1056893
				S	NA	96284454	rs10592692
				S	NA	96255974	rs10707238
				I	A	96247182	rs11135482
				I	G	96247321	rs11135483
				I	G	96247645	rs11135484
				S	NA	96312725	rs11135485
				S	NA	96357847	rs11311774
				S	NA	96370825	rs11414909
				I	A	96247097	rs11750025
				H	C	96291635	rs1216565
				S	NA	96289812	rs1216566
				S	NA	96289595	rs1216567
				S	NA	96289402	rs1216568
				S	NA	96288290	rs1216569
				S	NA	96287473	rs1216570
				I	T	96246767	rs12189125
				I	A	96279965	rs1230381
				I	T	96280110	rs1230382
				H	T	96254538	rs12516666
				H	A	96333392	rs12716486
				I	C	96247776	rs13167902
				S	NA	96304809	rs13170029
				I	A	96248383	rs13189819
				S	NA	96321566	rs13358339
				H	G	96278559	rs1363907
				S	NA	96278860	rs1363908
				H / I	A	96319572	rs1363974
				S	NA	96274642	rs1363975
				S	NA	96274551	rs1363976
				I	A	96274463	rs1363977

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				H / I	T	96324514	rs1423357
				I	A	96299523	rs1423566
				H	G	96310648	rs1477364
				H	A	96339986	rs1544777
				I	T	96329454	rs1559267
				I	G	96249877	rs1559354
				H / I	T	96252451	rs1559355
				S	NA	96252485	rs1559356
				S	NA	96252486	rs1559357
				S	NA	96268737	rs17087165
				I	T	96263169	rs171647
				H	T	96377824	rs18059
				S	NA	96278754	rs1820148
				S	NA	96332914	rs1820149
				H / I	G	96262870	rs187265
				I	C	96260628	rs193993
				H	C	96252291	rs1974871
				H / I	G	96294618	rs1981846
				S	NA	96260377	rs2042383
				H	G	96273749	rs2042385
				S	NA	40328876	rs210687
				H / I	A	96340258	rs2113050
				H	A	96259206	rs2113189
				I	A	96262074	rs2113190
				I	C	96272094	rs2113191
				H / I	G	96343901	rs2161548
				H / I	T	96258562	rs2161657
				H / I	C	96265401	rs2161658
				H / I	A	96255506	rs2247650
				I	G	96261652	rs2248374
				H / I	A	96274871	rs2255546
				H / I	T	96275079	rs2255633
				H	T	96275107	rs2255634
				H	G	96275134	rs2255637
				H / I	T	96250335	rs2278018
				I	A	96251008	rs2278019

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				H / I	A	96263082	rs2287988
				S	NA	96247939	rs2303208
				I	T	96247941	rs2303209
				H / I	C	96319685	rs2351010
				S	NA	96277431	rs2351011
				H / I	A	96396635	rs248215
				H / I	C	96260794	rs251339
				S	NA	96262168	rs251340
				I	T	96262599	rs251342
				S	NA	96283585	rs251343
				H	G	96284683	rs251344
				I	A	96298789	rs2548225
				I	G	96301169	rs2548516
				S	NA	96276759	rs2548520
				S	NA	96276684	rs2548521
				I	T	96276213	rs2548522
				H / I	A	96272696	rs2548523
				H / I	A	96272357	rs2548524
				I	G	96271373	rs2548526
				H	G	96270341	rs2548527
				H / I	G	96265976	rs2548529
				H	G	96265683	rs2548530
				H	A	96264334	rs2548532
				H / I	C	96264157	rs2548533
				I	T	96259364	rs2548534
				I	C	96258455	rs2548535
				H	T	96258158	rs2548536
				I	G	96257978	rs2548537
				H / I	T	96257898	rs2548538
				H	A	96257260	rs2548539
				H	T	96255934	rs2548540
				H	T	96255878	rs2549781
				H / I	T	96256756	rs2549782
				H	C	96257128	rs2549783
				H	T	96257276	rs2549784
				I	T	96258042	rs2549785

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				S	NA	96265593	rs2549787
				I	G	96266142	rs2549788
				S	NA	96268026	rs2549789
				H	C	96268168	rs2549790
				H / I	A	96268198	rs2549791
				H	T	96270305	rs2549794
				H / I	G	96270394	rs2549795
				H / I	T	96271099	rs2549796
				H / I	G	96271274	rs2549797
				S	NA	96271659	rs2549798
				S	NA	96271666	rs2549799
				S	NA	96275390	rs2549800
				I	A	96276020	rs2549801
				S	NA	96297394	rs2617434
				H	T	96293411	rs2617447
				I	T	96372034	rs27289
				H / I	A	96375844	rs27290
				S	NA	96376026	rs27291
				I	G	96382736	rs27292
				S	NA	96382934	rs27293
				H	G	96383016	rs27294
				H / I	T	96387382	rs27296
				S	NA	96388556	rs27298
				S	NA	96388807	rs27299
				H	T	96389163	rs27300
				I	A	96399506	rs27302
				S	NA	96359090	rs27305
				H	T	96360314	rs27306
				H	G	96364261	rs27307
				H / I	G	96366372	rs27397
				H / I	C	96356722	rs27436
				H	G	96365029	rs27613
				H / I	G	96299054	rs2762
				I	C	96387089	rs27621
				H / I	G	96369308	rs27659
				H	G	96371495	rs27711

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				H	G	96385668	rs27747
				I	G	96381359	rs27993
				H / I	T	96278345	rs2910686
				S	NA	96277457	rs2910688
				I	C	96299979	rs2910787
				S	NA	96302151	rs2910789
				I	T	96302142	rs2910792
				H	C	96277835	rs2927609
				S	NA	96259970	rs3096167
				S	NA	96259968	rs3096168
				I	A	96382420	rs31398
				S	NA	96364859	rs3214461
				S	NA	96322341	rs33918743
				S	NA	96268622	rs33934033
				S	NA	96243448	rs34037881
				S	NA	96353305	rs34323164
				S	NA	96354765	rs34340727
				S	NA	96258006	rs34701361
				S	NA	96306710	rs34815125
				S	NA	96314264	rs34962665
				S	NA	96344773	rs35304156
				S	NA	96357125	rs35475916
				S	NA	96371146	rs35562078
				S	NA	96301058	rs35929998
				S	NA	96314613	rs36019589
				H / I	T	96254184	rs3734015
				H / I	G	96342514	rs3797796
				I	G	96378979	rs38029
				H / I	T	96379440	rs38030
				S	NA	96381204	rs38031
				H	T	96347643	rs38032
				H / I	A	96347892	rs38033
				H / I	C	96348175	rs38034
				H / I	C	96349036	rs38035
				H	A	96349259	rs38036
				I	G	96353419	rs38040

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				H / I	A	96361106	rs38042
				H / I	G	96362547	rs38043
				S	NA	96363546	rs38044
				H	T	96260289	rs3849749
				H / I	A	96260334	rs3849750
				S	NA	96320877	rs3909451
				H / I	G	96390210	rs39602
				S	NA	96260692 or 96260693	rs3985004 or rs33912722*
				S	NA	96363405	rs42983
				S	NA	96357127	rs430827
				H	A	96318909	rs4360063
				H / I	T	96254981	rs4869314
				H	A	96255028	rs4869315
				H	G	96259219	rs4869316
				S	NA	96259011	rs5869737
				S	NA	96278700	rs5869740
				H	G	96251952	rs6556942
				S	NA	96260062	rs6859160
				S	NA	96260071	rs6859168
				S	NA	96249932	rs6868302
				I	C	96307418	rs6871162
				S	NA	96260108	rs6873441
				S	NA	96260131	rs6874656
				S	NA	96345686	rs6879678
				I	G	96303477	rs6887500
				H	G	96290756	rs716848
				H	G	96333368	rs7700332
				I	G	96315986	rs7703341
				H / I	A	96313894	rs7713127
				H	C	96318762	rs7716222
				H	G	96312042	rs7719705
				I	T	96345247	rs7722694
				S	NA	96306799	rs7726445
				H / I	G	96314716	rs7731592
				H	G	96315467	rs7736466
				I	A	96397921	rs9127

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				I	T	96346342	rs9314181
LNPEP	GA (A)	96305246	rs10051637	S	NA	96346167	rs10038651
				H / I	C	96346251	rs10044354
				H	T	96323283	rs10058476
				S	NA	96309577	rs10061936
				I	G	96310559	rs10069361
				H / I	G	96326898	rs10071975
				H / I	G	96280573	rs1019503
				S	NA	96251278	rs10434708
				I	C	96251530	rs10434709
				I	G	96298936	rs1046395
				I	T	96345363	rs10476696
				S	NA	96276415	rs10537702
				S	NA	96276948	rs10546363
				H / I	T	96271195	rs1056893
				S	NA	96284454	rs10592692
				S	NA	96255974	rs10707238
				I	G	96247321	rs11135483
				I	G	96247645	rs11135484
				S	NA	96312725	rs11135485
				S	NA	96357847	rs11311774
				S	NA	96370825	rs11414909
				I	A	96247097	rs11750025
				H	C	96291635	rs1216565
				S	NA	96289812	rs1216566
				S	NA	96289595	rs1216567
				S	NA	96289402	rs1216568
				S	NA	96288290	rs1216569
				S	NA	96287473	rs1216570
				I	T	96246767	rs12189125
				H	G	96237497	rs1230358
				I	A	96279965	rs1230381
				I	T	96280110	rs1230382
				H	T	96254538	rs12516666
				H	A	96333392	rs12716486
				I	C	96247776	rs13167902

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				S	NA	96304809	rs13170029
				I	A	96248383	rs13189819
				S	NA	96321566	rs13358339
				H / I	G	96278559	rs1363907
				S	NA	96278860	rs1363908
				H / I	A	96319572	rs1363974
				S	NA	96274642	rs1363975
				S	NA	96274551	rs1363976
				I	A	96274463	rs1363977
				H / I	T	96324514	rs1423357
				I	A	96299523	rs1423566
				H	G	96310648	rs1477364
				H	A	96339986	rs1544777
				I	T	96329454	rs1559267
				I	G	96249877	rs1559354
				H / I	T	96252451	rs1559355
				S	NA	96252485	rs1559356
				S	NA	96252486	rs1559357
				S	NA	96268737	rs17087165
				I	T	96263169	rs171647
				H / I	T	96377824	rs18059
				S	NA	96278754	rs1820148
				S	NA	96332914	rs1820149
				H / I	G	96262870	rs187265
				I	C	96260628	rs193993
				H	C	96252291	rs1974871
				H / I	G	96294618	rs1981846
				S	NA	96260377	rs2042383
				H	G	96273749	rs2042385
				S	NA	40328876	rs210687
				H / I	A	96340258	rs2113050
				H	A	96259206	rs2113189
				I	A	96262074	rs2113190
				I	C	96272094	rs2113191
				H / I	G	96343901	rs2161548
				H / I	T	96258562	rs2161657

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				H / I	C	96265401	rs2161658
				H / I	A	96255506	rs2247650
				I	G	96261652	rs2248374
				H	A	96274871	rs2255546
				H / I	T	96275079	rs2255633
				H	T	96275107	rs2255634
				H	G	96275134	rs2255637
				H / I	T	96250335	rs2278018
				I	A	96251008	rs2278019
				H / I	A	96263082	rs2287988
				S	NA	96247939	rs2303208
				I	T	96247941	rs2303209
				H / I	C	96319685	rs2351010
				S	NA	96277431	rs2351011
				H / I	A	96396635	rs248215
				H / I	C	96260794	rs251339
				S	NA	96262168	rs251340
				I	T	96262599	rs251342
				S	NA	96283585	rs251343
				H	G	96284683	rs251344
				I	A	96298789	rs2548225
				I	G	96301169	rs2548516
				I	G		rs2548517
				S	NA	96276759	rs2548520
				S	NA	96276684	rs2548521
				I	T	96276213	rs2548522
				H / I	A	96272696	rs2548523
				H / I	A	96272357	rs2548524
				I	G	96271373	rs2548526
				H	G	96270341	rs2548527
				H / I	G	96265976	rs2548529
				H / I	G	96265683	rs2548530
				H	A	96264334	rs2548532
				H / I	C	96264157	rs2548533
				I	T	96259364	rs2548534
				I	C	96258455	rs2548535

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				H	T	96258158	rs2548536
				I	G	96257978	rs2548537
				H / I	T	96257898	rs2548538
				H	A	96257260	rs2548539
				H	T	96255934	rs2548540
				H	T	96255878	rs2549781
				H / I	T	96256756	rs2549782
				H / I	C	96257128	rs2549783
				H	T	96257276	rs2549784
				I	T	96258042	rs2549785
				S	NA	96265593	rs2549787
				I	G	96266142	rs2549788
				S	NA	96268026	rs2549789
				H	C	96268168	rs2549790
				H / I	A	96268198	rs2549791
				H / I	T	96270305	rs2549794
				H / I	G	96270394	rs2549795
				H / I	T	96271099	rs2549796
				H / I	G	96271274	rs2549797
				S	NA	96271659	rs2549798
				S	NA	96271666	rs2549799
				S	NA	96275390	rs2549800
				I	A	96276020	rs2549801
				S	NA	96297394	rs2617434
				H / I	T	96293411	rs2617447
				I	T	96372034	rs27289
				H / I	A	96375844	rs27290
				S	NA	96376026	rs27291
				I	G	96382736	rs27292
				S	NA	96382934	rs27293
				H	G	96383016	rs27294
				H / I	T	96387382	rs27296
				S	NA	96388556	rs27298
				S	NA	96388807	rs27299
				H	T	96389163	rs27300
				I	A	96399506	rs27302

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				S	NA	96359090	rs27305
				H / I	T	96360314	rs27306
				H / I	G	96364261	rs27307
				H / I	G	96366372	rs27397
				H / I	C	96356722	rs27436
				H	G	96365029	rs27613
				H / I	G	96299054	rs2762
				I	C	96387089	rs27621
				H / I	G	96369308	rs27659
				H / I	G	96371495	rs27711
				I	T	96389819	rs27712
				H	G	96385668	rs27747
				I	G	96381359	rs27993
				I	T	96365244	rs27997
				H / I	T	96278345	rs2910686
				S	NA	96277457	rs2910688
				I	C	96299979	rs2910787
				S	NA	96302151	rs2910789
				I	T	96302142	rs2910792
				H	C	96277835	rs2927609
				S	NA	96259970	rs3096167
				S	NA	96259968	rs3096168
				I	A	96382420	rs31398
				S	NA	96364859	rs3214461
				S	NA	96322341	rs33918743
				S	NA	96268622	rs33934033
				S	NA	96243448	rs34037881
				S	NA	96353305	rs34323164
				S	NA	96354765	rs34340727
				S	NA	96258006	rs34701361
				S	NA	96306710	rs34815125
				S	NA	96314264	rs34962665
				S	NA	96344773	rs35304156
				S	NA	96357125	rs35475916
				S	NA	96371146	rs35562078
				S	NA	96301058	rs35929998

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				S	NA	96314613	rs36019589
				H / I	T	96254184	rs3734015
				H / I	G	96342514	rs3797796
				I	G	96378979	rs38029
				H / I	T	96379440	rs38030
				S	NA	96381204	rs38031
				H / I	T	96347643	rs38032
				H / I	A	96347892	rs38033
				H / I	C	96348175	rs38034
				H / I	C	96349036	rs38035
				H	A	96349259	rs38036
				I	G	96353419	rs38040
				H / I	G	96356058	rs38041
				H / I	A	96361106	rs38042
				H / I	G	96362547	rs38043
				S	NA	96363546	rs38044
				H	T	96260289	rs3849749
				H / I	A	96260334	rs3849750
				S	NA	96320877	rs3909451
				H / I	G	96390210	rs39602
				S	NA	96260692 or 96260693	rs3985004 or rs33912722*
					NA	96260693	
				S	NA	96363405	rs42983
				S	NA	96357127	rs430827
				H	A	96318909	rs4360063
				H / I	T	96254981	rs4869314
				H	A	96255028	rs4869315
				S	NA	96259011	rs5869737
				S	NA	96278700	rs5869740
				H / I	G	96251952	rs6556942
				S	NA	96260062	rs6859160
				S	NA	96260071	rs6859168
				S	NA	96249932	rs6868302
				I	C	96307418	rs6871162
				S	NA	96260108	rs6873441
				S	NA	96260131	rs6874656

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				S	NA	96345686	rs6879678
				I	G	96303477	rs6887500
				H	G	96290756	rs716848
				H	G	96333368	rs7700332
				I	G	96315986	rs7703341
				H / I	A	96313894	rs7713127
				H	C	96318762	rs7716222
				H	G	96312042	rs7719705
				I	T	96345247	rs7722694
				S	NA	96306799	rs7726445
				H / I	G	96314716	rs7731592
				I	C	96311577	rs7733312
				H	G	96315467	rs7736466
				I	A	96397921	rs9127
				I	T	96346342	rs9314181
AVPR 1A	CT (C)	61837421	rs10877970	H	G	61816874	rs7972829
				H	C	61824913	rs10784339
				H	T	61827101	rs3803107
				H	G	61840232	rs11836346
				H	A	61844229	rs7308008
				H	G	61849214	rs11835545
				H	A	61851233	rs7959001
				H	T	61852342	rs11832877
				H	C	61853617	rs10877977
				H	G	61860197	rs2201895
				H	T	61862861	rs7302323
				H	T	61868529	rs10877986
				H	A	61884651	rs2030106
				S	NA	61824725	rs10747983
				S	NA	61833506	rs10877969
				S	NA	61834359	rs7294536
AVPR 1A	AT (T)	61827101	rs3803107	H	G	61816874	rs7972829
				H	C	61824913	rs10784339
				H	C	61837421	rs10877970
				H	G	61840232	rs11836346

Gene	Tag SNP (IRP)	Tag Polymorphisms	Polymorphism RSID	Cohort	LD Allele	Polymorphism in LD	RSIDs of Polymorphism in LD
				H	A	61844229	rs7308008
				H	G	61849214	rs11835545
				H	A	61851233	rs7959001
				H	T	61852342	rs11832877
				H	C	61853617	rs10877977
				H	T	61862861	rs7302323
				H	T	61868529	rs10877986
				H	A	61884651	rs2030106
AVPR 1A	CT (T)	61890334	rs1495027	H	T	61807179	rs10877962
				H	T	61830476	rs1042615
				H	G	61900977	rs16856
				S	NA	61825030	rs36014760
				S	NA	61826743	rs11174811
				S	NA	61828619	rs34462214
				S	NA	61831947	rs3021529
				S	NA	61833506	rs10877969
				S	NA	61834359	rs7294536
				S	NA	61824725	rs10747983

NA as used above indicates that the LD allele with the information currently available to the inventors could not with any confidence be assigned without further routine analysis, due to the lack of suitable information currently available regarding the corresponding allele designations. However, it would be well within the abilities of a person of skill in the art to make LD allele designations for the NA polymorphisms using routine analysis.

It will be appreciated by a person of skill in the art that further linked polymorphic sites and combined polymorphic sites may be determined. A haplotype of vasopressin pathway associated genes can be created by assessing polymorphisms in vasopressin pathway-associated genes in normal subjects using a program that has an expectation maximization algorithm (i.e. PHASE). A constructed haplotype of vasopressin pathway associated genes may be used to find combinations of SNPs that are in LD with the tag SNPs (tSNPs) identified herein. Accordingly, the haplotype of an individual could be determined by genotyping other SNPs or other polymorphisms that are in LD with the tSNPs identified herein. Single polymorphic sites or combined polymorphic sites in LD may also be genotyped for assessing subject response to vasopressin receptor agonist treatment.

It will be appreciated by a person of skill in the art that the numerical designations of the positions of polymorphisms within a sequence are relative to the specific sequence. Also the same positions may be assigned different numerical designations depending on the way in which the sequence is numbered and the sequence chosen, as illustrated by the alternative numbering of the equivalent polymorphism (rs3803107), whereby the same polymorphism identified C/T at position 3536 of the NM_000706.3 (GI:33149325), which corresponds to position 201 of SEQ ID NO:9.

Furthermore, sequence variations within the population, such as insertions or deletions, may change the relative position and subsequently the numerical designations of particular nucleotides at and around a polymorphic site.

Polymorphic sites in SEQ ID NO:1-10 are identified by their variant designation (i.e. M, W, Y, S, R, K, V, B, D, H or by “-” for a deletion, a “+” or for example “G” etc. for an insertion).

Polymorphic sites in SEQ ID NO:11-264 are identified by their allelic change (i.e. A, C, G, T or by “-” for a deletion, a “+” or for an insertion).

An “rs” prefix designates a SNP in the database is found at the NCBI SNP database (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Snp>). The “rs” numbers are the NCBI | rsSNP ID form.

TABLE 1C below shows the flanking sequences for a selection of vasopressin pathway associated gene SNPs providing their rs designations and corresponding SEQ ID NO designations. Each polymorphism is at position 201 within the flanking sequence, and identified in bold and underlined.

GENE	SNP	SEQ ID NO:	FLANKING SEQUENCE
LNPEP	rs18059	1	TTAAGTTAGATGATTTTCTGAGGTCTCTTCTAATGGTTAAGATTTTATC ATTTTCTATTTTCATAAGGCTTTCAGCTAGCAGCCTTAATAAAAACCAAGTG CCTGGAACATGACCTGGCCTGTAGTGACACTCAGTAAACGTTGAGTGAAT AAATGATTGAAACACACCAGAAACAAGTGCATTTGAGTGCTTTTACACAC <u>Y</u> GTGCTTAGTGCTTAATGTAGATTACCTCATTTAATTATCACACAGTGCC AAGGTAGATATTTCTACCCCCATTAAATAAACGAGGAGACGGAATAGCTT CTTTAAAGTCACTTACCTAGTAAGTGATAAAGCTGAAATTCAAACCCAGA TAAATTTCACTCCAAAGACTTCTGTTTCTGTTATATTGCTATTTGTAAAA TCAATTTGTGTCTTAGCAACGTCGTCTTTCCAGGATACCTTTAGAAAAAT TAAAGCTTTCTTCTTGTGCATATTCTTTTGAAAAGCTTGCAGACCATATAT TTAAGGTTTCAAGTGACTGGCCACATCTAGTTGTTCTCCTAAAAATGAA ATTGTCAACTTAAGAGA
LNPEP	rs27711	2	TTTTTTCTATTCTCAAAAGAAAGGTAGCAGAGAGGGTGACTTCAGGCTTC TTTTATGCTGTAATACTTTAGTATAGTGTATTATTTTGATGCTTGATGGT TGGTAAATCTTTAATATATTTTCTTTCTTTTAAATATATTTTCATG TGTTCTAATTCAAGGGTTGTTGGGTAGTTTCATTAGTTTCAGTTGTATATA <u>R</u> GAGTTATGTTTGGTCAATGTATTTGTCTCCTTTCTCACATACATGAGT

			TTTGAACAATTAGTATTTTATTGTGCACAAGAAATGCTGATGGGGCCATTT TTCCAGTTTACATATTGAGGAATTATATTTTTTAAAGTTTCCCTCTTCCC TTTCTTCCCTCCCTCTCTCTCTCTCTTTCTTATCCACATTTTACTCAGACC TAAGATCTTTAACTATAGGAGATTTTCGTATTAAATCTAATGCAAAACAT TCATGTTT
LNPEP	rs38041	3	TGTGGGGAAGAATCTCTTTCCCTAAGTTGCACCCTTCTGACAACCTCAAAC TGTAGCTGTCTAGGGCTGGATTTTTTTTTTTTTTTCATCTCCTGCCGGAATG GGGTTCCTCTGTTAATTTTGGAGAGGGGGTTTCTGAGAAAATGGCAAAGGG TACTGTTTGTATGACATGGAGAGAAAAGAAAATATATGGGTACATA R CACCCCCATTCTTCCCTAACACCTTGTCTCTATTTTGCCCTAGATGAGG TGCTTAAC TAGCATTTGGGTATGGTTTGGGTGATGTCTACAGATGGCAGG ATATGAATAGGATGTATTCTGGTCAGTTTATTTTCTACATCAAACACCTT ATATGAATCTAGCCTTTGTGAAGACTTCATGACAAGCTGGCATATGAGCA
LNPEP	rs10051637	4	TGGCCAGCCTACTATTCTTTATAGCCTGGCTTTGCTTCACTTTTCTACTG GTGCTTGTGATAGAACAATGAACCAATTAATTTTTTAAATTTCCATCCT TAACATGTAAATGAGGAGGAAACCAGGTCATTTGCCAAATAAGGAAAATT CAAGCTTCCAAGGGAGTTTCAAAAAACAATGGAGGATCAAGTTCAATTGT R GGAGACTTTTTGAAATTTCTTTTCTTCTAATACATATTGCTTAATGAAG GTACTCCTGGGCATTCCACATATTTCAAAAATGTAGTCACTGAACCAGAA CTTGAATCAGTTGTCTGAATTTCTCTGGATTGTGGGGCTCAGAGTCTTCT CCAGCCAATGATCTGGGGTGAAGGAAGTTAAAGAAGGCTTCTTCAACTGA
AVP	rs1410713	5	GCTATTAGATCTAATAAGTACATTTAGCAAGATCACAGGGTACAAAGTCA ACAATAATTCATAATTCTATATACTAACAATAACTACTTGGAAATTAAT TTTAAACACAGTACTATTTAAATAGTGTGAAAAATATGAAATCTTTTG GGTAGAAATCTTACATAATATATACAAATCTATATGCTGAACATAATAA M TGCTGATGGAAGAAATAGAAGACCTGAATAACTGGAGAGATATATTTGT TTATTGATTTGGAAGACTCATCAGAGTAAAGATGTCTCTCCCCAAAT TGATTGAAAGATCCAACACAATTTCTAATTAACCTCCCAATAGGATTTTTT TGTAGAAATCATTAAAGTTGATTCTAAAATTTATACAGAATGACAAAGGAA CTAGAATAGCCAAAACAATTTGAAAAAGAACAAGTTGGAAAAGCCACA CAACCTGATAAAGTTATCATATTTCAAAATAGTATAATATTATAGAAAGGA TAGATCTAGGCCAGGTGCGGTGGCTCACGCCTGTAATCCCAGCACTTTGG
AVP	rs857240	6	CAGGCCTGGCTGAAATTCAGGGATGGCATCTAGGGCTTCCCCACTCCTGT CTGGTACCCTCCACATGTCTGAGTGTCCCTCTCTGTGGCAAGGGGACAGC CACAAAATGGGTTCCTCTTCTGAGCCTCTCCGCTCTCAGGAGGAGAGAA CCTGCCCAGAGTCCCCACCCCTAAATCCCTCCAGACTGGACAAGCACCAC Y AGCCGGCTGCCTTCTTTGGGTTAGGCCAGCCAAAGCTCACCCCTAAGAT TAGGTGTGCTCACAGGCCCTGACAAAATGGGGTCTGTTGGTGAGGAAG AGGAGGGACGGGACTGGCTGCTGGGTGAGTAAGTGGGGTATTTGTCCCCG GCCCCAGGCTGGAAGGCATTGGTAGACTTGTACAGACTCACTTCACTTGTG GGGACCTGTGGCACAGAGAGACCCCGTGGCTTGTCCGGGACACACAGC TAAGCCGGGCAGAACTACTGAGCGAGGAGCCTATCAGTCCTGGTTCCCAA
AVP	rs857242	7	CCAGAGGAAGGCCAGCTGCAAAACCACTGACCCCAATGTGCGGCATCTGAG GGACGGACACGCCCAGGGGTCAAGAGAACGGAGCCTGGGAGTGGCATCCA CAGGGTCTGCTGTAGGCGACTCCAGTGCCTTCTCTTGATCCCTCTGCTC AGGTGCCCTACTCCAGGGAGGGGTGGCTTTTTGGATTAGGTTGGATGATG M CCATCCTCAAGTGTCTGAATAAAGCTCCTTCAGAGTGAATGCAATGGAG AAAGGGTAGTGCCTTGAGAGGATCTCAGGATGATAGTAGGAAGGGAAATA AATGCTGTAAAGCTAAGCAGCCCTCACCCCCACAAATCCACTGAGATCTT TTCTTTTCTTTTAGAGAGGGTCTCACTCTATTGCCAGGCTGGGGGGCAG TGGCACAACACAGCTCGCTGCAGCCTTACCTCCTGGGCTCAAGCGATC TCCCCATCTCAGCCTCCTGAGTAGCTGGGACTACAGACGTGTGCCACCAT GCCCAGCTAATTACGTTACCCAGGCTGGTCTTGAACCTCCTGGGCTCGAAC
AVPR1 A	rs10877970	8	ATGGCTTTTTTAAATTTAAATCATTAAATGGTTGAGTTTAAGACTTTT GCTCCTAATGAATTCATATTCATTTGGGTGTTCTGCATCTTCATGGTCAG CAGTTTTGTCTATCCTGTCTAAATTTGATCATCAAGACTCATTCTTCCAGC ATGCTGGCAACATTGAGACTACCTCTGTGTATTCTAATTTGTTTTTCA Y GAGTGAAAAGGTTTGCATTGTTTGAAGGGTGTGAACAAAGTTGTGATA CTATAATTTTTTGTATTATCTGCTGTGAATACTATTTATTAGAATTTTAA ATACTTATTTGCCTCTATTTTTCTTTAGGTTTGACAGGGGTTAGTTTTTA AAAAATATATTCTTTTTTAGGCATATTTAATTTAATTTCAAGTAATCAATT
AVPR1	rs3803107	9	AATCAATTCATTGTGTATGAGACTGTGTTTCTAGTTGCATTTTCATATTG CTACCAAAAAC TAGACATTATTTGTATGGAATATTAATGGAAACATGCT GTACTAAAATATGCAGGTCTGATTCCCAGAAATACAACAGAAGTTATATT

A			TTTAAAGGAAAAATCATAACCACCCTAGCTTTATATTTTGTGTAGTTT <u>Y</u> TTTTATTTTCATTTCTAACATAAGTAAGACTTGATTGGTTTAAAAGTCA CATAAAATGCGGCACTATTTCTGAACAAAGAGAGCTCATCATCAGTCTTA ATATTCAGAGAAAACCTTCAGAGAAATTATGTTTTTCATCCATTAATAATTA TTTGTGCATCAGAAAATGCAGCCTTAAACAGTGTCCAGGAGATGGGATGG
AVPR1 A	rs1495027	10	CATATCAAGAAGAATGTGAGTATTTTGGAGGTCCATCCTAGTTATAAGGA AACTTCAAACCGTATCATGAGAGAAATGTTGAAAATAACTGTTTCTACTG AAGAAACAGTAAAGGCTCTAGATTTCAAATATTTTGAGAGTCATTATGTG TAACAGGAATTAGACTTGTCTGAATGTTCCATAAGAATGGAATGAGTGT <u>Y</u> AAAGTTTGTAATTTACATTTATTTGCACGATTACTTGTTTTATATGTT TCCCCCTCCGCTGGTGTCTAAGCTTCCTGATGGCAAAAGTTAGATTTGGTC ACCAATTTATCCCCAGTGCCTAACATGCATAAGAGCCACTTATATAATGG TTAACAGACTGAGAGAAATTTTTTTTATTCTCTAGTGTAGGAGTTAGGGT ACAAAATAAGTTGTTATAACAAA

The Sequences given in TABLE 1C (SEQ ID NO:1-10) above and in TABLE 1D (SEQ ID NO:11-264) would be useful to a person of skill in the art in the design of primers and probes or other oligonucleotides for the identification of vasopressin pathway associated gene SNP alleles and or genotypes as described herein.

TABLE 1D below shows the flanking sequences for a selection of vasopressin pathway associated gene SNPs in LD with the tagged SNPs in TABLE 1C, providing their rs designations and corresponding SEQ ID NO designations. However, where a SNP in LD is also an htSNP it only occurs in TABLE 1C above. Each SNP is at position 200 of the flanking sequence (unless otherwise indicated) and is underlined.

GENE	SNP	SEQ ID NO:	FLANKING SEQUENCE
LNPEP Region	rs10038651	11	TCTTCAGACCCTCCAATAAACTTATTTAATCCTAAATGGGTCTCTGT TAAAAATTCCCTTCATTATTTTGTTCATGCTTTAAGACCCAGGCAAAAC TCTTGGTGGGCTTTTGTAAATTCAGCCTTTGTATAAGGGCACTGG CTTTTAAATATTTAACTTAACCACTCAGCCAGTACTGAAACAGTTGTT ATGGAGGCCTGCTTATAGTGAGATCTGGCTTGCCACACTTGTGTTACC CACTCTTTCCAGAGTATACTTTCTTCCCTTCTTCACCTTTTCAAATA CTCATCTTTTTTAGGCCCTCTTCAGGTTTCTGCATGTTTCCTTATAA TATCTTCAACCTCTAGTCAGAATTTGTTTCCTTCCCTTTGTTCCCAT TGCTTTATTTTCATTGTTAGGACAT
LNPEP Region	rs10044354	12	CAGGCAAACTCTTGGTGGGCTTTTGTAAATTCAGCCTTTGTATA AGGGCACTGGCTTTTAAATATTTAACTTAACCACTCAGCCAGTACTGA AACAGTTGTTATGGAGGCCTGCGTTAGTGAGATCTGGCTTGCCACAC TTGTGTTACCCACTCTTTCAGAGTATACTTTCTTCCCTTCTTCACC TTTTCAAATACT <u>Y</u> ATCTTTTTTAGGCCCTCTTCAGGTTTTCTGCATGT TTCCCTTATAATATCTTCAACCTCTAGTCAGAATTTGTTTCCTTCCCT TTGTTCCCATTTGCTTTATTTTCATTGTTAGGACATGACTTACAGCCT GATGTAAGTTTCTGTTCAATTGTATAAACCTCTGCCTTTCCAGTTTA TTGCAGATCCTTTAGTAACCTAGGAT
LNPEP Region	rs10058476	13	TGAGGATTGGTTCCAGGATCCCCCTCCCCCTACCAAAATCCACCAAT ATTCAATCCCTGTATATTTGCATATAACCAGTTTACACGAATCATCC CATTTACTTTAAATTATCTTTAGATTACTTACAAAACATAATACAAT GTAAATACTATGTAAATTATACTGTATTATATTATTTTGTATTT TTTCAATTTTTT <u>W</u> AAATCTGCCATTCACTCTATAGATCTTGAACCTG TAGATAACAGACTAAGTATTTGGATAATTTTATAATTTTAAATGAGA GAAAGGGGAGAGGGGAAAGCCTGGTTTACTGCCCATGATGAAGTAGT AATACAGTAAATTTAGTTGAGACATCAGCCAACCTTTTTTGAATACC TACTAAGTACCTGGCTGAGAGAGTT

LNPEP Region	rs10061936	14	TCCATTTTTCTCTTTTTGAATTTTTTCCTTTTCACATTACTTTAGTA ATTTGTTCTTCATCTCTTATTTTTATCACCTAGACAGAAAATATAGC AAAGCATAAATCATTTTTTCAGGTCACCATGCTTCATTCTTCTTTTAT TGGGGAAGGGGCAGTGGTGATCCGGAAGAAGCATAGTGTAACATT TTAATACAAATTCTCTTTTTTTTTTTTTTTTGGAGATGGAGTCTTGCT CTGTCTCCCAGGCTGGAGTGCAGTGGCAGATCTCGGCTCACTGCAA CCTCTACCTCCCGGGTTCAGTGATTCTCCTGCCTCAGCCTCCCGAG TAGCTGGGATTACAGGCATGCACCACCATGCCCGGCTAATTTTTATA TTTTTAGTGGAGACAGGGTTACACC
LNPEP Region	rs10069361	15	ATATTCAAATCCTGGCTCTTTATTCACTAGCTCTCTGATTCTTAAGG ATATTACCAGAATATCTTAATATCTTTAGTTAAAAACCTAAAATGTA CATTCAAAACCTTAAACCTTTTTTGAATTAGCAGTGGTCTAAGATAA GTGGTGGTTTGGAGCATATTCAGCCTTAGTGAGGTTTTGAAAAGCTG GGAACATAATGGTCTTTCTTGGATCCTAATTCCTTACTAAGGGCTTGA GGCCATTATAGGAGGATCTTTCCATTTTCATATTTATTAACAATTTT GAATTTGCAACACTTTTCATGGAAGTGTTCCTAAAGCATGGGTCCCC AATTTGCATGTCAAGGACCATGCTAGGAAGTGGGCTTCACAGCAGGA GGTGAGCAGTGGGCAAGTGAGCGTT
LNPEP Region	rs10071975	16	ATTTGGGTCCACTAATTAGAGTTCTTCATCTTTCTTTTTACATGTGG ATATGTGTTGCCTTTTCATTCATCTGTAATTTCCAGGTCCTAAAAAA AAAAAGTAGATTGAGAATGCAGGCATTTTGAAGACTGGGTGCAAAAA TCCTAGAATTCTGCCTCCCAACCCCAACCCCAACCCCAAGGTATTA GGTTTTTCTTGCSCATACCTAATTTGGCAGCAGTGTTATTTTGAGGA CTCATTTTTGTAGGATCTTTCTGATACATAACTCAGTTTTCATAAAA ACAATTTTTATATTTTTTCATTTAATGACACAATATTTAATTATTATA AAACCATAATTACAAGTTTAACTAACATAAATCAGCTTGAGAACAAA CAACTAATTCTTAGAGTAGAGTGCC
LNPEP Region	rs1019503	17	TGCTCTCTGAAATGCCCTGCTAAATGCTTCTCTTAATTATTTGAATA AGGTAGTTTGAATAAAGAAAGAAAAGATCACTCTACATACAGATAG TAACTTAAATTTGTGATCCTATATATGAGACAGTATAAAAAATACAGA TAAGTTTTAGAAAGACTCAAAACAATATGTAAATGACTGATGTTTGC ATTATTAAGGAAACTTGGGATGTTGGGTCAAGAGGGGAAAGTGTTA GTCAATCCACTTTGGAGCAATATCATGAAGGTCAATTATAATTCCAT ATACCTTTCTTTGATGCCACAGTCAGAGATAGAATACAGTTTGGGTG GCCATGGATGTGCCCCAATACAGTACACATTTTTTGGTTAAATTTGT TTTCAGATCATTTTCATGGAATCTTT
LNPEP Region	rs10434708	18	GGAAAGAGATGGGGAGAAAAAGAAGGAACACAGTGACTGCTCTGTTT AAAATAGGGGTCCACATGTCCAAGATGCTGTGGCTCCCTGTGGCGGA CATCAACGCTCTCATCCATTATGCTCCTCTTCTGTGGGAGGGAAACA CACCTCCCATCGTGCTGCTCTTCTATGCCAGCAGCATTTGATTAGAG AATGGATTTTCCWTTAAAAAATACATACACACACACACACACACA CACACACACACGCATTGCATATTAGAATTAGAGGGATTCTTGAGGGA ATCACCATACCTTATTTGTACAAGGTCAGCAATCTTTTATAAAAGTT GTCAAAAGTTTATGTAGAGAGAGAACTGAAACTATGCTTCCATCCG TTATCTGTGTTGGGCACTGAGGTTG
LNPEP Region	rs10434709	19	CATATTAGAATTAGAGGGATTTCTGGAGGAATCACCATACCTTATTT GTACAAGGTCAGCAATCTTTTATAAAAGTTGTCAAAAGTTTATGTAG AGAGAGAACTGAAAACTATGCTTCCATCCGTTATCTGTGTTGGGCAC TGAGGTTGGATGGTAAGACTGTGGAACAGATTTTTTAAAAAATTGCAG GAAACAGATCATYTG GTTGTGGTAGTAGGCTTTACATGAGATGATA CTCATAGTCTATCTTGCTTTTAATTTTCTATCTTAAAAAATAAAAAA CGTTATTTTTAGAAAGTTGTAGAGAAGCGATCCCCAACCTTTTTTGAC ACTAGGGACCAGATTTGTGGAAACAATTTTTCCACGAAGATTGGGTG GATGGTTTTTGGATGAACTGTTCC

LNPEP Region	rs1046395	20	TTGTATGCTGTGCTTCATTCATGGGGCTGTGAACTACTGATTATATT CTCCCTATTCCTAATGTAGAATGCTTTATTCTACTGCCATCTTTCTG TCTGCACTGTTTAATTAGGCTTACTGATAACAACCTTTAATTCTGAAT TTTCTTTCTCATTACAGTTCTATTTGTAATTACTAAGACTTAAAGAA TAGTCTGGTGAAR TT TACTCGAAGAATTAAGGAAGGTTTGAGCTAAAA TGAAGTAGAGACCATCTAGTACTTTAGTGTAATAATATGTTTAATACA AGTCGTTAAGTCCTTGTAAGTGACTATTCCAATGTTTCATTCTTTGTT TTTGGAAGAATGCTTGGAGTTACCATGTTTTTAAATGTGAAATTTCA TCTAAATTAAAAAAAAAAATCTCTGT
LNPEP Region	rs10476696	21	TCCCAAAGTGCTGGGATTTTCAGGCGTGAGCCACCTGGCCTGGACTGT AATTGAGGATTTTTCTGTGTCATATTCTCAACTGTTGTTGGTGTGCT ACAGAAAGAGGAGGAAATTTTTTTAATCTCTGAGGCGAGTAAAGGA AACCAGAATACTACAGGACACCTAATTTTTTCAATCTTCATGAAAT GCAAGCTGTGAAR TT TGAGGTTTGGTATCGTGAAGCCAGAGTCTGTAC AGATAATTGCGAGCAATTAATGACCACCCTTCTTAATAATCTTCCAT CAGAAACCTTTTTAAGACCTCAGTGGCCAGTTGCAGCCTACCTTTGT GGCTTCATCTCCAGCCACACTGGACAGCCACCCCCAGTTTCTGCACA TGCCTGCTCTCTTGTGTTCCCGGA
LNPEP Region	rs10537702	22	TGAGAGTTCAACCAAGTAACATTGCCCCACTAAACACAATGTTTAAA CACAGTGGTATCCAAAATGGGATGAGGAAGTGCAAGAAGTGCAAT ACATTAGAGTGTCTATTATTTCTTATCTAATTTTAAATTTTATATTG TTATAAATTTATAAACATAAATGATATATAGTATAAAAAGTTAAATA AATACATTATTT ATTT/- TTTCATGCTTTTAATTTTTTTTACCATACCTTAACATATGCATATAAT TTTTTTTAAATTAATTTATTTTTTTTGAGACGGAGTTTCATTCTCGTT GCCCAGGCTGGAGTGCAATGGCGCCATGTTGGCTCACTGCAACCTCC ACCTCCCGGTTCAAGTGACTCTCCTGCCTCAGCCTCCTGAGTAGCT GGGATTACAGGC
LNPEP Region	rs10546363	23	GTGTGAGCCACCGCGCCAGCCCATATAATTTATAAATAAAAAATATG TATATTGGGAAGTTCTTGCTCAAAAAATCTTTACTGACTGGAGTATG TAGTAACAAAAAAGTAGGGAACACTGCTTTAAACAGAAACATAAAA TTAAACATAAACATTGCTGAATAACTAACCATATTTCCCAAAGAAGC TGTATCTACATTT TT/- TCATTTTATAGTAAATTTGATAAGTTTCACAGCTTTAGAATTGTAC TGGATGAATGTTATTATGGTAATTCACCGTATCTATTGTAATACACA AGCTTATCACATAGTTATTAATATACATTAAAAATATAATACATGAT ATAATAAACATAAAGTCAAGTATTTCTATGACTTTCTATGGTGTCTCT TTTTATTTTCAG
LNPEP Region	rs1056893	24	GGACTAAATTTAGCCTCTCTGTTAACCATCTCATATTTTCTGCAGCG TTACCTTCTTCAGTATTTTAAGCCAGTGATTGACAGGCAAAGCTGGA GTGACAAAGGGCTCAGTCTGGGACAGGATGCTCCGCTCGGCTCTCTTG AAGCTGGCCTGTGACCTGAACCATGCTCCTTGCATCCAGAAAGCTGC TGAACCTTCTCT Y CAGTGGATGGAATCCAGTGGAAAAATTAAAGTAGA TGTAAGCTTCTGTCTACCTTTTGTCTTTTCTCTTTGATGTAAAAG TCTTTGATCAAGCAAGACATTAGGTCTAAAACCTTTTAGTGAGGATA GAAAAAAAACATGCTGGGCATTACAAACCTGTTTCATGCTCTCAC ATTGTAAGTGCTATGTATGGAGACT
LNPEP Region	rs10707238	25	CTTCAGAAGATTGCTGCCCACCTGTAAAGTAATCTGAAGACTGTCAG AAAAGGAATAGTGCTTAACTGTTTCTAGAAGCTACAGACTTATAAT TTTCTGTTCTGTAACCTATAACCAGGCTCTTCTGAATCTTAGAATCTT ATTGTTGAAGCTTTGGTCCGCTAGAGATTTTAACTCTTAGAGACATA CACTAGATGTGCA A/- GTATTAGGCATATAGACTAAAATAAAATAAACATAAAAGCACATAAAA GAATAGTAATATTTAAAAATGCATAATACAGATCAAAATATAGGTAAAG GGTAAATATGTCAATATATTTATGCATCCTTTTTATTTGATTTATA TATTTTTTAAATCTTAGACCTTTATTGTTTCTAGTGGCCCACTGAAG TAAGTCAGGGGC

LNPEP Region	rs11135482	26	TGTAGAATTTAGTAGCAAAAAACATTTGCCATCAAAGTAGACTAGATA ATTTATGGTAATGCTTCAAGCTATTTTCTCTTGCCAAAGCAAATCGT AATCTTATCCAACATGTCAAACATGCTTAATAAGCTGCAGTCAGCAT CATCACAAGCCTGACTCCCAGAAAGGGCTCAGGGATAGAGGTGGGGA AGAGCCTGTCTA R GAGTTGTGACTAGCTTGAAGAAAAATGTTTTCAGA TTATTGGATCTGTATCCATTCAGTATTTGGGGGCATTGTACCATGGT GAAGACCATCTCTGAGACAAGCTGCCAGACCAAATGAAGATAGAAAT TCAGTCATTACCCAGTGATCTTGATAGATGCAGCTGACGAGACTGCA GGCTGAAAAGTTTCTGCTTCCTCAG
LNPEP Region	rs11135483	27	ATCATCACAAGCCTGACTCCCAGAAAGGGCTCAGGGATAGAGGTGGG GAAGAGCCTGTCTAGGAGTTGTGACTAGCTTGAAGAAAAATGTTTTCA GATTATTGGATCTGTATCCATTCAGTATTTGGGGGCATTGTACCATG GTGAAGACCATCTCTGAGACAAGCTGCCAGACCAAATGAAGATAGAA ATTCAGTCATT A SCCAGTGATCTTGATAGATGCAGCTGACGAGACTG CAGGCTGAAAAGTTTCTGCTTCCTCAGGAGATGGACAGAAGCTTAA TTACTAATGACCTCCTTGGCCTGACTGCTTTTCATTGCTGAATCAATG AAGCAAAGATAAAAATAAGACCATGACTCAAGCTGTCACGCAGCAAGT GAGAGAATGAGCATCATCTTTGGAG
LNPEP Region	rs11135484	28	CAATGAAGCAAAGATAAAAATAAGACCATGACTCAAGCTGTCACGCAG CAAGTGAGAGAATGAGCATCATCTTTGGAGTCACACGGTCACATCCA CATCTTGGTCCCTACCGTGGAACCTAGCCATGTGATCTCCAACAATTCT GTGAACATTTCAAGAGTCTCTGTTTCCCTCACCTGAGAAACAACACCAA CCTCACACCCAC R TAACAGGATTAAAAGATAATGTGCAGCCTCTAGT TCAGTTTCACTTCTCTGTTTCTTTTCCACAGGGGTGTACTTCTTGT ACAACAAATAAAGGGAAAGGGGCCATTATCTGGTATTTTACTTAAAA GCACAGAAGTTGAATTGATGCCAGTGTGGAAATTATTGCATTTTAA GAAAATAGAAATATGTAATATTTTT
LNPEP Region	rs11135485	29	TTCTTGCTGTGTCTCCTCACATGGTCTTTGTTCCTGTGCATATGTGGAGA GAGCGAGCTTTGCTGTTTCTTTCTATCAAGGACACCAATCCTATTGG ATTAGGGCTCTACCCCTTATGACCGAATTTAACCCTTAATTACCATCTT AAAAGCCCTGTCTCCAAATGCAATCACAATGGGGGTTAGTGCTTTTTT TTCTTTTTTTGG S GGGGGGCGCGGGGGACAGAGCTTGGCTCTGCCAC CCAGGCTGGAGTGCAGTGGCGCGATCTCAGCTCACTGCAAGCTCCGC CTCCCGGGTTCACGCCATTCTCCTGCCCTCAGCCTCCCAAGTAGCTGG GACCACAGGCGCCACACCACGCCCTGGCTAATTTTTTTGTATTTTTTA GTAGAGACGGGGTTTCACTGTGTTA
LNPEP Region	rs11311774	30	ATATTTTATTTTTTAAAGTAAATTTATACAACTTTTGTAAGTTCTAAA TTAATTTGAATATAGTTTGTTTTAACTATAGTATCAGTATATCTTTA AGATATTGTAATCAGGTTATAGATAATTAATATGACACTTCAGCCAA TTATTTAAAAAATTCCTGAGGCTGTAAATATCCTGTGGGTTAATTGT TTTCTCTCCCC C/- AGTGGTTTGGCAATCTGGTAACAATGAAGTGGTGGAAATGACCTATGG CTAAATGAAGGTTTTGCCACTTTTCATGGAGTATTTCTCTTTGGAAAA AATATTCAAAGAGCTTTCTAGTGTAAGTACAGGGTTTCTTTGGCCTA CTATGAATGCTAGGAGGAAAAATAGTCAAATCACATTTTCATGTATT TTCTGTGCATCT
LNPEP Region	rs11414909	31	CCCTTGCCCTCCTCACTCCCTCGGCCTACTCCTGTTTATCTCTCAGAT CTTAGCTCAGCCATTGCTTGCTCCAGGAAACCTTTCCCTCCCTGAAG ACAGTTTATAGATGCCCTACTTAGGTTTTTTTAAATAACATTCCTACTTC TCCACTCATAATATACTGTAAGTACTGTTCACTCATATCTATCCTCA TATTAGGTATTT C/- CCCCATTGACGGTAGTGATCATGGCTATATGAATCACTGTAAATCAC TTTTAGCACTTAGTAGGCACACAAAACTTAATGAATTAGTAAATTT TAGTCCATAATGAAGTGACTCCAGTCTCACTATAAAAAATTTCTAGGA AAAGAACATGCAAAGCCTGATAAAATGATGTTTTCTTTTCTCTTCC TCTTCTTAGTAA

LNPEP Region	rs11750025	32	CTTTTCTTACAGTATTTTATCAGTACCTTCCTCTTTATTTGGAGCTTA GAAATAGATTTCAAATAGAATTCAGCAAAATTTAAATTCGTAGAATT TAGTAGCAAAAACATTTGCCATCAAAGTAGACTAGATAATTTATGGT AATGCTTCAAGCTATTTTCTCTTGCCAAAGCAAATCGTAATCTTATC CAACATGTCAAA ~~M~~ ATGCTTAATAAGCTGCAGTCAGCATCATCACAA CCTGACTCCCAGAAAGGGCTCAGGGATAGAGGTGGGGAAGAGCCTGT CTAGGAGTTGTGACTAGCTTGAAGAAAATGTTTTTCAGATTATTGGAT CTGTATCCATTTCAGTATTTGGGGGCATTGTACCATGGTGAAGACCAT CTCTGAGACAAGCTGCCCAGACCAA
LNPEP Region	rs1216565	33	TAAAAATCTAAGCCTCCCAAGTGACTGAACAGACCATGTCTTGGCCA AGGGGACCCAGGGTAACCTTGAAAACAAAATTCATTCATGACAG GATGCCAGGGTCAAACAAGCCTTATTATACCCCTTCCTCAATATTCA GGATTAGCCTTTCTTCCCTAAGGGCTAAACGGAAACCAGCCCTTTTG AAAGATTCCAC ~~M~~ CTAATATCAACCAACCACCTGATATTGCCCTCTAG TTTTTTGCCCTGATAAGAGATCACACATGGAGTGGTTCTGGCCCATC TCCAGAGAATGCACAGTAAGAGTTTTCATGTCTCTGCTTCACCTTT TGATGTCAGAGGACTGAAAACCCACCCCTCGGATCATGTTAACACTG CCATTTTTTTGTATATGGGACCCATG
LNPEP Region	rs1216566	34	GTGCTGGGATTATAGACATGAACCACCACGCCTGGCTATCTTTTCAT TTCTTGATACTATCCTTTGAAGCATACTTTGTTGATACTTATCTTCA ACCTTATTTCCATTACAAATGAAGTTGTTATGAGTTGAATAGTGTCT CCAAAATTTATCTGTAAATTTATAATCCCCCATATTTTCAGAATGTG ACCTTATTTGAARITAGGGTTGTTGCAGATGTATTAGTTAAGATAAGG TCATACTGGAGTAGGGTGGGCTTCCAATTCAATATGACTAGTGTCT TATTAAGAGGAAGTTTGGACACAGGTATGCACACAGGAAGAATGT CATGTGAACACTGGAGTTACTTTGCCACAAGCCTAGGGACTATTAGAA CCTAGGAGATAGGCCTAGAACAGAT
LNPEP Region	rs1216567	35	TTGCTCTTTTGCCAGGCTGGAGTGCAGTGGCATGATCTCTGCTCAC TGCAAACCTGCTTTCCAGGTTCAAGTGATTCTCATGCCTCAGCCTA TTGAGTAGCTGGGATTACAGACACAGACCACCATACACAGCTAAATTT CTTGATTTTTGTATTTTTAGCTAAGCTGGTCTCAAACCTCTGGCCTC AAGTGATCCGCC ~~Y~~ ACCTCAGCCTCTCAAAGTGCTGGGATTATAGACA TGAACCACCACGCCTGGCTATCTTTTCATTTCTTGATACTATCCTTT GAAGCATACTTTGTTGATACTTATCTTCAACCTTATTTCCATTACAA TGAAGTTGTTATGAGTTGAATAGTGTCTTCCAAAATTTATCTGTAA ATTTATAATCCCCCATATTTTCAGAA
LNPEP Region	rs1216568	36	TCCCAAAGTGCTGGAATTACAGTCCTTTGCCTACTTTTAATTGGATT ATTTATCTTTTATCATTAATAATTTAAAAATTCCTTTATATATGCTAGAT ACAAGTCCCTTGTGAAGTCCCTTGGTTTGTAAATTTTTCTCCTATT CTGTGAACCTGCTTTTTCATTTCTTTCTTTCTTTCTTTGAGACA GAGTCTTGCTCT ~~K~~ TTGCCCAGGCTGGAGTGCAGTGGCATGATCTCTG CTCACTGCAAACCTCTGCTTTCCAGGTTCAAGTGATTCTCATGCCCTCA GCCTATTGAGTAGCTGGGATTACAGACACAGACCACCATACACAGCT AATTTCTTGTATTTTGTATTTTGTAGCTAAGCTGGTCTCAAACCTTCTG GCCTCAAGTGATCCGCCACCTCAG
LNPEP Region	rs1216569	37	AGCCTGGGCAACCTGGTGAAACCCCGTCTCTATGAAAAATAAAAAA TTAGCCAGGCATGGTGATGCATGTCTGTAGTCCCAGCTACTTGTGGG GCTGAGGCGGGAGGTTTCGCTTGAGCCTGGGAGATCGAGGCTGCAGCG AGCTGAGACTGCACCAGTGCACCTCCAGCCTGAGCAACAGAGTAAGAC CCTGTCTTGAA ~~M~~ AAACAAACAAACAAACAAAAATGGTAGATGAATG TTCATAGCTGCATTATTACAATAGCCAAAAAGTATAAACACACAA ACGTCCATCAACTGATGAATGGATAAATAGAATGTGAAACATTTATA TGTATAATAGAATATTATCAACAATAAAAAAGAAAGTACTGACATGT TAAACATAGATGAACCTTTTAAAA

LNPEP Region	rs1216570	38	TTGAATGAAATCTGTACCTTTTTTAAATAGTAGCAACCAGATGGGGGA AAACAAACTTGCTTGAGCAATGGTGAATGGAGATACTCAGATATAA TTTGCTTTTTTTTTTTTTTTTTTTTTTTTGGAGACGGAGTCTCGCTCTGTC GCCCAGGGCTGCAGTGGCGTGATCTCGGCTCACTGCAACCTCTGCCT CCCAGGTTCAAGYGATTCTCCTGCCTCAGCCTCCCAAGTAGCTGGGA CTACAGGCGCGTGCCACCACGCCCCGACTAATTTTTTGTATTTTTAGT AGAGATGGGGTTTACCGTGTTAGCCAAATGGTCTCAACCTCCTGA CCTCATGATCTGTCCACCTGGGCCTCCCAAGTGCTGGGATTACAGG CTTGAGCCACCATGCCAGCCATTA
LNPEP Region	rs12189125	39	AACCATAGCAAACGCCCATTTGCTTCCGAACCATCTCTGCCACCAGC CTTCTAGTAGCCAGACGTATTTCCCCATAGTCTCACAGCCTCACGC CTCTGCCAGTAACCCCTCCACACACTTGACTAAATGGTTTTGCTGCT GAGTTTGGTCAGAAGACCACAATAATACCCAGCTCTCAGCCCCCTAC CATAAGACAGCA <y>CTCCTCTGTCTGGGAGTGGATATCCAGAGAACT GGTTGAATCAGCTTCTTAAAAATGGAGACGGTTGTTGGGGAAAAATTA ATTTGCTGAGTAGAGTTCTTAAAAATTACAGCCCTGTATATACTTTG ACTTTTCTTACAGTATTTTATCAGTACCTTCTCTTTATTGGAGCTT AGAAATAGATTTCAAATAGAATTCA</y>
LNPEP Region	rs1230358	40	TGCTAAATCTGGGTACTGGAAGGATAAAGAGAGGGCAGAGCAAAGG CCAGAGGTTTCATCTTTGTGGAAGGTCTGTATTTCAGAGCAGAGAGGA AGTTGAAGCCCAACTCAAACAGGCAGATAAAGAGAGATCAAAGAGAT GAGCATGAGATACAGTCCCTCGTGCCCAAGGAGACAGGGTGGTTAC AGACATGGAAAA <y>CTGAGAATAATCACCTCTGATAAAGATCACAGAA GCTGCCCCGGGAGGTGTTTGGTAAGCTTGGAGTTACGTTTGTGGGGTG GATGGGCAGAAAGTCAGATTTTCATAGCACTGAGGATGCAGCACAAAGGA GAAGTTCAAGATCAATTCTTAAGACAACAACCTTGGCACTAAAAAACA TAACTATGTTCTGAAGGCTTTACC</y>
LNPEP Region	rs1230360	41	TTGAGAGAGAGCCTCGCTCTGTCTGCCAGGCTGGAGTGCAGCAGCAC GATCTCGGCTCACTGCAACTTCCACCTCCCTGGTTCAAGCGATTCTC GTGCCTCAGCCTCCCGAGTAGCTAGGACTACGGGCATGTGCCACCAT GCCCCGGCTAATTTTTTGTATTTTTTAGTAGAGGTAGGGTTTACCATGT TGGTGAGGCTGGYCTCGAATTCCTGACCTCAGGTGATCTGCCCCACCT TGGCCTCCCAAAATGCTGGCATTACAGACCTGAGTCACTGTGCCCCG TCCTGTTTCTTTATCTGAACACTAAGGACTTGTACTAGCTGGCCTTT ACAACCCTTACTAGTTCTAAAGTTAAAGACTGTGTGAGTAAAGCTTT TCTCTCTACTCTTATCAATCAAGTA
LNPEP Region	rs1230363	42	GGGCAACATGGTGACACATTGTCTTTCAAAAAAATAAAATATGGCC AGGCGCAGTGACCCACGCCTGTGATCTCAGCACTTTGGGAGGCTGAG GCAAGTGGATCACCTGAGGTCAGGAGTTCGAGACTAGCCAGGCCAAC ATGGTGAAACCCCGTCTCTACTAAAAATACAAAAATTAGCTGGGTGT GGTGGCACATAC <y>TGTAATCCCAGCTACTCGGGAGGCTGAGGGAGAA GAATCACTTGAACCCCAAGAGGCAGAGGTTGCAGTGAGCCAAGATAGT GCCACTGCATTCCAACCTGGACAACAGCGAGATTCCGTCTCAAAAAC ATAAATAAATGAATAAAAAATAAAGTAGGCTGGTCACAGTGGCTCACG CTTGTAATCCCAACAGTTTGGGAGG</y>
LNPEP Region	rs1230364	43	CAGCACTTTGGGAGGCTGAGGCAAGTGGATCACCTGAGGTCAGGAGT TCGAGACTAGCCAGGCCAACATGGTGAAACCCCGTCTCTACTAAAAA TACAAAAATTAGCTGGGTGTGGTGGCACATACCTGTAATCCAGCTA CTCGGGAGGCTGAGGGAGAAGAATCACTTGAACCCCAAGAGGCAGAGG TTGCAGTGAGCC <y>RAGATAGTGCCACTGCATTCCAACCTGGACAACAG CGAGATTCCGTCTCAAAAACATAAATAAATGAATAAAAAATAAAGTAG GCTGGTCACAGTGGCTCACGCTTGTAATCCCAACAGTTTGGGAGGAT TGCTTGAGTTTAGGAGTTTGGAGACCAGCCTGGGTAACAGGGAGACCC CCATCTCTACAAAAAAGGTAGCCGA</y>

LNPEP Region	rs1230365	44	CCGTCCTCTACTAAAAATACAAAAATTAGCTGGGTGTGGTGGCACATA CCTGTAATCCCAGCTACTCGGGAGGCTGAGGGAGAAGAATCACTTGA ACCCAGAGGCAGAGGTTGCAGTGAGCCAAGATAGTGCCACTGCATT CCAACCTGGACAACAGCGAGATTCCGTCTCAAAAACATAAAATAATG AATAAAAAATAAAATAGGCTGGTCACAGTGGCTCACGCTTGTAATCCC AACAGTTTGGGAGGATTGCTTGAGTTTAGGAGTTTGAGACCAGCCTG GGTAACAGGGAGACCCCCATCTCTACAAAAAAGGTAGCCGAGTGTGG CGGTGTGTGTCTGTAGTCCCAGCTACTCTGGAGGCTGAGGTGGGAGG ATCACTTGAGCCCAGGAAGTTGAGG
LNPEP Region	rs1230381	45	AGTATTCTATAGTTTGGCCCAACCAGTTTACGTCCAAGGAAAAATTAG CCAATGCATAAAAAATACAAACTATGAAAGGCAAGGATCAGGAAACC AGAGACTTTGCCACCAAATCTCAGATTATTAGAACTAGGTGTCAGG GTTTATCAAGAAGGCCAGGAAGGCCCTTTGGGTAAAGCCTTACATTC ATGAAGAACCTCAGGGTAGATTTTGGAGAGCATTCCAAATGAATGG TCTCTGGTCAAATGAATGAATGGTCAAATGAATAAATCTGCCCTCAC AGAGATACAAAAGGAAAGGAATATAATTCATACCATTGGTTTAAAG CCTTACATTTCATGAAGTACCTCAAGGGTAGATTTTGGAGATCATTC AAATGAAGTCGAATCTGCCCTCACA
LNPEP Region	rs1230382	46	ATCAAGAAGGCCAGGAAGGCCCTTTGGGTAAAGCCTTACATTTCATGA AGAACCTCAAGGGTAGATTTTGGAGAGCATTCCAAATGAATGGTCTC TGGTCAAATGAATGAATGGTCAAATGAATAAATCTGCCCTCACAGAG ATACAAAAGGAAAGGAATATAATTCATACCATTGGTTTAAAGCCTT ACATTCATGAAGWACCTCAAGGGTAGATTTTGGAGATCATTCCAAAT GAAGTCGAATCTGCCCTCACAGAGACACAAGAAAGGAATATAAATTC TACACTATTGCAATTTTAAATAAATCTTTTGAATTTGCAGAAATTAGA TTGTATTGTGTATTTTCGGTTAAATGATAATTGAATGTAAATATTTA GATGCAGCACCATATTTTATAACCC
LNPEP Region	rs12516666	47	CATAATGAAATACTTCAAGTGAAATTTGATGGGTTGATGATCCTGGG CACATACCTAACTCTCTGAAGTTCAGTGTCCCCTATCTATAAAATTAA GTTAATAATAGTTCTGTTTCATAAAGCTGTTCTGAGGATTATGGATA GGGAAAGTGTGCGGATCACATAGTAAGCACTCAATAAGTATTAGTTA TTAATGATGATGWCACAGGCCACTACAACACAAGAAATACTACTAT TTCCTTGCAAAATAACTTATCTAAGGGCCATCTATCAACACTGTATTA CATACAAATGTGGAATTGTAAAAC TAGGTCTATAGATATTGGAGACT ATTCCCTCTATTTTCAATTTCTGAAAACCTCTCAGTAATGCAGTAAATTA TTAAAGTCACCAAAATTGTCTTTCA
LNPEP Region	rs12716486	48	TTCTTTTTTCCCTCTCATTTAGTTCTTTTTTAGTCTTGATTTCCCCA CGGAGAGTCTCATCTATTCACATATTCCTCATTTTTTCCTTTTTAAAA TACATCTTCCCTGCTTAATGATGGGGATACAAATGAAAAATAATAAAA CACGTCTTCTTCAGGGATTCTTTTTTATTTATAATGGCTACTCTAAA GACTCACTAAATRCAATGCAATATCTGGACCACCTTAAGATTGCCTT CTAATGATTTTGTCTTACTTAGGGTTCACATTTCTTGTTCATTAAA TGTCTAGTAATTTTTTATTACATATTGAATAGTGTCAATGGCACATG GTAGAGATGCTGAATTAATAAAAAACTCTGTAAAATGTTGATTTTTCT CTCTCTGTCTCTGTAGACAGCTTAG
LNPEP Region	rs13167902	49	CAACAATTCTGTGAACATTTTCAGAGTCTCTGTTTCCCTCACCTGAGAA ACAACACCAACCTCACACCCACATAACAGGATTAAAAGATAATGTGC AGCCTCTAGTTCAAGTTTCACTTCCGTGTTTCTTTTTCCACAGGGGTG TACTTCTTGTACAACAAAATAAAGGAAAGGGGCCATTATCTGGTATT TTACTTAAAAGCMCAGAAGTTGAATTGATGCCAGTGTGGAAATTAT TGCATTTTAAAGAAATAGAAATATGTAATATTTTTATGCTTTCAATC AACAAAATGAGATTTGGCATTTTTGTGCTTTGGGGATCTCAAAAGCA GGGCTTTTTTGTCTTCAACAGAGTGTGGGGTAAAAGCAATGGAGGTA AGAGAGGCTACAGAATACTAGGAGA

LNPEP Region	rs13170029	50	AGCCAGGAGTTGAGGTTGAAGTCACCATTCAGATGCTTAAGTCAAC TATTTTAAATAAATGATTACCAGTTGTTTAAAAAAAAAAAAAAAAAGAAAA CTATAGAGAGCTATCTACCTTTTGGGACTACCATGGTAGCAGTCATT TGCTGTTCCCTTTTGGGAGGGACGGGAACAGGGTCTTGCTTGGCT GGAGTGCAGTGGYACGGCCACAGCACTGCAGCCTTGACTTCTCAGGC TCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTAAC TGGGACCACAGG TGCACACCACCATGCCTGGCTAATTTTGTATTTTGTAGAGATGG AGTTTGGCCATGTTGGCCAGGCTGGTCTCGAACTCCTGGGCTCCAAT GTTCTGCCTGTCTTGACCTCCCCAA
LNPEP Region	rs13189819	51	ATACCTTGTAGCCTACATAGTTTGTGATTTCCACTCTCTGAGTGGCT TCACTTCATCAGGGGTCAAGGTGAGACTGAGTTCTAACGTTCTACGC AGTGCAGAAAAGTGTCTGAGAGCAATGAAC TTTGTTTCTCATGT TTTTCATTGTTATCAAAGTATTATGTTTATATACAAAGAGATAG ATAAAAACTAAATTTAAAAATTATCCATAGTCCGTGCACCAAGATAC AACTACTGATAATATTAATGTAAGCCTTCCAAATATTTCTATATGT ATGTCAGCATATATGGGTGTACATAGTAACAGTATTTACTTACTATA TATGTAAGGTAATTTTCAAAGTATATATATATATATATATATATAT ATACACACACACACACACACACACA
LNPEP Region	rs13358339	52	ATTCAGCCAAC TACTTTTAAAA TTTATCTTTT TTTT TTTT TTTT TTTTGAGACCAAGTCTCACTCTTTTGCC CAGGCTGGAGTGCATGGT GTGATCTTGGCTCACCACAACCTCTGCCTCCTGGGTTCAGTGATTC TCTTGCTCAGCCTCCCGAGTAGCTGGGATTACAGGCATGTACCACC ACACCTGGCTAAATTTTGT TTTTAGTAGAGATGGGGTTTCCACCATG TTGGCCAGGCTGGTCTCGAACTCCTGACCTCAGGTGATCCACCTGCC TTGGCCTCCCAAAGTGCTGAGATTACAGGCGTGAGCCACCGTGCCCTG GCCAAAATTTATCTTAATTCAGACTTTACAATTGACTTTATTTAAATA AATATTTTAAGTAGAAGAAATGTT
LNPEP Region	rs1363907	53	AAATCATTTAACTTCTTTAGCCACATTGTGGTCAC TTTGTAAGATGAG GATTTATAATTTTGTCTTACTTTACCTATTGTTTGAAAATAAAGTG AACAAATTATGCAGAAAAGTAGAAAAATAACCTTTTAGAGGTTGGCAGA GAAATGCCCTATACCTGTGTGTATGTAATTTGCAAGCTCTTTTGAAAA TTTTTGGAAGACRAAGTGGTTTTATGTTTCTTTATTTTGAACCTG CCTCGCTCTGTGAGCCAGGCTGGAGTGCAGTGGCACCATCTTGGCTC ATTGTAACCTCCACCTGCTGGGTTCAAGCAATCCTCCCGCCTCAGCC TTCCAAGTAGCTGGGACTACAGGCATGCACCATCATGTCCGACTAAT TTTGTGTGTGTGTGTGTTATTTT
LNPEP Region	rs1363908	54	GGGTTCAAGCAATCCTCCCGCCTCAGCCTTCCAAGTAGCTGGGACTA CAGGCATGCACCATCATGTCCGACTAATTTTGTGTGTGTGTGTGT ATTTTGTGTAGAGTCAGGGGTTCTGGCATGTTGCC TAGGCTCGTATT GAACTCCTGAGCTCAATTGATCTGCC CACCTTGGCCTCCCGAAGTGC TGGGATTACAGGYGTGAACCACCACACTCGGCCAAGACAAAGTGTTA GTAATTTTCTTCAATATTTTACAGGTGAACTATTTTGTGAATC TCTTGAGGCTCAAGGATCACATCTGGATATTTTCAAACGTGTTCTGG AAACGATAACCAAAAAATATAAAATGGCTGGAGAAGAATCTTCCGACT CTGAGGACTTGGCTAATGGTTAATA
LNPEP Region	rs1363974	55	AACTTTTGCAGGTTTCATGCACAGATTTAAGGGATCCTCTTTTCTGAT TCTCTCCCTCTGGGATTTCCCCCATGCTGTATAGCCTACAGGGTCT ACTCTGGTTTCTCTGGATAGAAATATGGGACTCATTTGGAATTTTAC CTGTTGGCATTTCCACACCACCTCTGTGACCAAAGCCTGCC T CAGGG CAAAGTAGAGAAAGGAAATGGAACAATATTTAAACAGAAAC T CACCC CTGTGTGTTTTCCTCAGCAAGTTTGTGACCCTATAACCTATTATAA AGTGAAATGAAATGTGGACACCTGTGAAGCGTCCGAGTGCAAAAT TTGTCTAGACTTTCAATTTT TTTTCCCGAGTCTTTTAGAGTTGTCTCC TACCTAATTCACAACAATTTTAGT

LNPEP Region	rs1363975	56	GCATGAAGGAGAGCTGCCAAGTTCTGTGTCTTGATAACCTTTTCCTTC CATTTCCTAGTTCAATTAACCTGAAGAAAGAAAAATAATTTGTTTCTA AATAGTAGGTATTATGTACATGGACATTAACCTCAAGCCACCAATATA TTAAAAGAATAGAACAGAAAGAGGCATGATAAAAGTATAATTACCAA TTTTTTAATGTTTCAATTAACCTTTTACTTTTTTAGAAATAATTTTT ATTTTGTTCCTATCAAAAACATTTACTTATTATTTCAAATAAGTTTG ATTAGCATCATTTACACATCTTATATGCAAGAATGTATTTTACAAC AATAATTTTTCTTCAAGTTTCTGAAGATAAAACATAACCGCTTGTCT AGTCTCAATCATATGATTAATAACT
LNPEP Region	rs1363976	57	CTAAATAGTAGGTATTATGTACATGGACATTAACCTCAAGCCACCAAT ATATTAAGAATAGAACAGAAAGAGGCATGATAAAAGTATAATTAC CAATTTTTTAATGTTTCAATTAACCTTTTACTTTTTTAGAAATAATT TTTATTTTGTTCCTATCAAAAACATTTACTTATTATTTCAAATAAGT TTGATTAGCATCTTTACACATCTTATATGCAAGAATGTATTTTAC ACAATAATTTTCTTCAAGTTTCTGAAGATAAAACATAACCGCTTG TCTAGTCTCAATCATATGATTAATAACTAGGGAATACCTGTTTTCAC TATTTGCATTTTGTCAATATATTCTTTTCTGAAAGTAAAGTTAAAGC CATACACATTCTGATTCAATTATCT
LNPEP Region	rs1363977	58	AATTACCAATTTTTTAATGTTTCAATTAACCTTTTACTTTTTTAGAA ATAATTTTTATTTTGTTCCTATCAAAAACATTTACTTATTATTTCAA ATAAGTTTGATTAGCATCATTTACACATCTTATATGCAAGAATGTAT TTTTACAACAATAATTTTCTTCAAGTTTCTGAAGATAAAACATAAC CGCTTGTCTAGTMTCAATCATATGATTAATAACTAGGGAATACCTGT TTTCACTATTTGCATTTTGTCAATATATTCTTTTCTGAAAGTAAAGT TAAAGCCATACACATTCTGATTCAATTATCTTATGCCTTTAAACTG GTGGCTGAAGTTTATAGTGAATTTACTGAAATTTGTGTCAGTTACTTA TAACAATTTAGTTAAATTATTGAAC
LNPEP Region	rs1423357	59	AACATTGTCAGTGGTGGTAGTGACGATGATGAACCTTGGTTTTACTTT TTCAGTGTCTAACCTGGTCCCGTGCTAGGACCCAGGCAGAGCTTCC TATGAAGTCACGTACAACAAGGCCTTTGGGCTTAAGAGAAAAAGCTC ACAGCTGCACAGAGGGAGGAGTTTATATAAAGAATACAAAATGTT CTGAATACCAAGWGTTCATTCTCTCCTTATGTTTCTGAGTTGAAAT TTGAAGTAATCATGAGACACTGCATGTGTTCCTTCAAAAGATGCC ACAGAATCATAAACTAGTATGTAGCATATAATTTCAATTTTGTCTT AGGGGATAAATTAGTCTAAGAATAGTATACCAAACATTAATTGTGA TAATAGTGTAGTGATCAATTTATGA
LNPEP Region	rs1423566	60	ATCATCACACCCAGACCAATGGGAGCATTATACATGCATTTATTTTT GTACTCAAAAGGATGAAGTATATAACTGTCTACTGTACCATGTCATT TGAAAACACTAGAAAATTTACAGCAATCCTTCAAAAGTTTCAAAT AAATACCCGTCCATCTTAAACCTGAAAAGCACTTCAAATTGCTAAC ATTTAATTTCTTCTTTGACTGTAGATATTGTCGTTTCTGTTTTCCCTG TAAAAGGATGCTAAATAAGGCTCCAAGGAGTGATTGCTACATTAACC AAAATTATGCACTGCCAAGCTGTCTCCAGCATCAACTCTGAAAGATA GGAAAGAATCAGAAATCCAATTTCTTACATGAAAGTTGAAGCATGCT TTCTTTTTTTGTTCTCTCTGTGGG
LNPEP Region	rs1477364	61	ATCCCTCCCCAGTGCAGTTCACAATAGGGTTTCATGCTCCTATGGGAC TCTAATACCACCCGTGATCTGACAGGAGAGGCGCCAGGCGGTAACGC TCACTTGCCCACTGCTCACCTCCTGCTGTGAAGCCAGTTCCCTAGCA TGGTCCTTGACATGCAAAATTGGGGACCCATGCTTTAGGCAACACTTC CATGAAAGTGTTTCAAAATTTCAAAATTTGTTAATAAATATGAAATGGAA AGAATCCTCCTATAATGGCCTCAAGCCCTTAGTAAAGAATTAGGATC CAAGAAACACCATTAGTTCCAGCTTTTCAAAACCTCACTAAGGCTG GAATATGCTCAAACCACCCTTATCTTAGACCCTGCTAATTTCAAA AAAGTTTAAAGTTTTGAATGTACAT

LNPEP Region	rs1544777	62	CATGGTGTGCAGTATGGTTGTTTCCCATGGAAATATGTTGTACTTCT GAAAGCCATGGAAGCATGAAAAACAGATTGAATTATAATTTTATCTG ACTTTTATTGTCTTTTGTATCTTTTAAAAATCATTTCTTGCTTATGG AAATTTCCCATATAATTTGCTGCTTCCCATTTGCTGTGGGACAGAAA CATTCCTCTTTTGGGGAAAAACAATAACCCATCCTGTTGCTTAGCCA TACTCAATCTTAGAAATGGGCATACCAGCTTGTGGTGTCTCCCTAGAG AGAATGAGACTCAGGGATGAGACCCACAAATACCTTGGAAGCAGATT TGAGGCCTGTTGGACAGAAATTTGCGGATTGCAGTGCCCAACCCTA GAAGGGGAACCGTGGACTGTAGGTG
LNPEP Region	rs1559267	63	TCACTCTCTCCCCACTACACACCACTGGCAGCCCCCTCAACCCCTGGAA AAAGGAAATTATGCACACTATTTGCCTATACAGTCTTTCACATTTAG GATGAAATATTGAGTTCCAAAACCTGCTCTACATTTACTTTTCTAGA ATAACGGATACATTTCAATCCTGGTAACCTTTTGTCTGTTCAAGAATT AGAAGTTGAGGAWAGAAGGTTTAGGAACTCTCAAGGCCCGGTTTAT GCTGTAGAAAAAAGAATTTCTGCATAAGTAACTGCAATTATAAAT TTTGCTCCAAATATGAATAATTCCTCCAAGGAGAGGTTTATAACCTC ATTCATCTTTGTATTCTGGTGCCTAGCAGGGAAGAAACCTGCCATA AATGTTGAAATGAAAGTAGCAATAA
LNPEP Region	rs1559354	64	ATGAATATGTAGATATATGAGTTGTGTAGCACACATACACATCATGG CACCTCTGCACTTAGACATGGATGTCTATGCATAGACATGGATGTGC AGGAGGTGAATGGCACTTCAGAGGACAGGTTCTGTGACCTCTTTG GATTCACGTCCAGCTCTACAACCTTCAGCCTGGGTGATCTGGAGCA AGTTACTAAATCTTTATGTGTTTTATTGCTTACCTATAAAATGCC ACCTGCTTCATAGAGTGGGCACAAGTATTAAATTAGATTTTATACGT AAGCATTCAGCACAGTGCCTGGTAACTGTCAAAAAATGGTGGCCGT TTACATTTTTTCTGCATAAAAGTTTTGAAGGACTTCAGTTAATTCAG AACATAAAAGTGGGTCATGAAATAA
LNPEP Region	rs1559355	65	TATATACTCTTTAGTACAGATATACTAAATCCCATTTATATGTAATT CACTGCTGTACTTTAGATCAAAAGTCAAGGAAAGATTAAATACAGCC ATCAACAATATTAATGTTGTTCTTGAAAAATGCAGTCTTAAAGAGCA TATGAAATATCTTTAAGACTAACGGAAAAAGAAGCATGCAGCTTAGGA AAAAATAGAGCAKATATAAGTCCCCTACTATAAAAAATCATCAATGCG ATTTAGAAGAAAAAGTCATTTCCACATTTGAAGTGCCTAACGAATACTA ATCTTTATTAGCGCTAATTTAGTTTTTTGATTGTGTTATGTATACCTG TTTTTAATGTACTAGAAATTAACAGTATTAACCTCCAGACAATGTAAT TATAAGCCAAGTGACTTGGTTCATT
LNPEP Region	rs1559356	66	TTTATATGTAATTCACCTGCTGTACTTTTAGATCAAAAGTCAAGGAAAG ATTAATAACAGCCATCAACAATATTAATGTTGTTCTTGAAAAATGCA GTCTTAAAGAGCATATGAAATATCTTTAAGACTAACGGAAAAAGAAGC ATGCAGCTTAGGAAAAAATAGAGCAGATATAAGTCCCCTACTATATAA AATCATCAATGCGRATTTAGAAGAAAAGTCATTTCCACATTTGAAGTG CTAACGAATACTAATCTTTATTAGCGCTAATTTAGTTTTTTGATTGTG TTATGTATACCTGTTTTTAATGTACTAGAATTAACAGTATTAACCTC CAGACAATGTAATTATAAGCCAAGTGACTTGGTTCATTTCAAACCTTT TAAAAAATTATCTTTTTTTTCCAGCT
LNPEP Region	rs1559357	67	TTATATGTAATTCACCTGCTGTACTTTTAGATCAAAAGTCAAGGAAAGA TTAATAACAGCCATCAACAATATTAATGTTGTTCTTGAAAAATGCA TCTTAAAGAGCATATGAAATATCTTTAAGACTAACGGAAAAAGAAGCA TGCAGCTTAGGAAAAAATAGAGCAGATATAAGTCCCCTACTATAAA ATCATCAATGCGRTTTAGAAGAAAAGTCATTTCCACATTTGAAGTGC TAACGAATACTAATCTTTATTAGCGCTAATTTAGTTTTTTGATTGTG TATGTATACCTGTTTTTAATGTACTAGAATTAACAGTATTAACCTC AGACAATGTAATTATAAGCCAAGTGACTTGGTTCATTTCAAACCTTT AAAAAATTATCTTTTTTTTCCAGCTA

LNPEP Region	rs17087165	68	AAGAATATGATGTTATTTCTCAAAGGTACAATCTAGCTGAAATCATA TACAAGTAAGTAGGTGTGGACTTTTACTGTTGAGCTAAGGTTTATGT TTATATATGTTTTATTCTTTAAGCTAAACAAACATTCAGATAACATT CTATGCATTTTTTTGAAGCATAGGGTTAGTAATGAGGACTTAGATTTT TTAATTAAACAAATTCAGTAACATATATAAAAAAGAAAGGAGTCCCTTA TGAATAAATATTTAAATTTAAAGAAATAGGCAACTATAAAAGTAAGT ATTTTTTAATAATGGCATTGATTTTAGTAAGAAATCAATTAGGCTGGG CTGGAAAGAAAAACTGGCTTAAATATAAAGTAGTTTTAATATGTCAAA TATTCTTCTTAAATTTGTGGCCCTG
LNPEP Region	rs171647	69	GCCTTTCTGGGGGAAAAATGCAGAGGTCAAAGAGATGATGACTACATG GACTCTCCAGAAAGGAATCCCCCTGCTGGTGGTTAAACAAGACGGGT GTTCACTCCGACTGCAACAGGAGCGCTTCTCCAGGGGGTTTCCAG GAAGACCTTGAATGGAGGGCCCTGCAGGAGAGGTGGCTGCTTTTCTT CTTTAGGTCTAGTTACCTCATCTCAGTTTCCTCGTTATTTCCCTTAG CTTTCTCTCAGCTCATCTGGCAACTTTGTAGGATGCTAGTTCCATAT AAGAATCAAAGGCCTAAAGTAGACTTGATAAGATTTAAAGAGCTTCA TATAACCCGGACTTCTTTGTTGAGGAGCACCATTCTTAGTGATTCCA TCAGCCTTGAGAACTTCAGTTCTTG
LNPEP Region	rs1820148	70	TTGAGCCTCAAGAGATTCAAAAAATAGTTTCACCTGTAAAAATATTGA AGAAAAAATTAATAACACTTTGTCTTGGCCGAGTGTTGGTGGTTTAC ACCTGTAATCCCAGCACTTCGGGAGGCCAAGGTGGGCAGATCAATTG AGCTCAGGAGTTCAATACGAGCCTAGGCAACATGCCAGAACCCCTGA CTCTACAAAAAAATTAACAACAACAACAACAATAATAGTCGGACATGA TGGTGCATGCCGTAGTCCAGCTACTTGGAAAGGCTGAGGCGGGAGG ATTGCTTGAACCCAGCAGGTGGAGGTTACAATGAGCCAGATGGTG CACTGCACTCCAGCCTGGCTGACAGAGCGAGGCAGTTTCAAAAAATA AGAAACAATAAAACCACTTCGTCTT
LNPEP Region	rs1820149	71	ATGTAGCATTTGTTTCCAGGTTCTCTTAAAGGTTTTCTTTTTATCTTT AGTTTTAAGCAGTTTTGACCATGATGTGCTTAAGACATTATTATTTG TGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGT TTGGGGGTTTGTGTAACATTTTGGATCTGGTAAGTGGTGTTTTTTCAT CAAACCTTAATAAAWATTTTAACTATTATTTCTTCAGATATTTCTCTCT GCTGCATTCTCACACTCCTTCTGTGGCTCCTGTTAGATACATGTTAG ACTGTCTGATACTGTCCCCAGATCCCTGATGCTGTGTTTATTTTTTC TTCAATCCTTTGTCTCATTTGTTCTTCAAAATGGTAATTTCTAATGAT CTGTCAAGTTTATGGACTCTTTCTT
LNPEP Region	rs187265	72	TTGAAAGGGGTGAGGAAAGAGACTCCAGTCTCAACCTCCTTTTCACT GGCTTTTCTGCCATGTATTACCCCTACTATATCCTGTATATATCCC TCAATTCAAGTAATTTGCAGAGAGCAGCCCTGGGATAGCCATCCCTA ATCCAGTTGCCGTGATTACCCCTCCCTGAGATACCAGTCCGAGTCTT CTGTTCCCAAGSCTTGTCTTCTGGCATCCAAGGAGATGGAAGTTTCT GTCCCTCTGTCTTTGGATTGTCTCCTCTCTCTTGAAGTTATCATAGTC ACCTGTCAATTCAGCTCGCCTTTCTGGGGGAAAAATGCAGAGGTCAA GAGATGATGACTACATGGACTCTCCAGAAAGGAATCCCCCTGCTGGT GGTTAAACAAGACGGGTGTTCACTC
LNPEP Region	rs193993	73	CAACACGGAAGAAATCTATCATTTGGTGTGCATACTGGCAGTAGAGGG TGGGAGTTAAAAAGAAAAATTTGGCCAGCAATTACCAGATCATTTTAG GCCAGCAGTGTAATTCCTGTGTATTATTTTGTACATCATGCTTAT AATCATCTCAAAAGATAAAGTAATCATCATTAATCTGTGTTTATAAG TGAGAAAACTGAYACTAAGGGACAGATTTGCCCAAAGTCACCAAGTC AGTGAGAAAAATCAGTACTTAAAAATTTGTCTTCTAAGTCCAATAGTTA TTCAATTATATCACAGCTAGTTCCTAGTTTTAAGAAAAAGTCCCCCAT CAATCTTCCCCTAAAGGTCCTAGATTTTGACCAACTCTCTCTGACA CCAAAGGGCCCTGTAGTATTAAAAAT

LNPEP Region	rs1974871	74	TTTTTCGCCTCTTGCCCTCAACTCCAATGCATTTTTCCTTACATAAAT TAAAAGGGACCATCAATTGGCATAACAGTTCCAGGCTTAAAAAATTA AAAGCTATATCCAGGGACTTATTTTCGATAGTTTCTGAGTCTTACTCT GCTATTATTGTGCAGGTTCTATATACTCTTTAGTACAGATATACTAA ATCCCATTATATA ~~Y~~ GTAATTCAGTCTGTACTTTAGATCAAAAAGTCAA GGAAAGATTAATAACAGCCATCAACAATATTAATGTTGTTCTTGAAA AATGCAGTCTTAAAGAGCATATGAAATATCTTTAAGACTAACGGAAA AGAAGCATGCAGCTTAGGAAAAAATAGAGCAGATATAAGTCCCCTA CTATAAAATCATCAATGCGATTAG
LNPEP Region	rs1981846	75	CCGGAGGGTGAGGCATGAGAAGCTGAGGCATGAGAATCACTTGAACC CGGGAGGCGGAGGTTGTGATGAACCAAGATCACACCACTGCCTCCA GCCTGGGCGACAGAGCAAGACTCCATCTCAAAAAAAAAAAAAAAAAA AAAAAAGACGTGGTTTTGTATAAGAAGTAAAAATAGTAAACAAACGA AATGTTTCAGAA ~~K~~ CCCTACCTAGGAGCAAAAGAATAATAATGAAGTTT GTTTTGTTTCAACGGATACTGTTTTACATTTGACTTCATAGAGCCTT TTTGAGGGAATATGATATCACAATTCACAACCAAAACCCATATGT TTTTATCTTTAACACCCGCTATCCTCCACACAGAACTTCCTCTTT AGTTTAAGAATATGACAGTTTAAGT
LNPEP Region	rs2042383	76	GACAGAGTGAGACTCTGTCTTAAAACAAAACAAAACAAAACAA CAAAAAACATATAAAGATGCTCTTTACTATCCATTTCCATCACCAC CGTCAGTGGTCCAGACACACTTTCTCCATGCTTCCGCTTAAGCTTCT CAGCACCAAGTATTGTGTTGCTTCTGTCTCTCATCCCCCTCCATTT CCTCTCCCTTGC ~~Y~~ ATGTGTGTGTGCATGTATGTATATTTGTAGACAT CAGTTTAGCTCCCCCTCAACACGGAAGAATCTATCATTTGGTGTGCA TACTGGCAGTAGAGGGTGGGAGTTAAAAAGAAAATTTGGCCAGCAAT TACCAGATCATTTTAGGCCAGCAGTGTAATTCCTGTGTATTTTTTT GTCACATCATGCTTATAATCATCTC
LNPEP Region	rs2042385	77	CTGAGGCAGGAGAATGGTGTGAACCCCGGGGGCGGAGCCTGCAGTG AGCCCAGATCGCGCCACTGCACTCCAGCTTGGGCGACAGTGAGACTC CACCTCAAAAAAAAAAAAAAAAAAGAAAAGAAAAGAAAATGCCCTTC AACTTGGTGATAAAAAAGCATCAAGTAATCATCTTTAAAAAATAAT CTTATAGCACCA ~~R~~ TAGTGGCCACTAAATGATAGAATTTATATAAAAC AGTAGTTTTGTATTTTCAAGAAAGCTTTTATATTTGTTGATTACATCAA CTTCTATTTTCACTCAGAGTAGGTTAAAATTTTATGCTTATTTTC TTGCTAACATTTTATCATCAGTAGGAGATAAAACACAAATAATTTGC AGAGTAAAAGCACATAAAATATTTT
LNPEP Region	rs210687	78	CCACCACCCCTGGCTAATTTTTTTTTTTTTTTTGTATTTTTATTAGAG ATGGGGTTTTCACTGTCTTAGCCAGGATGGTCTTGATTTCTCCTCACTTC GTGATCTGCCTGCCTCAGCCTCCCAAAGTGCTGGGATTACAGGCATG AGCCACCGCGCCCGGCTCTTTTTTTGACTTTTTTAACAATAATCATTC CGGCTGGTATGA ~~R~~ ATGGTATTTTCATTGTGGCTTTAATTTGCATTTTT CTGATGATTAGTGATGCTGAACATTTATTCATGTTTCGTTGGCCACTT ACATGTCTTCTTTTGAGAAAGTGCTGTGAGACGGCATATTCATATAAG CAGTTGAGAATATCAGAGTACTAAGAAAATAATTCCTGGAATAAGAAT TATAAGGCCCTCACAGCTGTAATC
LNPEP Region	rs2113050	79	ACTGAATTAAATAAGATGTTTTATACCATTTAGTTCATCCATTAAAAAC TAAAAACATAAAATAAAGTATACCACAGTTATGAAACAAGAAAGCTAA ATAAACAGGCTATTATATTTTTTAAAAAGTTAGCTGAGATAATATACT AATTTCCCTTAATATACTCCTGCCCCACAACCTGGGACCTGCCCTGG GCTTGAGAGGG ~~M~~ CTGTTTTGGCATTCCTCTGACTATGTCTGTCCCC ACCAGGCGAGGAGTCAGTAGGATCAAAGGATGTGCCACCTACAGT CCACGGTTCCCTTCTAGGGTTTGGGCACTGCAATCCCAGAATTTCT GTCCAACAGGCCCTCAAATCTGCTTCCAAGGTATTTGTGGGTCTCATC CCTGAGTCTCATTCTCTCTAGGGAG

LNPEP Region	rs2113189	80	TTTTTTAATGTGATAGCACCTAGCATATGTTGATCTTATAAATAGTGA TTAATAAGCAGTTAATGATTGATTAAAAGAACTTATGGTCTGTCTTTTG GGATTCATGTAGATAATAGGAAAGGCAAAGCAGAAAAATTCAGTTAA TTCAGATGATTCTAATAATTATTTAAAAATATTTTAAAAATTTCCAACCTG CAAAGAAAAATAA ~~W~~ TTTTTATAGAACCATTAGACCCAGAGAACTCATA CCTGTAATTAGAAGAACCCTAAGTCATTGTAGACAGAAGAGATCCCTT TCTTTTTTACAAGCACTTGTGTCCCAGGGACAGTAATAAATATTGTTT AATATTTCTGCAGCAGTTTACAGTTTAAAGACACTTTTCATGGCCGGG TACAATGGCTCACGCCTGTAATCCC
LNPEP Region	rs2113190	81	CCCCACTGCTAGCTAAAAATATCTCAGCGCAAAATGTTTTTGGAGTGG TTACTACTGCATTGGCATCCCTTAAGCTCTGAAAAATGCCAAAATAA GTATGCTGTTAGGTTTGGAAATACAGTATATGTTTTCTTTTCTCCTT ACCTCTGGGAAGTTATAGAATCACTACAGGAAAGAGAAAAAGAAATC ATCACAGGGGAA ~~R~~ AAAGGAAAACTTTTTATTTAAACAAAGAGTCATG CTAATCCCCCTGAATATATATATACATAAATTTATATTTATTTATTTT AGACAAAGTCTCACTCTGTGTGCCAGGCTGGAGTATAGTGGCACAAT CTCAGCTCACTGCAACCTCCACCTCTCTGGTTCAACCAATTCTCTCTG CCTCAGCCTCCCAAGTAGCTGGGAT
LNPEP Region	rs2113191	82	AAGCCTGAAATCAGTTT ~~T~~ TAGAAAAA ~~AAAA~~ AACTTAAAAA ~~AAAA~~ ACCTT TTAAATCTATTATTCTCTCTTTTGTCTGTTTCAATGGGTGTA TGAGTGAAAGCTAAAAATGTAAACATCCTACTGCCCTATACAAAAATAGA ATACTATTATTTTCATCTTTATGCTAGTTACAAGAAAGATAATCTTAA CCTGCAGTAACCT ~~Y~~ ACCTACAGTAGATATAAGTGTTCACATGTTGAA TATACCTATGAAAAATATTTCTAGGTAAACTTATTTATGCTCACAAATCA AAAATATGTGATTAAATATTGTTGGTTTTTTCTTAAACTCCAAGATTG CTAGTATGAATTTTAAATGAAGAATTTCTTTACATAGATTAATTGATT ACTTCATTCAATTTGTGGATTTGAAA
LNPEP Region	rs2161548	83	GTTCATACTTGCTTTCTCTTGTACATTGTTATCTCCAGTGTGTTGAAA TTCTCTTATCCCCAGTTAATTTGTAATTGCTTGAACACTACTTGAT AAAGTGTTCAACTTTAGTATTTTCAGAAAGGAAATATACTCTCCAGTG AAAGAATAAGCTTCAAGTTATTCAGCATAGATAGAACAGGTATAAG TATTATCAAGCA ~~R~~ CAGCCTTCTCAAAGGGATTTTATGTGAGATAGT TATGATTGGATCTCTTAACAACAGTTTAAGGCTTTTTTCGCCCTTAGTG TGTTATGATCTAATTTTATCCAAAAGTGGTGGGTCTCTCTGTATG AATAGTAGGGATAACATCAAACCTTTATTTCCCTGGTCCCTTATGCTTC TCTTCCAAAATCTTCTGTAACTAC
LNPEP Region	rs2161657	84	TCTAGAAAAGTAACAGAATAATTGTGAATGTTTATAAATAGCTATATA TTGTCAGTCAACCATATTTATTTCTGCTTGCTATGTTGTCATGGTCTA TAGAAGGCAGCACTTCCCTTTTCTCTTAACACCACACTAGGATGTC ACGCTGGGGTGGCCCCAGGGGCTCACTATTTGACCTGACTTTCCTTG GTTTCTCTTCTA ~~Y~~ GACTAATCCTACACTTTTATGTTCCCTTGATCTA AAATCTTTAAAAATGTTGTAATTTCTACCATATAACACCTAATCTCTG GCAAAATTTAAGGTTGTCAACTGTATTTCCCCAATGTGTATATATTTG TTGAGCAAACTAATCTTCTCTCTTATAAGAAGAAATCTTGCTCAAT CTCTAGATCATTTGTGCCATATTTT
LNPEP Region	rs2161658	85	TATAATTGTAATCCAATATTTTAAAAATGTGGAGAACTTTACCTAAAA ATCCTGACCTCTGGAATCTCTTAAAAATGATATTTGGCAACTGTGGG TCTTTATCCTGTGGGCCACAGGATAGCTATAAAGGAGAGTGCAGTGG GCCAAACTCTCTTTAGGCCAGGCCTACTTTCTCCCAAGCACCAAAAGT CCCAAATGGCCT ~~S~~ TTTTCATTCACTTAGTGTGGACTCTCTAAGTATTT GAGCTTTTCGACCCACATTTAAAAATGTATTTATGTTATTAGCTGCTA CACCAAATACCGGTGTAATCTCTTAAAGGAAAAAGTACAAATATAGTCT TAACCTTTTATAATTTTAAATGGGTGTTATGAAATCTATTCACTACT TACACTGGAGAAATTAGTATGACGT

LNPEP Region	rs2247650	86	AACTGATTCTAGCCACTTTACCAGTTAGCAAGACTAGTTTATTCATT CATTTCAGTAAATACCTACGGAGAACCCTACTGCGTTTCCTGGCACCATG CCATATGTTAGAAATACAAAGATGTATATAATATAGCCACTGCCTCA ATACAAATGATGGAGGTCAACCAGTAGACAAATAAATACAGTAAAGC AGGTGCTAAGATMAATGTCTTTGCCAGGGACAGAGGGGATTCCAGGA GGAAATAATCAGTTTTGCCAGGACAGTGTTCATTTCTGAGCCTTGT AAATAGTACTCAGGTATGCTGAATATCAGGTAGTAGGAGCAAAGGCA GAGTGATACAACCTGGCATGTTTCAGAAAATGGCAGGTAATCTTGGAT GGCTAAAGCTTAGGTGTAGGCAAGA
LNPEP Region	rs2248374	87	TTCATTATCATGTCTGGATGAATTATTTTCATATAGCTCTTTTAATAA ATGCCTGCATCCATGGCTAATGTGCACGTTTCAGCCAATAATGATGC CTACATTGCAGTGCTCTTTTGTCTTGTCTTTGTAGAGTTGTTTAGAA AGTGATTTTACATCTGGTGGAGTTTGTTCATTTCGGATCCCAAGATGAC AAGTAACATGGT ~~R~~ AGGATAAAGAGAGTACAGAGTAGAAGAGATCTG TGGAAATAGCCTGACCTAGAGTGAGTATGACATACAGAGTAGCCACC TGTCCCTTTTAAAAGCTGGAGAGAAAAGAGAGCCCCACGATTTTCTC TAAAACAAAACCTGAAGGGGAAATGCTTGGGGTATTTAGGGGGACAAT GCTGTTGCTACTATATTTTTTGTGT
LNPEP Region	rs2255546	88	TTTGGGCTAGGGAGTTTCAAAGTTGACTCCACTGAACTATTTGGATA CAAATGGTATTATTTATATGCTTTGAGAAACATTTGATTACACTTGG TTTGAGGCAACTGAGACATCTGCATGGAAGAACAACATTGGATGAA AATGAATACCAACTTTTTCAGAAGATGGGTCCAATTTCTCTTACAA AATCCCATGCTA ~~R~~ TTGCTGCCCCTTTGGACGCTCTGGCAATCGCATGA AGGAGAGCTGCCAAGTTCTGTGTCTTGATAACCTTTCCCTCCATTCC TAGTTCAATTAACCTGAAGAAAAGAAAAATAATTTGTTTCTAAATAGT AGGTATTATGTACATGGACATTAACCTCAAGCCACCAATATATTAATA GAATAGAACAGAAAGAGGCATGATA
LNPEP Region	rs2255633	89	GCCACATATGTGTGATGCACTATACAAGGCATCTTGGGATTTCTTCTG GGCTGAGGAGAGAGCCAAAGAAGGGATGGTGGGAGGGGGCTGATGACT GCATTTAATTCAACTCGGACTTGATGCCAGTGGTTTCTTGCCCTGGAC TGAATGAGAGAAGGCTGTTTCCCATTCCCTTATTCTCATGTCTCTCC CTTACTCCTGGAYAGGATAATTTGGGCTAGGGAGTTTCAAAGTTGAC TCCACTGAACTATTTGGATACAAATGGTATTATTTATATGCTTTGAG AAACATTTGATTACACTTGGTTTGGAGCAACTGAGACATCTGCATGG AAGAACAACATTTGGATGAAAATGAATACCAACTTTTTCAGAAGATG GGTCCAATTTTCTCTTACAAAATCC
LNPEP Region	rs2255634	90	CCAGTACAAAACCTGCATTAAACAAATGAGGCCACATATGTGTGATGCA CTATACAAGGCATCTTGGGATTTCTTCTGGGCTGAGGAGAGAGCCAAAG AAGGGATGGTGGGAGGGGGCTGATGACTGCATTTAATTCAACTCGGA CTTGATGCCAGTGGTTTCTTGCTGACTGAATGAGAGAAGGCTGTT TCCCATTTCCCTTTTCTCATGTCTCTCCCTTACTCCTGGACAGGATA ATTTGGGCTAGGGAGTTTCAAAGTTGACTCCACTGAACTATTTGGAT ACAAATGGTATTATTTATATGCTTTGAGAAACATTTGATTACACTTG GTTTGAGGCAACTGAGACATCTGCATGGAAGAACAACATTTGGATGA AAATGAATACCAACTTTTTCAGAAG
LNPEP Region	rs2255637	91	TCTTACCAAAAATTCCTGAGATTTTCCCCCAGTACAAAACCTGCATTAA CAAATGAGGCCACATATGTGTGATGCACTATACAAGGCATCTTGGGA TTCTTCTGGGCTGAGGAGAGAGCCAAGAAGGGATGGTGGGAGGGGGC TGATGACTGCATTTAATTCAACTCGGACTTGATGCCAGTGGTTTCTT GCCTGGACTGAA ~~K~~ GAGAGAAGGCTGTTTCCCATTCCCTTATTCTCAT GTCTCTCCCTTACTCCTGGACAGGATAATTTGGGCTAGGGAGTTTCA AAGTTGACTCCACTGAACTATTTGGATACAAATGGTATTATTTATAT GCTTTGAGAAACATTTGATTACACTTGGTTTGGAGCAACTGAGACAT CTGCATGGAAGAACAACATTTGGAT

LNPEP Region	rs2278018	92	TGATAGCTAATTTCTTTGGGGGAGCCATTGAACATATTTGAGCATTT CTTAGTTTAAAGCAAGCTTGACAGAGGGCGGATCCAATAAGTTCTTC ATGGCTTCCCACATAGGTCTAGAAGAAACCTATGTTTTATTTGAATT GTGTTTGTGGTCATCATTTTGGAAAGCTAGTTGACAAGTGTTAAAGT ATATCATAGAGA ~~Y~~ GAACTCAAGTGGGTTCCTCTCTATGATATACTTG GATTATGATACAATGGGTAAACATGATTTGAAAGTTACAGATGAGCA CTGAGGAAATGGATTGTAACAGAAGATTCAGGGTGTTGTAAATTTTC AAGACTGACTTTTGCTTTAATACTTCACAGAACCTCTTATCCTTATT GACAACATGCTTAATGGTATCTTAA
LNPEP Region	rs2278019	93	AAACTTGCTTTGATCTCTTCCCTCTTTCTCTTTCTATGTGATTTAAA TGAGCACTGAGGAATTCAGTTAGCTCAGGAAAAATAATTTGTTCCCT CAGAGATGATTCTTGAGTGTAGAAAATAAAATATTTATGACATGCCC CAACAGTGTGGATCATTTCTCTATTCTTTTATCAGGTTTAAACGTTAA CATATCTGCATC ~~R~~ AACCTCTTTCCAGGCTGATCAGAAAGGGCACACA CTGGAGGCTGGGACGGAAGCCAGGTAGAGGGTCCAGGAAAGAGATGG GGAGAAAAAGAAGGAACACAGTGACTGCTCTGTTCAAAAATAGGGGTC CACATGTCCAAGATGCTGTGGCTCCCTGTGGCGGACATCAACGCTCT CATCCATTATGCTCCTCTTCTGTGG
LNPEP Region	rs2287988	94	CATCCAAGGAGATGGAAGTTTCTGTCCCTCTGTCTTTGGATTGTCTC CTCTCTCTTGAGTTATCATAGTCACCTGTCAATTCAGCTCGCCTTTC TGGGGGAAAATGCAGAGGTCAAAGAGATGATGACTACATGGACTCTC CAGAAAGGAATCCCCCTGCTGGTGGTTAAACAAGACGGGTGTTCACT CCGACTGCAACA ~~R~~ GAGCGCTTCTCCAGGGGTTTCCAGGAAGACC CTGAATGGAGGGCCCTGCAGGAGAGGTGGCTGCTTTTCTCTTTAGG TCTAGCTTACCTCATCTCAGTTTCTCTCGTTATTTCTTACGTTTCTC TCAGCTCATCTGGCAACTTTGTAGGATGCTAGTTCCATATAAGAATC AAAGGCCATAAGTAGACTTGATAAG
LNPEP Region	rs2303208	95	GGGAAAGGGGCCATTATCTGGTATTTTACTTAAAAGCACAGAAGTTG AATTGATGCCAGTGTTGGAAATTATTGCAATTTTAAAGAAAATAGAAAT ATGTAATATTTTATGCTTTCAATCAACAAAATGAGATTTGGCATTTT TTGTGCTTTGGGGATCTCAAAAGCAGGGCTTTTGTGTTTCAACAGAG TGTTGGGGTAA ~~A~~ RGCAATGGAGGTAAGAGAGGCTACAGAATACTAGG AGAGGCCATTGCCCCCTAGGAGGTCATCGATTGTCTTTCAGAGTAT GAGGCTTGCTCTTAACCTACCTGCCATAAGTCATAGGCATGGTTATG AAATACTCCAGTTTTCAGTACTGATTATTCCTTTTCTCTTCTGTAG GTTAAGACAATTGAACCTGAAGGAG
LNPEP Region	rs2303209	96	GAAAGGGGCCATTATCTGGTATTTTACTTAAAAGCACAGAAGTTGAA TTGATGCCAGTGTTGGAAATTATTGCAATTTTAAAGAAAATAGAAATAT GTAATATTTTATGCTTTCAATCAACAAAATGAGATTTGGCATTTT GTGCTTTGGGGATCTCAAAAGCAGGGCTTTTGTGTTTCAACAGAGTG TTGGGGTAA ~~A~~ YAAATGGAGGTAAGAGAGGCTACAGAATACAGGAG AGGCCATTGCCCCCTAGGAGGTCATCGATTGTCTTTCAGAGTATGA GGCTTGCTCTTAACCTACCTGCCATAAGTCATAGGCATGGTTATGAA ATACTCCAGTTTTCAGTACTGATTATTCCTTTTCTCTTCTGTAGGT TAAGACAATTGAACCTGAAGGAGT
LNPEP Region	rs2351010	97	CGAGTTATGCTTGGTATAGCTATTAGGTAATTCATTAACCTTGCAAA ATAGATGAAGAAAGCAATTCGAGAAGATCAGCTGAAATCACTGGAA AAACTCAAAAAGGCAAGCCACTAAAATTTGTTGTTGAATTAGGTAGGA GACAACTCTAAAAGACTGGGGAAAAAATTGAAAGTCTAGACAAAT TTGCACTCGGAC ~~Y~~ GCCTTACAGGTGTCCACATTTTCATTTACTTTA TAATAGGTTATAGGGTCAAAAACCTTGCTGAAGCAAAACACACAGGGG TGAGTTTCTGTTTAAATATTGTTCCATTTCTTTCTCTACTTTGCCC TGAAGGCAGGCTTTGGTACAGAGTGGTGTGGAAATGCCAACAGGTA AAATTCCAATGAGTCCCATATTTCT

LNPEP Region	rs2351011	98	TCAGCTCACTGCAACCTCCGCCTCCTGGGTCCAAGTGATTCTTCTGC CTCAGCCTCCCAAGTAGCTGGGACTACAGGTGCGTGCCACCACATTC TGCTAATTTTGTATTTTATTAGAGACAGGGTTTCACCATATTGGC CAGGCTGGTCTCGAACTCCTGACCCCATGATCTACCTGCCCTTGGCCT CCCAAAGTGGTG ~~X~~ GATTACAGGTGTGAGCCACTGTGCCTGGCCAAGT GTCAGGTTTAAATCCTGTCCCTTCCATTACTTGTATATGGCATTG GACAAACAACCTTTTTTAAAAAATAAAATGAGAACTTCAAATCAGATT ATATCTAAGTTTACTTTCAATTCCACAATTTGAACATTTATTTTGAA ATTGTTAAAAACAGAAAGTCACAAA
LNPEP Region	rs248215	99	ACATTTTAATGTATATAAAATATTTGCTACATTCTGTGTGTTATATAA TGTGGTACCCAGTCTCTGCTGGGACATGGATGTACATAATGAAACA TGGAGGTCCAGACGTATGATAACTCTCCTGTTTCCCTTCCCTCATTG CCTACAGGGGCAATAGTTTCATATCTTGGGTTTTTTATTGTTTAAAT TTTTTTTATGGG ~~R~~ AGGGGTCTTTGGGTGGGTAATAGTCAGGGGGAA AGGACAGTGTCTATACTTTTTTAAAGATGTATATAAATGTTTCATGTT ATTGGTTTTGTACCTAGTCCTTTGCATGGATATATAGGTACCTAATG AAAATCGAGGATCAGTGTATGACAAATCTCCCATCTCCCTTTCCCT TATTGCCTGTGTGGCAATAGGAAG
LNPEP Region	rs251339	100	ATCATTACTCTGTGTTTATAAGTGAGAAAACTGATACTAAGGGACAG ATTTGCCCAAAGTCACCAAGTCAGTGAGAAAACTAGTACTTAAAAAT TGTCTTCTAAGTCCAATAGTTATTCAATTATATCACAGCTAGTTCCCT AGTTTTAAGAAAAGTCCCCCATCAATCTTCCCTAAAGGTCCTAGAT TTTGACCAACTC ~~Y~~ CTTCTGACACCAAGGGCCCTGTAGTATTAAAAAT AATAAATTACTGAAAAATATCTTGCCCAACCATTTGTGTACACATAAAGTC AATTCTAATACATGTCAATAGCAACTTGAGAATGAGAAGAATTAGTT GCTGTTATTTTTTCATAAGATCATTTAAAGGCATTTGAGAGCCTTAGC ACATTCTTCATTTTTTCTCATTTGC
LNPEP Region	rs251340	101	GTATGCTGTTAGGTTTGGAAATACAGTATATGTTTTTCTTTTCTCCTT ACCTCTGGGAAGTTATAGAATCACTACAGGAAAAGAGAAAAGAAAGTC ATCACAGGGGAAGAAAGGAAAACTTTTTATTAAACAAAGAGTCATG CTAATCCCCCTGAATATATATATACATAAATTTATATTATTTT AGACAAAGTCTC ~~R~~ CTCTGTGCCCAGGCTGGAGTATAGTGGCACAAT CTCAGCTCACTGCAACCTCCACCTCTCTGGTTCAACCAATTCTCTCTG CCTCAGCCTCCCAAGTAGCTGGGATTACAGGCACACACCACCATGCC CGGCTAATTTTTTTGTATTTTCAGTAGAGATGGGGTTTACCATGTA GGCCAGACTGACCTCAGGCAATTCTG
LNPEP Region	rs251342	102	ACAGGCATGATCCACGGCGCCTGGCCCTAAATTTGTGTTTTCTTAAAGG AAGGTTTACAGCATCATCCAGTGATCAGAAACCCATACTAGCAGTGCAG CAGCCAGAGGTTTTGTTCTCCATTCACTACACCTCTATTGATATTAA ATTGTTCTGTTGAAATATTTAAAGCTTCCCTAAAGACAGATATTTCC CTCGTAAACCAC ~~Y~~ CCTCCTGGATTCTACTGTTATTTGAGGGTTTTGT TTGTTTGTGTTGTTGATTTGTTTGTGTTGCTTGTGTTTTGAAAGGGGT CAGGAAAGAGACTCCAGTCTCAACCTCCTTTTTCACTGGCTTTTTCTTG CCATGTATTACCCCTACTATATCCTGTATATATCCCTCAATTCAAGT AATTTGCAGAGAGCAGCCCTGGGAT
LNPEP Region	rs251343	103	AGAATAAATTGTCTGTGAAAATACTGAAAACATACAAAGGACATTTT TTTCTCAGTTTTTAAACTGTATTCCGCTTTAAAAACTGTTTTCTAGG CCGGGCGCGGTGGCTCACGCCTGTAATCCACGACTTTGGGAGGCCG AGGCGGGCGGATCACAGGTCAGGAGATCGAGACCATCTGGCTAAC ACGGTGAAACCC ~~Y~~ GTCGCTGCTAAAAATACAAAAAATTAGCCGGGCG CGGTGGCAGGCTCTTGTAGTCCCAGCTACTCGGGAGGCTGAGGCAGG AGAATGGCACGAACCCGGGAGGCGGAGCTTGCACTGAGCCGAGATCA GGCCACTGCACTCCGGCCTGGGCGACAGAGAGACTCCGTCTCAAA AAAACAAAACAAAAACAAAAAAAC

LNPEP Region	rs251344	104	AGCTGGAGTGTACGATCGTAGCTCACTGTAACCTTTCAGTTTCTGGG TTCAGGTGATCCTCCTGCTTCAGCTTCCCACGTAGTTGTGACTGAAG ATGTGCACCACAATGGCTGTCTAATTTTTATTTTTTAATTTTTGTAG AGATGGGGTCTCACTATGTTTTCCACACTGGTCTCAAGCTCCCGTC CTGCCGCCTTGG <u>S</u> CTCACAAGGGCTAGAATTACAGGTGTGAGCCAC CACGCCAGGTCCTGGCTGTTTGGATTTTAAGACCAAGGGAAACATAC TATTTGTTGACCCCTCGGTCTCACTGAGGACCTGGAAAGAAATAACA GCAACAGTGTGGCCTTGCAAATCCAAACCTAAAACGTGCTGTCTAA AAAAAGAACTTCAGGCGGGGCGTA
LNPEP Region	rs2548225	105	GACATGTTTTGCTGAGTGTGGTTGGTTACTTCAGGTACAGTATCACA TTAATAGGGGCCACAGTCTATATCCCTGTTTAGTTTGTAGTTACCA CTCAAGAGCAGACAGATATTGTCCACTTTATCCCAATCCCAGCCAG ACTTTGTTGTATGCTGTGCTTCATTCATGGGGCTGTGAAGTACTGAT TATATTCTCCCT <u>W</u> TTCCCTAATGTAGAATGCTTTATTCTACTGCCATC TTTCTGTCTGCACTGTTTAATTAGGCTTACTGATAACAACCTTTAATT CTGAATTTTCTTTCTCATTGAGTTCTATTTGTAATTACTAAGACTT AAAGAATAGTCTGGTGAAGTTACTCGAAGAATTAAGGAAGGTTTGAG CTAAAATGAAGTACAGACCATCTAG
LNPEP Region	rs2548516	106	CACATTTTTGAGAAGTGATGCTAAAAATTTTTTTTTTAAAAAGACTCA CATATCTATAGAACAATTGTTATTTGTAAGATTAAGATGGAATCA CAATTTTATACTGTATTACAACCCACAAATATCTCATTTGTTGCCCA GACTTCCCATTTTTGAAGTTGAAAAATACTTTCAACTGGATACCAAT CTGAACATGAAA <u>R</u> CAAAAATAATTTTTTAAGACAATAAGTCCCTCT TGTTTGATTATGCACCACACTGCGGTAATAAAAGTGATTCATAGGAC CTACATTCATATGAAAAAAAATACTATTTATGTTTTAGTTCTGGGA CCTCAAAATGCCAAAATACCAACCTTTAGATATACTTTAGAATATAT CACAACTAGAAAGTATATATACTT
LNPEP Region	rs2548520	107	ACTATAAAATGAAAATGTAGATACAGCTTCTTTGGGAAATATGGTTA GTTATTCAGCAATGTTTATGTTTAATTTTATGTTTCTGTTTAAAGCA GTGTTCCCTACTTTTTTTGTTACTACATACTCCAGTCAGTAAAGATT TTTTGAGCAAGAAGTTCCTCAATATACATATTTTATTTATAAATTAT ATGGGCTGGGCG <u>Y</u> GGTGGCTCACACCTGTAATCCCAGAAGCTTTGGGA GGCCGAGGTGGGTGGATCACCTGAGGTCAGGAGTTTGAGACCTGCCT GACCAGCATGGAGAAACCTATCTGTACTAAAATACAAAAAATTAG CTGGGCATGGTGGTGCATGCCTGTAATCCAGCTACTCAGGAGGCTG AGGCAGGAGAGTCACTTGAACCCGG
LNPEP Region	rs2548521	108	TATGTTTCTGTTTAAAGCAGTGTTCCTACTTTTTTTGTTACTACAT ACTCCAGTCAGTAAAGATTTTTTTGAGCAAGAACTTCCCAATATACAT ATTTTTATTTATAAATTATATGGGCTGGGCGCGGTGGCTCACACCTG TAATCCCAGAAGTTTGGGAGGCCGAGGTGGGTGGATCACCTGAGGTC AGGAGTTTGAGA <u>Y</u> CTGCCTGACCAGCATGGAGAAACCTTATCTGTAC TAAAATACAAAAAATTAGCTGGGCATGGTGGTGCATGCCTGTAATC CCAGCTACTCAGGAGGCTGAGGCAGGAGAGTCACTTGAACCCGGGAG GTGGAGGTTGCAGTGAGCCAACATGGCGCCATTGCACTCCAGCCTGG GCAACGAGAATGAAACTCCGTCTCA
LNPEP Region	rs2548522	109	ATAAATAATGTATTTATTTAACTTTTTTATACTATATATCATTTATGT TTATAAATTTATAACAATATAAAATTTAAATTAGATAAGAAATAAT AGACACTCTAATGTATTGCACTTCTTGACACTTCCTCATCCCATT TGGATACCACTGTGTTTAAACATTGTGTTTAGTGGGGCAATGTACT TGGTTGAAGTCT <u>Y</u> ATTACGGCCACAGAATGCATCCTTCAACCCAAT GTTTTATATATGGAAGTGTACTACAGGTCAAAGTGATTCATGTT GATAAAGCAGAGCACAGTTACAGCTCAGAAAAAATATGGTTCCAAG TCTAGGCTCTGCACATGGTTGGGCAGGGGCATCATTTCTGTTTAAA ATGAAATCCACAGCATTTGTAGATTA

LNPEP Region	rs2548523	110	TGATTTTTTATTATCTTGAGGACATTAACCAGTTTTTTATTCTAAGTGG GCATATGACTTTTTAAATCCCAAATGTCAACGGATCAATAAGAAGTGT TATTGATGTCTCAGAAAAACACAACACAGAGCATTGAGGAGGGAGC CAGAAATTTGCATTTGTCAAAAGTGACCATATGGTAGAGATTGTAC TAGTCTCCATACMTCTTATTTAACTGTCAAAGCTACCCTCTGAGAT AGTTATTATCCTGATTTTTTTAAGCGGAAATAAATCTCAGAAAAGTT AAGTAACCTTGCACAAGATGACATAATTTGCCATTTGCAGATGGGATT TAACCCATGATTTCTAATGCTTTGGCTACTTCCTCTATACTATATGT ACTTAAATACCCCAAGTGACATTTG
LNPEP Region	rs2548524	111	ATTCTAATGCTTTGGCTACTTCCTCTATACTATATGTACTTAAATAC CCCAAGTGACATTTGAATAATATAATAAAGATCAAATAATTATAATA CATATTGTTTTCATTTTAGTGTATTTTGCTGAACAACCTTTATAACAA TTGGTAACAAACACATTGTAAGCTTCTTGAAGGTAGGCCACATGGTT GTTTTGTTTACCWCTTTATCCTTAGCTCCTACAGCAATACCTGGCTG GCATAAAGGAAATGTGCAACTAGTTACATTTCAAATCCACAAATGAA TGAAGTAATCAATTAATCTATGTAAAGAAATTCTTCATTTAAATTCAT TACTAGCAATCTTTGGAGTTTAGAAAAACCAACAATATTTAATCACA TATTTTTGATTGTGAGCATAAATAA
LNPEP Region	rs2548526	112	TTTGCATTTTTTAGTGCAGACAGGGCTTCACTATGTTGGCCAGGCTGG TCTTGAACCTCCTGACCTCAGTGATTCACCCTCCTTGGCCTCCCAAAG TGCTGGGATTATAGGCGTGGGCCACTGCATCCAGCCAGCACCAGGAAT AATGGACACCATTACATTTTCATGGTAGAGATTGTACTAGTCTCCATA CATAGCACTTACRATGTGAGAGCATGAAACAGGGTTTTGTAATGCCCA GCATGTTTTTTTTTCTATCCTCACTAAAAGGTTTTAGACCTAATGTC TTGCTTGATCAAAGACTTTTACATCAAAGAGAAAAGAACAAAGGGTA GGACAGAAGTCTACATCTACTTTAATTTTCCACTGGATTCCATCCAC TGGGAGAAGAGTTTCAGCAGCTTTCT
LNPEP Region	rs2548527	113	GTCCATCATGTGGTAAAACGATTCCAAGTAACCTCAGACCTTCGAGAA GTGCGGGGCTGCTTGTTCATGTTGGAGGTAGTAAGTCATGTCAAGA GCTTTGTCTAGGGTCAGTCTCCCTGCACTGAAGTATAAAACAAATGT CAGTGGTTTTGTGCATATCTTATAGTTTTTAATATTTTTAACATTAAA ACAAATATGAAAKAGAGAACAATAACAGAAGTAGGTCATTATAGCTG GGCCATTCACTTTAAATCTTAGCTCTGCCACTGACTAGCTGAGTAAT CTTGGACAAATTACCAAACCTCTCTGGACCTATTGCTTCTTTATAC AATGGGGATAATAATACTATCTTCCTCATAGGCTTGTTGTGAGGATT AATGACCTAATATTTTTAAAAAGCAT
LNPEP Region	rs2548529	114	TTTTCCAAGTCTTGCATTGTTAATCTATCTTCTCTTCAATCTACTCA GAGCTTCTCCTTTGAGCAGGCAAACCTCCTTCAACTAGCAATAGCTT GCTTCTTAGCTCACCTTTTCATGCATTCACTCATATGTAGGATGGTGT TTTTCCCTAATTTTGGCCTCCAATGAGCTATGCCTCCAAGATGTTCT GAGACCCACGGGRCTGAGGATTAAGCCTCACTTCCTCTTTTCTTTCT AACTAGAGGATTTTAGTGTACCGAGAACTTTGTCTCAGAGATGTCC TGCTGGTCACTTTCACTCAATTTGACCTAAATAAGCTCCTGAAAGAA AATTATATGTCACATTGAGTAAAGTGAGTGCATCACAGTAATTCTCA GAATAGGGAAAGCTTGCAATGCACA
LNPEP Region	rs2548530	115	TTCCTCAATTTGACCTAAATAAGCTCCTGAAAGAAAATTATATGTC ACATTGAGTAAAGTGAGTGCATCACAGTAATTCTCAGAATAGGGAAA GCTTGCAATGCACAATATACTTCTTGGTCTCAATTCCTCCAGCCA TTGGTGATCTTGTGACCTGATTCATTCCACACATTATTCTGTTTCATG ATACATAGAAAAAGAAAGAAAACACTTTGTCTTCCAGGAAAGTCTA GAGAGGAATGAATGCAAACAGCCATTTATTACTTCATTTCCCTACAA ACGTCATACTAATTTCTCCAGTGTAAGTAATGAATAGATTTTCATAAC AACCCTTTTAAATTTATAAAAGTTAAGACTATATTTGTACTTTTCT TAAGAGATTACACCGGTATTTGGTG

LNPEP Region	rs2548532	116	GGAATTTGGCTTAATTTGATGATGTCCTTGTCTCAAGGTTTGTAGTCAC TAGTCATTGAAATATGTATGTGTAAATAGGTGATCCATTTGTTTCATT TTAGTAAAGAAGGACTCCAGGTAAAGCATGACTTTGTGACGGAAC CTCTCAAATTTTATTAAAGTGTTTAGAAGAAAATTAAATTATACTA TGTATTTTTTAATRTGGCATATATTATACTAGAGGGTAAAATTACATT ATAATATTCTCTCAACAACCTCTGTGAGGTTTAGTCTTTATTCAACAT AAGATGAAAAAATTGAAGCTCAGGATGAGTGTGTACATTTTCTTAAG GTCACACATCTAATAAGTGAGAGAGTGAGGACTTGAATCCAGAAGCA ATCAATTTTAAAGTATGTGCTTTTT
LNPEP Region	rs2548533	117	AAATTATACTATGTATTTTTAATGTGGCATATATTATACTAGAGGGT AAAATTACATTATAATATTCTCTCAACAACCTCTGTGAGGTTTAGTCT TTATTCAACATAAGATGAAAAAATTGAAGCTCAGGATGAGTGTGTAC ATTTTCTTAAGGTCACACATCTAATAAGTGAGAGAGTGAGGACTTGA ATCCAGAAGCAAACAATTTTAAAGTATGTGCTTTTTTCCACTGAACA TTTTTGCCTTATCCATAACCTGTAAAAATAGATTAGTGGGTATTAT AAGACATAAGATAGATTCTGTATTCTTGTATGTAAATAATCTGTC TCTAAATGATAAAAAGCGCAAGAGAACCTCCCACTGAATGAAAAATCC AGATTTTCTTACTAAAAGAGTTATT
LNPEP Region	rs2548534	118	CCTGCCTTAGCCTCAGAAATAGCTGGGATTACAGGCAAGCACCACCA TGCCAAGCTAATGTTTGTATTTCTAGTACAGACGGGGTTCCACGAAT TGGCCAGGCTGGTCTCAAACCTCTGACCTGAAGTGATCTACCCACCT TGGTGTCCCAAAGTCTTGGGATTACAGGCGTGAGCCATTGTACCCGG CCATGAAAGTGTATTTAAACTGTAAACTGCTGCAGAAATATTAAACA ATATTATTACTGTCCCTGGGACACAAGTGCTTGTAAAAAGAAAGGA TCTCTTCTGTCTACAATGACTTAGGGTTCTTCTAATTACAGGTATGA GTTCTCTGGGTCTAATGGTTCTATAAAAAAATTATTTCTTTGCAGTT GGAAATTTTAAATATTTTAATAAT
LNPEP Region	rs2548535	119	CTTAAATTTGCCAGAGATTAGGTGTTATATGGTAGAAATTACAACA TTTTAAAGATTTTAGATCAAGGGAACATAAAAGTGAGGATTAGTCG TAGAAGAGAAACCAAAGAAAGTCAGGTCAAATAGTGAGCCCCCTGGGG CCACCCCAGCGTGACATCCTAGTGTGGTGTAGAGGAAAAAGGGAAG TGCTGCCTTCTAYAGACCATGACAACATAGCAAGCAGAATAAATATG GTTGACTGACAATATATAGCTATTTATAAACATTCACAATTATTCTG TTACTTTTCTAGATTAAATAACAGTCTATCGTTACCAACATATGACT TACATTTGACAGACTGCTCCACAAGTCATCATTCTTAGCATTCTAT AGCTGAACCTCTTTAAGTACTGAAT
LNPEP Region	rs2548536	120	AATAACAGTCTATCGTTACCCAACATATGACTTACATTTGACAGACT GCTCCACAAGTCATCATTCTTAGCATTCTATAGCTGAACCTCTTTA AGTACTGAATTATTCCTTTCTGGAATTTCTCCTCACCAGAAAATCC TTGAGCATATTCAAATACAAGCTCCCTTTAAAAAAGAG TTGAAAAAGAGWTAAAGAAAATGGTAGTATGGTATGTTTTAAAGG AAGCTTAAATTTTACGGAACATGTGTGATGTCTGAAAAGTGAACAAA TAAAAAGTGAAACAAGTAGCAGGAAGTGGCACCAGTGACTTAAACTG CTGATTCTATAGTCATTATTACACTTCTGAAAGCAGAGCTTCCACCT GCACCTGATATTTACTACCTTGTTA
LNPEP Region	rs2548537	121	CAAAAGAGTTGAAAAAGAGATAAAAGAAAATGGTAGTATGGTATGTT TTTTAAAGGAAGCTTAAATTTTACGGAACATGTGTGATGTCTGAAAAG TGAACAAATAAAAAAGTGAAACAAGTAGCAGGAAGTGGCACCAGTGAC TTAAACTGCTGATTCTATAGTCATTATTACACTTCTGAAAGCAGAGC TTCCACCTGCACSTGATATTTACTACCTTGTATAGGAAACTTCATC AAACATTTCTGTATTTGAGTCGGGGTTTCCGCTGGTTTGGAGATAG GGCGGGATGAATTCATGAATCTTTTGTAAATTACTTCAAAACACACA TTCAAAAAATAGTCATCCTAAACAGGGAGAAAAATGTTTAGTTTGTAG TTTCTATTTGACACTGTAAAAGCAA

LNPEP Region	rs2548538	122	TGATGTCTGAAAAGTGAACAAATAAAAAAGTGAAACAAGTAGCAGGAA CTGGCACCAGTGACTTAAACTGCTGATTCTATAGTCATTATTACACT TCTGAAAGCAGAGCTTCCACCTGCACCTGATATTTACTACCTTGTTA TAGGAACTTCATCAAACATTTCTGTATTTGAGTCGGGGTTTCCGC TGGTTTGGAGATWGGGCGGGATGAATTCATGAATCTTTTGTAAATTA CTTCAAAACACACATTCAAAAAATAGTCATCCTAAACAGGGAGAAAA ATGTTTAGTTTTAGTTTTCTATTTGACACTGTAAAAGCAATAGAAAAAC ATAGTAGGTTTAGTAAGATGTTCTTAGAGGTAAGATTTCAATCGATA TTTCTTGGGAGATGTTTCTTTTCTT
LNPEP Region	rs2548539	123	TAAGAATATATAAAGCTTTGGCATTAAAGCCACAAATTCAGTACATAC ACAGTAACAAGAAGAGCCTAACTTTGAATCCATGTCTGTCTATAGTG TACTGGACTAAATATATATCCCAAAGACCTAATTAACCATTACTAAC CACCTTGATATGCAAATTTGTGTAGTGTTCAGACCCTATATTCGTT TTTAAAAAAGACRTACCTGAAGAAATCCCTTCACACATTTTGGGGAA GCCAGCAGACCCTTTGGAAATTCTAGAAAAGTACACCCCCAATGATG TTGATTTTCAGGTTACATGCCGAGAATCTCTATAGTACCTAGTAGCC ATGAGCATTCCTGTGCAGATGTATACAAACAGTGATGTTCTTTCTC TCAACCCACATACACAGTTCTACAT
LNPEP Region	rs2548540	124	GTCTAAGATTTAAAAATATATAAATCAAATAAAAAGGATGCATAAA TATAATTGACATATTTACCCTTTACCTATATTTGATCTGTATTATGC ATTTTAAATATTACTATTCTTTTATGTGCTTTTATGTTTTATTATT TAGTCTATATGCCCTAATACTGCACATCTAGTGTATGTCTCTAAGATT AAAATCTCTAGAYGGACCAAAGCTTCAACAATAAGATTCTAAGATT AGAAGAGCCTGGTTATAGTTACAGAACAGAAAATTATAAGTCTGTAG CTTCTAGAAACAGTTTAAGCACTATTCTTTCTGACAGTCTTCAGA TTACTTTACAAGTGGGCAGCAATCTTCTGAAGGGCATTTCATGGAAAG GGAGAGGTGTTTCTCAATTTGAAA
LNPEP Region	rs2549781	125	GCTAACTGGTAAAGTGGCTAGAATCAGTTTATCCTGTACTTCTTATA TTCACCGGTTTTCAAATTGAGGAAACACCTCTCCCTTTCCATGAATG CCCTTCAGAAGATTGCTGCCCCTTGTAAGTAATCTGAAGACTGTC AGAAAAGGAATAGTGCTTAACTGTTTCTAGAAGCTACAGACTTATA ATTTTCTGTTCTKTAACCTATAACCAGGCTCTTCTGAATCTTAGAATC TTATTGTTGAAGCTTTGGTCCGTCTAGAGATTTTAATCTTAGAGACA TACACTAGATGTGCAGTATTAGGCATATAGACTAAATAAATAAACA TAAAAGCACATAAAGAATAGTAATATTTAAATGCATAATACAGAT CAAATATAGGTAAAGGGTAAATATG
LNPEP Region	rs2549782	126	AGAAGAAAATTGTACAGAGAGAAAAGGGTAGCAAAGAGAGAAGAGAG ATCCTAACTAATAAAAAAAGTTAGTAATATTGTATTTTTTGCTA AAGTTAATAATTTTTATTTGTTTAACTTCTAATAATATTGAGTTTTT ACCTCCTAGTGGTTTGGCAACCTGGTCACAATGGAATGGTGGAATGA TATTTGGCTTAAKGAGGGTTTTGCAAAATACATGGAACCTTATCGCTG TTAATGCTACATATCCAGAGCTGCAATTTGTAAGTTTCACAATCTGT GTATCATACTATATGGTGTAAGAATCATCAATTCACATATAAAATT TCAAGTGAATGTTAAACAGAAAACTACATAATGTTGTGGTTTTTGA ACATATGGCATTTTGTTTGATACAC
LNPEP Region	rs2549783	127	TTGAACATATGGCATTTTGTTTGATACACGAAACAGATCACAGAACT GGATGAAACATTGAAGGTTTTAGAAAACAATCAACATAAATCTGTCA CCCCAAAGTCTGTAAAGAGAGAAGGCAAACTAATACAAATGTAGAAC TGTGTATGTGGTTGAGAGGAAAGAACATCACTGTTTGTATACATCT GCACAGGAATGCYCATGGCTACTAGGTACTATAGAGAGTTCTCGGCA TGTAACCTGAAATCAACATCATTGGGGGTGTACTTTTCTAGAATTT CAAAGGGTCTGCTGGCTTCCCCAAAATGTGTGAAGGGATTTCTTCAG GTACGTCTTTTTTAAAAACGAATATAGTGGTCTGAACACTACACAAA TTTGCATATCAAGGTGGTTAGTAAT

LNPEP Region	rs2549784	128	GTGGGTTGAGAGGAAAGAACATCACTGTTTGTATACATCTGCACAGG AATGCTCATGGCTACTAGGTACTATAGAGAGTTCTCGGCATGTAACC TGAAATCAACATCATTGGGGGTGTACTTTTCTAGAATTTCCAAAGGG TCTGCTGGCTTCCCCAAAATGTGTGAAGGGATTTCTTCAGGTACGTC TTTTTTAAAAAC ~~K~~ AATATAGTGGTCTGAACACTACACAAATTTGCAT ATCAAGGTGGTTAGTAATGGTTAATTAGGTCTTTGGGATATATATTT AGTCCAGTACACTATAGACAGACATGGATTCAAAGTTAGGCTCTTCT TGTTACTGTGTATGTACTGAATTTGTGGCTTAATGCCAAAGCTTTAT ATATTCTTATTTGTAAAATGCATAT
LNPEP Region	rs2549785	129	TTTTTGAATGTGTGTTTTGAAGTAATTACAAAAGATTCATTGAATTC ATCCCCCCTATCTCCAAACCAGCGGAAACCCCGACTCAAATACAGG AAATGTTTGATGAAGTTTCTTATAACAAGGTAGTAAATATCAGGTGC AGGTGGAAGCTCTGCTTTCAGAAGTGTAATAATGACTATAGAATCAG CAGTTTAAAGTCA ~~Y~~ TGGTGCCAGTTCCCTGCTACTTGTTCACCTTTTA TTTGTTCACCTTTTCAGACATCACACATGTTCCGTAAAATTTAAGCTT CCTTTAAAAACATAACCATACTACCATTTTCTTTATCTCTTTTTTCAA CTCTTTTGTTTTTTTTTTAAAGGGAGCTTGTATTTTGAATATGCTCAA GGATTTTCTGGGTGAGGAGAAATTC
LNPEP Region	rs2549787	130	AATGGCCTGTTTCATTCACTTAGTGTGGACTCTCTAAGTATTTGAGC TTTCGACCCACATTTAAAATGTATTTATGTTATTAGCTGCTACACC AAATACCGGTGTAATCTCTTAAGGAAAAGTACAAATATAGTCTTAAC TTTTATAATTTTAAATGGGTGTTTATGAAATCTATTCACTACTTACA CTGGAGAAATTA ~~R~~ TATGACGTTTGTAGGGAAATGAAGTAATAATGG CTGTTTGCATTTCATTCCTCTCTAGACTTTTCTGGAAGGACAAAGTGT TTTCTTTCTTTTTCTATGTATCATGAACAGAATAATGTGTGGAATGA ATCAGGTCAAGATCACCATGGCTGGAGGGAATTGAGGACCAGGA AGTATATTGTGCATTGCAAGCTTTC
LNPEP Region	rs2549788	131	AGAAAGAAAAGAGGAAGTGAGGCTTAATCCTCAGTCCCGTGGGTCTC AGGAACATCTTGGAGGCATAGCTCATTGGAGGCCAAAATTAGGAAAA ACACCATCCTACATATGAGTGAATGCATGAAAGGTGAGCTAAGAAGC AAGCTATTGCTAGTTGAAGGAGGTTTGCCTGCTCAAAGGAGAGCTC TGAGTAGATTGA ~~R~~ RGAGAAGATAGATTAAACAATGCAAGACTTGGAAAA AATGGAGAATATTGACAATTCAGCAAATTAATCTTTTAGGTAGTTGT GAAATCTTTTTTGCTGTTTCTAGCCTATCCACTTAGATTGTCTAAAT TTAGTAGGAGGAAATTTGCAGTTATTGATGCATTGGTGGAAACTAA TCATCTTTTCTTCACTAAGTAGACA
LNPEP Region	rs2549789	132	AAGCGATCCTCCCACCTCAGCCTCCTGAGTAGCTGGGACTACAGGCA CACACCACCATGCCCAACCAATTTTTTAAATTTTTTGGCAGAGATGGC GTCTGCCTATGTTGTCCAGGCTGGTCTCAAACCTTCTGGGCTCAAGCA ATCCTCCTGCCTCGGCTTCCCCAATTGCTGGGATTACAGGTGTGAGC CACTGCACCCAG ~~M~~ ATGGAGAGAGAATTTGATGCAAGAATTGATATTT ATTTTAGTTTCGGTTTTTCATACATTTTAAATGTAATTTAAAGACAGGG GTCTTGGATAAGTTGAGTGGAATTGAAATGACAACCTCAATTTGCCT ATAGAAAAAGCTATATTTGTTTCTTTTAGTCCCACACCTTAAAGAGA AAACCCACATTGGGCGCAGTGGCT
LNPEP Region	rs2549790	133	TCCTCCTGCCTCGGCTTCCCCAATTGCTGGGATTACAGGTGTGAGCC ACTGCACCCAGAATGGAGAGAGAATTTGATGCAAGAATTGATATTTA TTTTAGTTTCGGTTTTTCATACATTTTAAATGTAATTTAAAGACAGGGG TCTTGGATAAGTTGAGTGGAATTGAAATGACAACCTCAATTTGCCTA TAGAAAAAGCTA ~~Y~~ ATTTGTTTCTTTTAGTCCCACACCTTAAAGAGAA AACCCACATTGGGCGCAGTGGCTCACGCCTGTAATCCCAGTACTTC GTGAGGCCAAGGCGGGTGGATCACCTGAGGTCAGGAGTTCAAGACCA GCCTGGCCAACATGTTGAAACCCCGTCTCTACTAAAATTATAAAAAAT TAGCTGGGCATGGTGGTGTGTGCCT

LNPEP Region	rs2549791	134	GATTACAGGTGTGAGCCACTGCACCCAGAATGGAGAGAGAATTTGAT GCAAGAATTGATATTTATTTTAGTTTCGGTTTTTCATACATTTAAATG TAATTTAAAGACAGGGGTCTTGGATAAGTTGAGTGGGAATTGAAATGA CAACTTCAATTTGCCTATAGAAAAAGCTATATTTGTTTCTTTTAGTC CCACACCTTAAARAGAAAACCCACATTGGGCGCAGTGGCTCACGCC TGTAATCCCAGTACTTTCGTGAGGCCAAGGCGGGTGGATCACCTGAGG TCAGGAGTTCAGACCAGCCTGGCCAACATGTTGAAACCCCGTCTCT ACTAAAATTATAAAAAATTAGCTGGGCATGGTGGTGTGTGCCTTCCCA GCTACTTGGGAGGCTGAGGCAGGAG
LNPEP Region	rs2549794	135	TATTAACCTTTTGCTATGTGGTAGACATTATTCTAAATGCTTTTTAA AATATTAGGTCATTAATCCTCACAACAAGCCTATGAGGAAGATAGTA TTATTATCCCCATTGTATAAAGAAGGCAATAGGTCCAGAGAGGTTTG GTAATTTGTCCAAGATTACTCAGCTAGTCAGTGGCAGAGCTAAGATT TAAACTGAATGGYCCAGCTATAATGACCTACTTCTGTTATTGTTCTC TATTTTCATATTTGTTTAAATGTTAAAAATATTAAAACTATAAGATA TGCACAAACCACTGACATTTGTTTATACCTTCAGTGCAGGGAGACTG ACCCTAGACAAAGCTCTTGACATGACTTACTACCTCCAACATGAAAC AAGCAGCCCCGCACTTCTCGAAGGT
LNPEP Region	rs2549795	136	TAGTATTATTATCCCCATTGTATAAAGAAGGCAATAGGTCCAGAGAG GTTTGGTAATTTGTCCAAGATTACTCAGCTAGTCAGTGGCAGAGCTA AGATTTAAACTGAATGGCCCAGCTATAATGACCTACTTCTGTTATTG TTCTCTATTTTCATATTTGTTTAAATGTTAAAAATATTAAAACTATA AGATATGCACAA ~~R~~ CCACTGACATTTGTTTATACCTTCAGTGCAGGGA GACTGACCCTAGACAAAGCTCTTGACATGACTTACTACCTCCAACAT GAAACAAGCAGCCCCGCACTTCTCGAAGGTCTGAGTTACTTGGGAATC GTTTTACCACATGATGGACAGAAGGAATATTTTCAGATATCTCTGAAA ACCTCAAGGTTTGTGTTGCTTTTAG
LNPEP Region	rs2549796	137	ATAAGAGAAATACGAAGATACACTGTTTGGGGAAAGATTGGGAAAGA TGCAGAAAGTTTAGAGTTGAGCCCTTTAGATGGGCAAGAAGCTGTGTT AAGGACTAAATTTAGCCTCTCTGTTAACCATCTCATATTTTCTGCAG CGTTACCTTCTTCAGTATTTTAAGCCAGTGATTGACAGGCCAAAGCTG GAGTGACAAGGGYTCAGTCTGGGACAGGATGCTCCGCTCGGCTCTCT TGAAGCTGGCCTGTGACCTGAACCATGCTCCTTGCAATCCAGAAAGCT GCTGAACCTCTTCTCCAGTGGATGGAATCCAGTGGAAAATTAAAGTA GATGTAGACTTCTGTCTTACCTTTGTTCTTTTCTCTTTGATGTAAA AGTCTTTTGATCAAGCAAGACATTAG
LNPEP Region	rs2549797	138	ACAGGCAAAGCTGGAGTGACAAGGGCTCAGTCTGGGACAGGATGCTC CGCTCGGCTCTCTTGAAGCTGGCCTGTGACCTGAACCATGCTCCTTG CATCCAGAAAGCTGCTGAACCTCTTCTCCCAGTGGATGGAATCCAGTG GAAAATTAAAGTAGATGTAGACTTCTGTCTTACCTTTGTTCTTTTC TCTTTGATGTAA ~~R~~ AGTCTTTGATCAAGCAAGACATTAGGTCTAAAC CTTTTAGTGAGGATAGAAAAAAAACATGCTGGGCATTACAAAACCTT GTTTCATGCTCTCACATTGTAAGTGCTATGTATGGAGACTAGTACAA TCTCTACCATGAAATGTAATGGTGTCCATTATTCGGTGCTGGCTGG ATGCAGTGGCCACGCCATAATCC
LNPEP Region	rs2549798	139	CCCACGCCTATAATCCCAGCACTTTGGGAGGCCAAGGAGGGTGAATC ACTGAGGTCAGGAGTTCAAGACCAGCCTGGCCAACATAGTGAAGCCC TGTCTGCACTAAAAATGCAAAAATTAGCCAAGTGTGGTGGTGCACGC TTGTAATCCCAGCTACTTTCGGAGGCTGAGGTGGGAGAATTGCTTGAA CCTGGGAAGCAG ~~M~~ AGTTGCCGTGAGCCAAGATCACTTCACTGCACTG CAGTCTGGGCAACAGAGAAAGGCCCTGTCTCAAAAAAAAAAAAAAAAA CTTTTCTGTGCCAAATTATTATAAGATGGTATCATAACTTCTCTCG CTATAACTAAATCTGTGAGCTTTTGGAAATCCTTTCTTGAATTCTTC TTTTTAAAAAAGTAATCAAGTTT

LNPEP Region	rs2549799	140	CTATAATCCCAGCACTTTGGGAGGCCAAGGAGGGTGAATCACTGAGG TCAGGAGTTCAAGACCAGCCTGGCCAACATAGTGAAGCCCTGTCTGC ACTAAAAATGCAAAAATTAGCCAAGTGTGGTGGTGCACGCTTGTAAT CCCAGCTACTTCGGAGGCTGAGGTGGGAGAATTGCTTGAACCTGGGA AGCAGAAGTTGCMGTGAGCCAAGATCACTTCACTGCAGCTGCAGTCTG GGCAACAGAGAAAAGGCCCTGTCTCAAAAAAAAAAAAAAACTTTTCC TGTGCCAAATTATTATAAGATGGTATCATAAATTCTCTCGCTATAAC TAAATCTGTGAGCTTTTTGAAATCCTTTCTTGAATTCTTCTTTTAA AAAAGTAATTCAAGTTTTCTTCTTT
LNPEP Region	rs2549800	141	ATCAGCCCCCTCCACCATCCCTTCTTGGCTCTCTCCTCAGCCCAGA AGAATCCCAAGATGCCTTGTATAGTGCATCACACATATGTGGCCTCA TTTGTTAATGCAGTTTTGTACTGGGGGAAAATCTCAGGAATTTTGGT AAGAGCTACTCCTCACCCCTAGAGCCCCCTGTGGAGGTGGCACAGTGG AGACCTTGGTTTCMGGTGAAAGAAACCTAGTCAGGAGTGTTTGGGGAG CCCTCCCTCCAAATTGTTTTGGTTCTGAGTCTTTCTGGGGTTTCAA CTTTGGGGAGAACTGGAGCTCATTTCAATATGTTCTTGGATCTAAAA TATCCCTCAGAAATAACCAATAATGATTAGATTTTGTGGAATGGAA TGTATAAGACAGCATTGCTTTCTGT
LNPEP Region	rs2549801	142	CTCACACAGCTTTGCGTAAGCAAAAAGCACATTTCCACTCCTCTCCC AAATGCTCAAGGAGTTGACGTCCACATGAGACCAAATAGAACTGCT TTAATATGTATGTTTGTGTATGTTTCTTTAAACTCTACTTGAGCC ATTGATTTGTCTGTTTTTCATGATTGTCATTTTCTCCTGAAATGATC AGCCTTAATCTAMAAATGCTGTGGATTTCAATTTAAACAGGAAATGAT GCCCCTGCCCAACCATGTGCAGAGCCTAGACTTGGAACCATATTTTT TTCTGAGCTGTAACGTGTCTCTGCTTTATCAACATGAATCACTTTGA CCTGTAGTACAAGTTTTCCATATATAAAACATTGGGTTGAAGGATGC ATTCTGTGGCCGTGAATGAGAGTTC
LNPEP Region	rs2617434	143	TGATTTTCTGGCGCAGTGCGGGTGTCTCGGCGTCCGGGATCGGGCGG GTCGCAGTAGGGCTCCACATTTGTTGAGTGACTGAACACCGTTCCCG GCCGGGAGAGCGCCGAGCCGGGTCCACTTCAGGTAGGGGCTGGGC TTTCCCGGCCCGCCTAGGCCCGCCCCAGCGCGAACCCTGCTCCCA CCTCGCCTGTCCRCGGAGCAGCAGGGGGTTGACTGTGCTTTTCCCT CTTGCTTCCCTCGCTCTTTCTGCAGCTGCCACGAAAAACCGGAACGG CGGAGCGGCGCGGCCCTCGCGGCACCTCCCTGGCAGCCCTTGGAGG CCGCGCTGGGCATGCTCAGTCAGTCAGCTGGGCCCTCAGCTCTCGGAGT AGGAAGCTCGGGCGCTCCGGCTGTA
LNPEP Region	rs2617436	144	CAGTAAGGAAGTAAGTAGAGGCAGGTGGTAGGGTGGCAGTAAGAAAT GATTCCCCCAAATTAACATATGCTGTTTGTCTAATTTTATATGTGTT GTAGCTTTACCCCTTCAAAAAGAAAGAACTTAGTCTATTTACAAAG GTAGTAAATTCAGTTTGATTTAATTGTGCTTTCAAAAGTAGTGTAAG GGGAAAAGAACCRACCTTAAAAAAATTTCTGTAAGAAATATTATAAAC TCAAAATTTATTTCCATGGCTTTTGACATATTGAAAAATAACTGGGG ATAAATACCTACCTTGACCAGCAACCTTTACACCAGTAGCCATAAAA TGAGGCCATTACAGATAATGTTATTGAAAAGAGGTGAAGTTCAATGCCA TTCGTAGTAATAATAATATCTGGTA
LNPEP Region	rs2617447	145	TAATTAGTAATGTTTGAAGTTGTATCAAAATCAAGAAATGTTTAGAGC ACAGAAGAAAGCAGAATAATTATCTAATAAAAGTTCAAGTAGAGCTTA GGCATTAGCAAAAAAACGCAGCCAAATAAAGTGAAAGGTTATTATTT GGAAAGAACAGTGATATACTAGTTTCAAGATTCCTTGGGCTACAAAAGA CAAACTCTGAGYAAAACTAGTTTAAATGATACAGACATTTATCATTT TCATATAACAAGTCCACTGATAAGATAATCTTCAATCACAGCTCACC AGCCTCATCAAGAGCCCCAACTTCTCTCTCTCCACTCTTCACTCCTCT ATATGAGCAATTCCCCAAAGCCCAGACTACCATATGGTCAAAAGTTG GCTGCAGCAGGGGAGGAAGAAGGAA

LNPEP Region	rs27289	146	AGGAAGGGCATATAGTAATTAATAATTTATCATGTGCCATTCTCTG CTCTTGCCTTTTTTTCCCTAATAAAGGAGAAAGAAAGGGGTATTAG AGAAGGGAATGCTTTTGAACAGGAGTGATAAAGTTCAATAGCATGTA TGATGCTAGCCCTCTGGAGCAAACGTACAGGAAATTTTGTAACCTTT GTAGTAAAAACGKGTTTTTTAGTTTCAGAACTTTAGTTTTTTGTAA AACAGTAGTTGATTTTCGTAGCTCATTGACAAATGGTTTTTAAAAAT CACTGTTAGATTACTTCATCTGGGCTTCTGCCATTTAATATTGCAGT TGCTCACTCTTTTTTGCTACTCAATAGACTGAAAATTGAAGTGTTAA TCTGTTGATGACTATAGTAAATTAA
LNPEP Region	rs27290	147	CATTGGTTTTGAGGGACATCTCTGATGGCTGGAGCCACCTTATCTGT ACTGCTTGCCTCCCCAACACCTCATGCATTATAGAATCCCAAAGCC AAGGATGACAGTGACCTCATGTAAACATATTCTCTGAATAGAATATT ACCAATTTAGATTGATGATAGGCTTAAAAACACTGACGTGTTCCCTTC TCATCTCCCTGGRCATTTCCATTTTGTCTCGTTTTTTATGAAGTGCC CTTCTTACGTCATCCTAGCCATTGCTGCTGTGATTCCCTATAAAATGG TTAATTTTAAAAATGTACTCACTGTAAATTCACAATAGACCTTGTC TAACAAGTTTGAAAAACAAATTCCCATTAAACCAACAAATAAAATTA AAAAAAGAAATCAGATACTCTCTAT
LNPEP Region	rs27291	148	TCCTTCTCATCTCCCTGGGCATTTCCATTTTGTCTCGTTTTTTATGA AGTGCCCTTCTTACGTCATCCTAGCCATTGCTGCTGTGATTCCCTATA AAATGGTTAATTTTAAAAATGTACTCACTGTAAATTCACAATAGACC TTGTCATAACAAGTTTGAAAAACAAATTCCCATTAAACCAACAAATA AAATTAATAAAAAA ¹ RAAATCAGATACTCTCTATGCTATCTCTTTCC TGGCAATATAACTAATTAATAAATAAAATAGTACTATTTCATCTTT TCTAACCCAAGATATTATACTTTTGCTGAGTTAGTAGCAATTTACAG GAGACTTAGGAATAAAAAAATGAGCTATTGTTTATCTTTCTCTTG AAATGCCTCTTTAATCTTGGGCCCTC
LNPEP Region	rs27292	149	GATTGGATGATATTAATGAATAACTATTAGTTTTCTTCAGTGTGATA AGGTATTATGGTTCTGTAAGAGAATGTTCTGATATCTGTGAGTTGCA TGCCAAAGTATTTATAAATGAAATATCGTATCTGTATATCACTTTTA TATTGTTTCAGCTAAAAACAAGAAAAACATGTGTGCGTATGTGTGTTAT ACACACTTGAAA ² R ² TGAAGCAAGTGTGAGAGTGTAAAAAAGCTGTTGA ATCTAGATGAACAGTGTATGGGTGTTGTACTATCTTTTTTTGTAGGT TTGAAAGTTCTTTAAATAAAAACTTAGGAGAAAAAATAAGCTATAAA CAACTATTCTTCCCTGCAGGTCTCATTTTCTTGCTAATTTGGTTAAT TTGTTATAACATCAAACCTAGTTAAT
LNPEP Region	rs27293	150	AAATGAAGCAAGTGTGAGAGTGTAAAAAACTGTTGAATCTAGATGA ACAGTGTATGGGTGTTGTACTATCTTTTTTTGTAGGTTTGAAAGTTC TTTAAATAAAAACTTAGGAGAAAAAATAAGCTATAAACAACCTATTCT TCCCTGCAGGTCTCATTTTCTTGCTAATTTGGTTAATTTGTTATAAC ATCAAACCTAGTT ³ R ³ ATAATGTTAAATATACCTTTAATATTGGATTGAG AAACATTTAAACATTAACCTATCAATAAAGAAGTTTATTTTCTTTCA TTGCTTTATAGGTTTATAGATTGTAAAGTCACAAGGTCAGGAAGTCC TGACATCCTTCCAGCAGTGGTTATAAGTGATACTTTTTTGGCAGGAAA ATAACTTCTAGCTGAGTATATGCAG
LNPEP Region	rs27294	151	GTTTGAAGTTCTTTTAAATAAAAACTTAGGAGAAAAAATAAGCTATA AACAACCTATTCTTCCCTGCAGGTCTCATTTTCTTGCTAATTTGGTTA ATTTGTTATAACATCAAACCTAGTTAATAATGTTAAATATACCTTTAA TATTGGATTGAGAAACATTTAAACATTAACCTATCAATAAAGAAGTTT ATTTTTCTTTCA ⁴ K ⁴ TGCTTTATAGGTTTATAGATTGTAAAGTCACAAG GTCAGGAAGTCCTGACATCCTTCCAGCAGTGGTTATAAGTGATACTT TTTGGCAGGAAAAATAACTTCTAGCTGAGTATATGCAGCATAAAGGTT CCCTACTGCACAGAAGTCATTAATTTTTTTCTGAGTTAACATCACTA AAAGTCCCCCTTAGCTATAGCAGCC

LNPEP Region	rs27296	152	GGTTTATACCATACCCAGTGTGTTTGTGACCATCTTTTGTAGTGAATGA TCAGTCTATGAGATTTTCCATGTCACTTCATGAAGCCTGCTTTATAT ATAAAAAAACTAAAGTGTGTTTATGGGTTTCTAATATTCTGTAGTA TGGCCCTATCATAATTTATTTAATCCATCACGTTTTGTTGGGCTTTT GTTTTTTTCTCTCTCTAAAAATACTGCCACAGTCTTGGAGTGGGGCGT GGTTTCTCACTATAAACAGATAGTATAGCATAGTAGATGAGAACTGC TTTTGTTTCAAGTGTGCGGCTTTGGTATTTATTACTGTGTGACTGTGG GTCAATTAGATAACCTCAGTTTCTTCAACTATAAAATTGAGTTAGGT AGTATTAATAAATACCTACTTTATA
LNPEP Region	rs27298	153	CGGAAATTTTACATTTGTTAACATAATTCCATAGCATGAATCATTT AACAGTAGCATTCATCTAAGTTCTAATTAAGCCTAGCCTTGCTTGG CACCAGGTACTTAGCTCAGCGTGGCTACAGACTATTTTCATAGCAAC CATTTAGCTATGCATATTGAAAAATACCTCTGTATGGCCGGGCGCGG TGGCTCACACCTCTAATCCAGCACTTTGGGAGGCCGAGATGGGCGG ATCAGGAGGTCAGGAGATCGAGACCATCTGGCTAACACGGTGAAC CCCATTTTCCACTAAAAATACCAAAATTAGCCGGGCATGGTGGCGGG TGCCTGTAGTCCCAGCTACTTGGGAGGCTGAGGCAAGAGAATGGTGT GAATCTGGGAGGCAGAACTTGCACT
LNPEP Region	rs27299	154	ATCAGAGACCATCTGGCTAACACGGTGAAACCCCATTTTCCACTAAAA ATACCAAAATTAGCCGGGCATGGTGGCGGGTGCCTGTAGTCCCAGC TACTTGGGAGGCTGAGGCAAGAGAATGGTGTGAATCTGGGAGGCAGA ACTTGCACTGAGCCGAGATTGTGCCACTGCACTCCAGCCTAGGCAAC AGGGCGAGACTCTGTCTCAAAAAAAAAAAAAAGGAAAAATACCT CTGCATTGCCAAGGCATCAGTTAAGAACTCACATTCAGTAGATGCA GATGTAGGTTTTTTGCTTCTTTCTCTCTTTTAAATCAATAATGGCAT TTCTGGGTGTACAGTGTGATCTTCGACAATGTTAAGCGGATTAATTG TCTGCATGTTCTGAACCTCTTCCCTT
LNPEP Region	rs27300	155	AATGTTAAGCGGATTAATTGTCTGCATGTTCTGAACCTCTTCCCTTTT TCTGCCCACCTTTCTTCCACCGACAATAAGTATGCATAGGGCTAC CCCGGTTTCTCAGTTGCAGTTCCGGGAGGAGGATTCCACTCTGGCT TTGGCATTAAAGACTTTTCTTGCCTCAGGAACAACGCTTTACCAG CAGCTGCCTAATTTTCTTGTCTTTGTTTGTGTTTCTTCTGCTTCC CTCTGGGGTCTTATACCATACAAAATATTGTTGCTGGATCAACTTAC CTGTTTTCAACAAAGACACATTTATCTGAGGTTGGTTTTATAAAATG ATAATACAGAGACTGGGCAACCCTCCGCACACCCGGACCAGGCTGCT CAGTTTTAGTGAGATGGTGGATTTT
LNPEP Region	rs27302	156	GTAAAACTTTGAGTGGATGCATAGGGCGGATAGCTAACAGTCACGG GAGCTCCATCAGGACCATTTTACTTTTTGGACTAAAGCAGTTCTT GTAAACACTCAGGTACCTAAGTAGCCAACCTGATGCAGTAGTCATAC AGTACCTAAATCAGTGTGAGAAATGTCATACGTGTCGTATGCCAGTG AAACCAAGGAACCTGTCTTACTTTGAAGGTGAGACATTGGATGTTA TCAGGGAAATACCCCTTGCGTTGATTACATATAAGTAGGAGTATGA GTGCACCTTTTTAGAGGCACACTGCCACGGTTACATTCCTGGTCAGG TCTACAAAAGGAGTTTCTTGGTTCTGTCTGCATGAGTAGCCTTGAGG AAGAACTGAGAATTTCTTAGGCTTC
LNPEP Region	rs27305	157	GAGATACACAGTTTGACCACCTTGGTGGTGCCAGAAATGTGTAAGAA GTCTAATACATGTTCTAGGGGAGCTCATCTGCTGAGCTCTTAAAGAA TTATTTCTGTTTAAAGAGTTACATTTTATTAAACCGACCTCAGGTA AGGGAAATGTATATTTCTTAGTAGAAATTCTAGACTATATATAAGA AATCAGCGTAAGTACCAGTTTTTGTCTTCTCTTTTAAATTTCAA GTTTCATTTAAAAAATATATGCTAACCTTTTGAATATTCATCTT GGATACTCAGAGTTGGCATTTGTTTACTTTGGTAATAGATTCTTAAT TTTCCCATATGCTGTTGTTTAGGAAATGCTAATTTAATGTGGCCAG GTTATAATTGTATCTTTAAATTTAA

LNPEP Region	rs27306	158	GTGATAACGGTGTCAATTCACATTTATGTTGTGGGGAGGGATGAATGT TATGGCTGTGACACAAGATAGAGAAGAAAATACACAAAATGTGTGAG ATACAGTCTATGTCATCAAGTAGCTGAAAGTTCAGATGGTTGGTACT TGTGGAGCAATAAGAGAGGTAATATGTGCTGAGTGGGACAGAATTTT TGCCTAGGATAA ~~X~~ GGAAGAGAACTTTTGGGAGGTAAATGGGAATTGA GTTGGCTTAAATAATTAAAAATATAGGTAAAGAGGAATGTGAAGTATA GGGTAGGGCAGGAATGGAACAATGAGGTCTGCAAAGAAAATGAAGTA CTAATGGGCAAGTGATGTTTTTTTCAGAGAGTCAGTGTGTGACCACAG TGGAAGCCACACGTGAAGAGGGAAA
LNPEP Region	rs27307	159	GTGCCTACTATGTAGTGGGCATTGTTTTTGTCAATTGGAGTTGAGTTT TCACTTTTTCTCTCAGCTTACTGCATAGATGAGGAAATAAATGTGT AACAGATACAGGATGCCATATAAATTGTATTGAAGATGGAGAAATGT GATTTCTATTTCAAACCGGGAAGGTCTTCACAGAGGAGGTGGTGTCT ATTTCAAGGATTG ~~S~~ GAATGATGACAAGCACATCAATGGATATAGTGTG GCCTTAATATTATGCTCCCTGCCCTATACATTTGTTAGTTCCAAGCA TTTTGAAGTGACTCTGCAGGAAGAAGAGAGATTCTGGTTACTTCACAA CACAATATACTAAAATAAGAAATTAATGACCTACCTAGCAGGGAGAC TTTTGAGAGCCTTGTCATTTTATTG
LNPEP Region	rs27397	160	ACTTTCTAGCTGTTAGTCTTTTGGCCAGAAGATATACCTTCCCTACT CTCTGAATTCCTCTTTGAGAAGTTATTACCTAACAGTTGTTCCCAAT CATTGTTTTTTCTCTGATCATATAGTAGTATTTCAATTGAAAGCC ACATTGTTTACTTTTATACTTACTGTCTTAATCTGTTGGCATTTAGAA CATATTTCTGCC ~~X~~ TTCTCATTGACTGCAACTTTTGCATCATGGTGT TTTCCATCCCAAGTAGTTCCCTAACATTATCCTCAGGTTTTTCAGCA CCCACATCAAATTATGCATTGGCCTCTTCACTTCAATACTGCTTCGA CACCCAAAAGCACCTTGGTTTTAGGCAAGCTTATTTCTTCTAATCC TCTGGTTTCAGAAATAAATAGGTCAG
LNPEP Region	rs27436	161	TGCACCAGTGCCTCCCGCCTGACAACAGAGTGAAACTCCATCTCAA AAAAAATAGGTATATAGATAAGATGTCTTTTGGGGGATCTCCTCT AGGTCTGTTATTTCTGAAGCCACCCATCACCATTGGGGAGTATTTCT CTGTTATTTCTCTTTAGGACTTAGAAATCATCTTCTCTGAAACAG GTTTTAAATAA ~~Y~~ ATCTTAGAAAAATGTTATTGTAATTCTCAAAGGT GTTTTGTTTTATGCAGTAACCTCGTCTTTTCGCTGCTGATTTGAGAT AAGCCCAAGACCACACTGACCAAATTACATATTTTACAACACTACTTT CATTTCAAGGATTTTTTTAGATAACATTTTTTAAGGAGAATCTCCTAT TATTTTTTTCTTTTTTCTTTTTCTTT
LNPEP Region	rs27613	162	GTATTCTATTATTTCTTTCTTTTCTCTACTTTTTTTTTTAATAGG GATCTTCTCTCTTGTGATGTTGAAAACTTACCTTAGTGAAGATGTG TTTCAACATGCTGTTGTCTTTTACCTGCATAATCAGAGTATGCATC TATTCAAAGTGATGATCTGTGGGATAGTTTAAATGAGGTAAGTGACC TGGGTAATTTAT ~~K~~ TAGCTCTTACTGTAAAAAGAGAGGAGTTCGTCTA TTTATACTTTTTAGCATGTGTGTAAGTTAATCTGTGGTACAAAGCAT AGTTATTTAAGAAAGGGGGGATGGAGCTTGCTATATAAATATTAT GAATGGAGCACTAAATTTTATGTCAAGAAATGGGAGTGCTGTCTTA GTTGTTGAAAAGACGTGTGTGGGC
LNPEP Region	rs2762	163	ATTCTATAAGAGAAAAAGACACCAATTTTAAAACTTGAGAAAGTACTT TAATTCTGTAGGCAAAGGTTTCAGCAAATCAGCTAGCACTAATCTTGA CCAAATGGGTGAGTCAGCCTCATCAGAGATTTTTTTTTTAATTTA GATGAAATTTACATTTTAAAAACATGGTAACTCCAAGCATCTTCCA AAAACAAAGAAT ~~R~~ AACATTGGAATAGTCACTTACAAGGACTTAACGA CTTGATTAAACATATTTTACACTAAAGTACTAGATGGTCTCTAGTT CATTTTAGCTCAAACCTTCTTAATTTCTTCGAGTAACTTCACCAGAC TATTTCTTAAGTCTTAGTAATTACAAATAGAACCTGAATGAGAAAGA AAATTCAGAATTAAAGTTGTTATCA

LNPEP Region	rs27621	164	TAAAGTATTAGCCAGCCTCTGACTTAAGCAAATAGAGAAAAATCACT GTTTTTAACTATGCTAGTAATACACTAAGAATGCCCATGATAAAGA ATTTAAACAGTACCTAAGAATATAGAGTAAAATATGAAAGTATTTCT CATGATCCTTCACTTCCATTCTCGTTTTCTCTGTTAACAACAGTGTC AGTCCTGGTCTT ~~Y~~ GTATTTCATCTGTGGGAATGGATATTTGTACATAT GTACGTACATACATACACACATACCTACATATTTAACTGCATTTTAA AAACCATATTAGGTTTATACCATACCCAGTGTTTTGTGACCATCTTT TtagtGAATGATCAGTCTATGAGATTTTCCATGTCACTTCATGAAGC CTGCTTTATATATAAAAAAACTA
LNPEP Region	rs27659	165	TTGTACTTAGTCAAAATCATTATGTATATATGATTTCTGTATCTTGC CTTTTTTAACTTAACATATATAGTAATTGACTTAACCTACTTGATTC ACCATTTGTTGTTATAAAATATTGCCCTAATTAAATATTTCAAATCT TAAAGGTTTTTCCATTATATGAAATTTTTTAAAGGAATGCTTTTCAAA AATGAAGACTGCRGTACCTTTTGTGATTTGGTACATATAACCAAATC GCCCTTTTTATTGTGTAGTTACAGTTGATAATGCCACCTGAAATACA TGAATGTGCCAGTTTCATTGCAGTTTACCATAGTGGAGTGTTAAAG CAGCAACAATCTAATTATTTAAAATCCTAGTGGTAGTTGGTAATGTC ATCATATCTTTGATAGCATAGCTGG
LNPEP Region	rs27712	166	TTTTAAGTTAGAAAAATGTATCTGTGTGGGAGTAAAAAGATTTCCCTT TTTAAATCATTTCAGATATCACCATACTTGATTGGGAACCTCCATGT AGATACCTTGAATATTAAAGTACTTCTTTCTACTGCTTTCAAGATAG CAGCACAGCCATCACTAAGTTAAAGCTTATTTTAAAGCTGGGGTTA CCTGAGGTTTAT ~~Y~~ GTCCTTTTCTCTTTTGAATTCCTCTGTGTGAA ACTTACAGGTTTCAGGCATCTTTGAAAATCAGTCAGAGGCAACCTTC CGGCTTCGTTGTGTCCAGGAGGCTTTGGAAGTCATTCAAGTTGAATAT CCAGTGGATGGAGAAGAACCTCAAAGTCTCACATGGTGGCTGTAGC ATGCACAACCGCACCTCATTTTGT
LNPEP Region	rs27747	167	TACCGTGCATTATGGAGAGAAGATTCAAGCATCAGATGAAGAGTTGG GGTGGAGGATTTGGATAACGTTTTGAGGTCTTTCCAGCTCTGAGAT CTTAATAAAGGCAGTAGACTGTGTTTTCTCCCTGCACCCCATTTACT GCTATAGTTCTACCATGAACTTATCACACTGAATTGTAATGCATAT AGTTATTGCTCT ~~R~~ TACTTCGTAGTAGCCTGTGAGTTCTCAGAGGACA GAGGCTCTCATTCCTTTTCCGCTCCCTAGTGTCCAGCCAGTCGCTG CCTGGTTCTTTGTGAGTACTCTGTGAATATTAAATTGAAGTATGTA TCCATAGACACACTACTAGGAAGATAGCAGTCACTGAATTAAACTTT TTCTCAACCCTAAATTGTGTACTCA
LNPEP Region	rs27993	168	TCAATGAGTATTGCCATTGTTCTTCACTGATTTTTTTTTTAAATAAG ATTTCAAGCATGTGATTTTTTTCTCACATTCTTCATTTGTTCCCTAT TTGACAGTTATGAGTAGGATTTGAATTTCTTTTGTCTCCAGTCATT TGGAAATGGTTTTCTATCATAATGCTATTGAGAAGGTAAGGCCAGTGA AGACACCACATA ~~R~~ CAATGCAGTTAGGTATGTCAAGTGGGATCCCCTG CATTGCTTGTCCGTTCCCTTGCATCGTCAGCGTAGCAAGTATTTTCT ACTTCATGTCTCCAGTGACTCAAAAGCTTTACCACCTACACATTC CACAAGGTGCTGTCTGTGTTTCATTGCTTTTGAAACAAACACAAG CGAGTTGACATGTTATACAAACCTT
LNPEP Region	rs27997	169	AAAAGAGAGGAGTTTCGTCTATTTTATACTTTTTAGCATGTGTGTAAGT TAATCTGTGGTACAAAGCATAGTTATTTAAGAAAGGGGGGATGGAG CTTGCTATATAAATATTTATGAATGGAGCACTAAATTTTATGTCAAG AAATGGGAGTGCTGTTCTTAGTTGTTGGAAAAGACGTGTGTGGGCTT GGGTAGCCAGTT ~~K~~ TTTTTTTTTTTCTGTACCTTAACCTCTATTCCT ATTTTGTAGGAAAGTTGTCTTCTCCGTATTAATGAATATTACTATAT TTTCATTATTTGACTTTTTTTCCAGAAATCTTTTTTCTATCCTTAC CCTTTTAGTTTTTCTGCCTCTTTTGAATGATTCTGTACTCTGCTCTA TGAATCTCTTGCCTTTGTGACTGTT

LNPEP Region	rs2910686	170	GTCTCGATCTCCTGACCTCGTGATCCACCCACTTTGGCCTCCCGAAG TGCTGGGATTACAGGCGTGAGCCACCAGCCTATCTTTTTTTTTTTTT TAAAGCATTATAGTCTTTGCACCTTCTTTTCACAATAAATCTTGAAT TTATTTACCCCTTTAGGCAAATTCAGAATTCCTGAACCTAAATCCCAG CTCACCATTAC ~~Y~~ CTATGACTTGGGTAAATCATTTAACTTCTTTAGC CACATTGTGGTCACCTGTAAGATGAGGATTTATAATTTTTGTCTTAC TTTACCTATTGTTTGAAAAATAAAGTGAACAATTATGCAGAAAAAGTAG AAAATAACCTTTTAGAGGTGGCAGAGAAATGCCTATACCTGTGTGT ATGTAATTTGCAAGCTCTTTTGAAA
LNPEP Region	rs2910688	171	TCAAAAATAAATGTTCAAATTTGTGGAATTGAAAGTAAACTTAGATATA ATCTGATTTGAAGTTCTCATTTTAGTTTTTAAAAAAGTTGTTTGTCC AATGCCATATAGCAAGTAAATGGAAGGGACAGGATTAAACCTGACA CTTGGCCAGGCACAGTGGCTCACACCTGTAATCCCACCACTTTGGGA GGCCAAGGCAGG ~~Y~~ AGATCATGGGGTCAGGAGTTCGAGACCAGCCTGG CCAATATGGTGAAACCCTGTCTCTAATAAAAAATACAAAAATTAGCAG AATGTGGTGGCAGCACCTGTAGTCCCAGCTACTTGGGAGGCTGAGG CAGAAGAATCACTTGGACCCAGGAGGCGGAGGTTGCAGTGAGCTGAG ATCACACCACTGCACTCCAGCCTGG
LNPEP Region	rs2910787	172	ATTGGATTTTGTTACACGTTTCATCCTCTTTTAATGGAATCTTTCCCA CTTACACTTTTTTCATGTATCCCTATATATGTAGAGAGGTGTATGAGC TTAACAAAAACAGTTTCAGTAATTTAGGACCACATATCTTTTAGTT AAAATCTTGTCAGTGGTTCCATCTACTGACCTATGCATTTGTAAAGG AAGTGAATTTAG ~~Y~~ TTATATCTTGTCACTCTAGCCTTCAATCACTC TATTCCAGTACGTTTTTTTTTTGTAGTTTCCCTGTTTTCTGTCCAAAGT TGCCACTGGTATGACCTATTTTTTGTGGGCCCTGCTCTCTACCTGTT GATAATTGGTTCAATTTGATGAATATCCTATGTTAACCTGTTTCAGGTA ACATACTTCTGCAACCCATTTAAAA
LNPEP Region	rs2910789	173	AAGAGAAATGAATAGAAGAACCCTAGTTTTGTTGTGTCATGCTAATATGA AATATGGAAACACAGAAGAAATAAAAAAGCAATAAAGTTTTGTCTAA GACAGTATTCTAATTATGAAATAAATGTACAGAACTGTTTCATACT GTTTGCATGTCTACTAATTTAGTGTAACTCCTATTAGGAAACAGC AGTATTAACCCCT ~~S~~ TCTATGAAAACATTAGGAAATTTGAGATTTGAAAG AGTTTAGCCAAGATTACCCAGATGTTGGGATGGACCTAGATGAGGC CTGTGGTTCTTGGCAGTCGAGGTGAGGTGAGTGCAGCTATGTTTTGT CAATTAGTCACCTCATGACTTGAAAACCTGTAGGGCAGCAGTCCCCAA ACTTTTCGGGACCAGGGACCACAGT
LNPEP Region	rs2910792	174	CCTGGTCCCGAAAAGTTTGGGGACTGCTGCCCTACAGTTTTCAAGTC ATGAGGTGACTAATTGACAAAACATAGCTGCACTGACCTCACCTCGA CTGCCAAGAACCACAGGCCCTCATCTAGGTCCATCCCAACATCTGGGG TAATCTTGGCTAAACTCTTTCAAATCTCAATTTCCTAATGTTTTCAT AGACAGGGTTAA ~~Y~~ ACTGCTGTTTCCCTAATAGGAGTATTACACTAAAT TAGTAGACATGCAACAGTTATGAACAGTTTCTGTACATTTATTTCA TAATTAGAATACTGTCTTAGACAAAACCTTTATTGCTTTTTTATTCT TCTGTGTTTCCATATTTTCATATTAGCATGACAACAAAACCTAGGTTCT TCTATTCAATTTCTCTTATTTAGGTA
LNPEP Region	rs2927609	175	AGGAGAAATGGCGTGAACCTGGGAGGCGGAGCTTGCAGTGAGCCGAGA TCGCAAGCCACTGCACTCCAGCCTGGGCAACAGAGCAAGACTCCGCC TCAAAAAAAAAAAAAAAAAAAAAAAAAAAGATAACTAGAAATTACCAACAAT AGTTTTGTAAAAAGATCATTAAGTACGCTTCCAACTTTAATATAA TCACTCTTGCAT ~~Y~~ GTAATACAATATGAAAGAAATAATACAAAAGGGC TCACCTCTCAAGTCTATTTTCATTTTGAATGCTATGAATACACGTAT TTTAAGTATTTTAAGAGTCAGGGGCTTTTTTTTGTGTTGTTTTTTG TTTTTGTTTTTTGTTTTTTTGTTTTTTTGTAGATGGAGTCTCACTCTGTC ACCCAGGCTGGAGTGCAGTGGTGTG

LNPEP Region	rs3096167	176	CTGGAGTCCAGTGGTGTGATCTCAGCTCATTGCAACTCCGCCTCCTG GATTCAAGTGATTCTCCTGCCTCAACCTCCCGAGTAGCTGGGATTAC AGGTGATCCACCAGACCTGGCTAATTTTTTTTTTTTTTTTTTTGT TTTTAGTAGAGATGGGTTTTTACCATGTTGGCCAGACTGACCTCAGG CAATTTGCCCAC ~~Y~~ TCGGTCTCCCAAAGTGATGGGATTACAAGCATGA GCCACCGCACCAGGCCTATAAGTATTTTGTAAAGTAAAAACTATGTA TTTGAATATGTCTCAGGATTTTCAAGAAATGCAAGTAAAAAATAGGA GCTGTGAAATAATTTTTTGATTGTTGGATTTTGTCTTTAACCACAA AATCACACATCAGTTGGACCATAAG
LNPEP Region	rs3096168	177	GGAGTCCAGTGGTGTGATCTCAGCTCATTGCAACTCCGCCTCCTGGA TTCAAGTGATTCTCCTGCCTCAACCTCCCGAGTAGCTGGGATTACAG GTGATCCACCAGACCTGGCTAATTTTTTTTTTTTTTTTTTTGTATT TTAGTAGAGATGGGTTTTTACCATGTTGGCCAGACTGACCTCAGGCA ATTTGCCACCT ~~Y~~ GGTCTCCCAAAGTGATGGGATTACAAGCATGAGC CACCGCACCAGGCCTATAAGTATTTTGTAAAGTAAAAACTATGTATT TGAATATGTCTCAGGATTTTCAAGAAATGCAAGTAAAAAATAGGAGC TGTGAAATAATTTTTTGATTGTTGGATTTTGTCTTTAACCACAAAA TCACACATCAGTTGGACCATAAGTG
LNPEP Region	rs31398	178	CCACTGCATTCCAGCCTGGGCAACTGAGCAAGACTCCATCTCAAAAA CAAAAAAAGAATACCTAAAAACATTTTATATCAGAATTTTTATT CTTTCTAGTGGTATTTCATAAAAGCATATTGCATATGATGCTTTTTAA AATATCATGTGCCCTCACCCCCCACCAGCATGCACAACCTGCAGAA TGGAAATACTTC ~~R~~ ACATGGTATTAACAGGTTTGGTGTTTTTATTTTG GAGAGAGATGAAAAAGGCGTCTGTAGTACCTTAATACCGCAAGTAT ACGTTTATGCAATGACAGCCAATACCAATGGACTAGATTGGATGATAT TAATGAATAACTATTAGTTTCTTCAGTGTGATAAGGTATTATGGTT CTGTAAGAGAATGTTCTGATATCTG
LNPEP Region	rs3214461	179	TACTCATTAATTCTTTTTCAAATCCTTTAAAATAATTTTAAAGACAGT TGAACACAGTCCACATCTATATGAGACTAAGTAGCAGTATATTATAA CTAAGTTCTACATATGAAAGTAAATTTTAGAATGACTGTAGTTTGA ATTTTAGATTCCCAATTCGATAATCTATAGTATTCTATTATTTCTT TCTTTTTCTCTAC ~~/-~~ TTTTTTTTTTAATAGGGATCTTCTCTCTTGTGATGTTGAAACTTA CCTTAGTGAAGATGTGTTTCAACATGCTGTTGTCTTTACCTGCATA ATCACAGCTATGCATCTATTCAAAGTGATGATCTGTGGGATAGTTT AATGAGGTAAGTGACCTGGGTAATTTATTTAGCTCTTACTGTAAAAA GAGAGGAGTTCTG
LNPEP Region	rs33912722	180	TTGGCCAGCAATTACCAGATCATTTTAGGCCAGCAGTGTAATTCCT GTGTTATTTTTTGTACATCATGCTTATAATCATCTCAAAAGATAAA GTAATCATCATTAATCTGTGTTTATAAGTGAGAAAAGTACTACTAAG GGACAGATTTGCCCAAAGTCACCAAGTCAGTGAGAAAATCAGTACTT AAAATTTGTCTTT ~~T/-~~ CTGACTAAGTCCAATAGTTATTCAATTATATCACAGCTAGTTCCCTAG TTTTAAGAAAAGTCCCCATCAATCTTCCCCTAAAGGTCCTAGATTT TGACCAACTCTCTCTGACACCAAAGGGCCCTGTAGTATTAAAAATAA TAAATTACTGAAAATATCTTGCCCAACATTGTGTACATAAAGTCAA TTCTAATACATGTCAAT
LNPEP Region	rs33918743	181	CAAAAACCAAATTTTAAAAATTAGTAGTTTATCACCTAGGCAGAAA ACTTTTCTATTAGAAATTATACAGTCTCTCATCTCAAATACCATGTT TTACTGTTCTAAGAATCAAATAGTGCTATAGTGAAAAAAGAGAGTA GTTTTTTTCTGAACTATCTACTATACTGTATAACATGAGAAATTTT TCAAAAAATATG ~~T/-~~ TTTTTTTTTTCCATAATCATGTCTGGTCTCTTTTTTGAGACCAAGATG AAACCATGTTGCTTGGTCTTCAACCATCAGCTTATCTGTTCTCTAAT GATTTTGTGTTGTTGGTCTTAAAGTTTTGAGAATTCATTTT ATTATAAATGTGAAAGTTCATTTAAATATTGTGTTCTTTTTGTTCCT GTAAAGGAAAAA

LNPEP Region	rs33934033	182	AGGTTGCAGTGAGCCAAGATTGTGCCATTGCACCTCCAGCCTGGGCAA CAGGAGTGAAACTCCATCTCAAAAACAAAACAAAACAAAACAAAACA GAAAACCCAAATTGGTGCCTTCAAGAATATGATGTTATTTCTCAAAGG TACAATCTAGCTGAAATCATATACAAGTAAGTAGGTGTGGACTTTTA CTGTTGAGCTAARGTTTTATGTTTTATATATGTTTTATTCTTTAAGCTA AACAAACATTTCAGATAACATTCTATGCATTTTTTTGAAGCATAGGGTT AGTAATGAGGACTTAGATTTTTTTAATTAAACAACCTCAGTAACTATAT AAAAAGAAAAGGAGTCCCTTATGAATAAATATTTAAATTTAAAGAAA TAGGCAACTATAAAAGTAAGTATTT
LNPEP Region	rs34037881	183	GGCAAAAAGAAACATTCCACTTGAATCTAACACTCTTTACAAAGATT TCCCACCCAATGACTTCAGCTAGACCAGAATGAGTCATAGCCTCACC AAGTCACAAGGTAGCCTGTAAGAAGTAACCTCTTATCTGGACTTGT TGCCTTCCTGAATAAAATCAGGATTCCACTGGAACCAAGGAAGGGAA ATGGGTATCAGGA/- AGTGACTAGCTGTGTCTACTACATCCTGCTCTTCCCTTCCCCACTTG GGTGCTCACTGCACAGCCTGCAGCCATCCACCTAGGACAACCTTTCC CCAGGCTCCTCTCTTTCCACATTCCCTTGGTGACACTTCCCCTCATT GCAGCCACAATCCTCAGGGGCTTGTTTTTCAGGCTCAGCACAGTATTG GATAGGAAAAGT
LNPEP Region	rs34323164	184	TTGATGGGATTGTTTTATTTTCTTGCTGATTTGTTTGAGTTCCTTTT AGATTCTAGATATTAGCCTTTGTGATGATGATAGATTATGAAGATTT TCTCCCACTTTGTGGGTTGTCTGTTCACTCTGCTGATTGTTGAATAA GATGTCTTTTCCCCACTTTATGTTTTTGCTTTGAGAAATTGTTGACA GTTTTAAATCA/- TAATGAGAACTAAAATTGGAGTTAAGAGTTCACCAATGTGCTTTTT CCAAATTATGAATTGTTCAAAAAGTTTCCATTTTCCACCTGTTGAGA TCTTCATTTTGAGGTTTTTATTTTCTACTGTGTCTAATCTACATCCC ACTTTTCCAGGTGAGTATAGAGGGCTTTTTAAATCAATTAGAAAAA AATAAATACTGTT
LNPEP Region	rs34701361	185	AACTAAACATTTTTTCTCCCTGTTTAGGATGACTATTTTTTTGAATGTG TGTTTTTGAAGTAATTACAAAAGATTCATTGAATTCATCCCGCCCTAT CTCCAAACCAGCGGAAACCCGACTCAAATACAGGAAATGTTTGATG AAGTTTCTTATAACAAGGTAGTAAATATCAGGTGCAGGTGGAAGCTC TGCTTTCAGAAGA/- AAGTAATAATGACTATAGAATCAGCAGTTTAAAGTCACTGGTGCCAGT TCCTGTACTTGTTCCTTTTTTATTTGTTCACTTTTTCAGACATCAC ACATGTTCCGTAATAATTTAAGCTTCCTTTAAAAACATACTACTAC CATTTTCTTTATCTCTTTTTTCAACTCTTTTGTTTTTTTTTAAAGGG AGCTTGTATTTTGA
LNPEP Region	rs34815125	186	CTCTTATCAGAACGTAAATGTGCCAGACTCTTAGTTAAATCTCTCC TGGATCAAAAAAGACCTGGGGTGGTGAGTGGCTCACACCTGTAAT CCTAGCACTTTGGGAGGCCAAGGCAGGAAGATTGCTTGAGGCCAGCA GTTCAAGACCAGCCTGGGCAACATAGTGAGAGCCTGTCTCTACAAAA AAATTTAAAAATT/- AAAAAAAAAATTAGTCAGGTGTGATGGTATGCACCTGTGGTCCCAGC TGCTTGAGAGGCTGAGGTGAAAGGATCACTTGAGCCTGGGCAAGGTG GAAGTGAGCTGTGGTCATGCCACTGCACTGCAGCCTGGGCAAGAGAG TGAGACCCTATCTCAAAAAAAAAAAAAAAAAAAGAGATCAGAAAGGT CTTTTCTATAG
LNPEP Region	rs34962665	187	CAGATGCCTTGGTTATGTGCGGATTCTACCGTCATTTATTTTCAGCCC TAGATGGTGCTAAAGTAGAGAGAGACAGATTTTTCTTAAACTATTGC CTTTAAAAATCATTATTTTTTATCCCCATTTTTTTTGTATATATCCA AAGGGTTTTCAACAAGCTGCCCCCTTTCCCAACACCCAGCCCCCTCAA CGAAAACATAATAG/- GAGACACATCATTTAATTTCTCAGCCCTTTCATGATCTCTTAGACTA ATCTTAGTTTTTCATAAATTAAAGGCTACTTGGCTAAGTTCATTAC TTTTTTTTTCTCCTACTTTTCTTGATCTCTGGACCCAGGAATCCCAG ATGATACAAAACCCCTTTGTTTCATACCTGCCCTGCCATAGAATGATC TAGACCTTTAAG

LNPEP Region	rs35199417	188	GAAGTAAGTAGAGGCAGGTGGTAGGGTGGCAGTAAGAATTGATTCCC CCAAATTAACATATGCTGTTTGTCTAATTTTATATGTGTTGTAGCTT TACCCTTCAAAAAGAAAAGAACTTAGTTCTATTTACAAAGGTAGTAA ATTCAGTTTGATTTAATTGTGCTTTCAAAAGTAGTGTAAGGGAAAA GAACCGAACCTTA/- AAAAAATTCTGTAAGAATATTATAAACTCAAAATTTATTTCCATGGC TTTTGACATATTGAAAATAAACTGGGGATAAATACCTACCTTGACCA GCAACCTTTACACCAGTAGCCATAAAATGAGGCCATTGAGATAATGT TATTGAAAGAGGTGAAGTTCAATGCCATTGCTAGTAATAATAATATC TGGTATCCAAAG
LNPEP Region	rs35304156	189	GTAGGTTACTGATTTGCCCAAAGTCATGTGGTTAGTAAATTATAGAG TCTGGGTCTTCTGACTCCAAATCTCATACTCTTTCTTTCTCTTAT CTTCTAGTAGTGGAACCTAAGCCCAAATGAGAGGCTACCACCTC CAAGTGGTGGTTGTATATGTGCTATATTGATTGGTACCTGAAATATG CACACCAGGGCCAT/- TATATTTGCCGTGATTATAGCCACGCTGGGATGATCTCCCAAGTTCA GATCTAGTTATTCTTTTACTTAACCTGAAAATCTGCATTTCTCCTTGT TTCTTTTATGCTTTTCCACCAACCTGTAATCGAGGACTTTTCTTTT TTTTTCCCTTGAGACAGCATCTTGCTCTGTCGCCAGGTTGGAGTGC AGTGGTGCAATC
LNPEP Region	rs35475916	190	ACTACCTCATAGAAGAAAATATTTAAAGCTCTTTCTGACTTCATTG TTTATATATGCCATCTTTTTTTTTTTGTTTAAAGAAAACAAGATCT CACTCTGTCAACCAGGCTGGAATGCAGTGGCATGATCATAGCTCACT GCAATTTTGAACCTCTTAGGCTCAACTGATCCTCCCGCCTCATCCTCC CGAGTAGCTAGGMC AACAGGCATACATCACCATGCCTGGCTTAATTT TTTTGTAGAGACAGAGTCTCTCTATGTTGCCCATGCTGGCTTGAACCT CCTGGCCTTAAGCAATCCTCCTGCCTTGCCCTCCTAAAGCACTGGGA TTACAGGTGTAAGCCACGATGCCAGCCTGTATATGTCAACTTAGTC TTAAGGAATGTTGTTTGAATTCTGT
LNPEP Region	rs35562078	191	GTCTCACTATAAAAAATTTCTAGGAAAAGAACATGCAAAGCCTGATAA AATGATGTTTTCTTTTTCTCTTCTCTTCTTAGTAAAGAGGAATATA CAAAATTCACTAGAATATAATTGATTAACTTAGAGCTGGAACTGGG CCAATACATGATGAAAGTAGTGTCTGTTACTTCTCTCTCAACTGT GTTATTTCCCTTGCT/- CTGCTGCTGCTGCTATTTTAATTCCTGCCATTTCTGGGTTTAGAGAGT CCACATGAAAACCTTCTGTCTTACGTTTGACCTGAGGACAGCTGAG CCTTCTTGGTTTCTTAATGCTCCTCAGTGAGAATTACTCTTAATTTAACT GCATTTTTATTTTTTCTATTCTCAAAAGAAAGGTAGCAGAGAGGGTG ACTTCAGGCTTC
LNPEP Region	rs35929998	192	AAATGAGGTTTTCACCATGTTGGCCAGGTGAACCTCTGACCTCAAGTG ATCCGCTCACCTTAGCCTCCCAAAGTACTGGGATTACAGGCATGAGC CACCGCGCCCAGCTGAAAGTATATATACTTTCTAGTTTGTGATATAT TCTAAAGTATATCTAAAGGTTGGTATTTTGGCATTTTGAGGTCCCAG AACTGAAAACATTA/- AATTAATAGTTTTTTTTTTCATATGAATGTAGGTCTATGAATCACT TTTATTACCGCAGTGTGGTGCATAATCAAACAAGGAGGACTTAGTTG TCTTAAAAAATTATTTTGGCTTTCATGTTCAGATTGGTATCCAGTTG AAAGTATTTTTCAACTTCAAAATGGGAAGTCTGGGCAACAAATGAG ATATTTGTGGGTTGTA
LNPEP Region	rs36019589	193	AACCCCTTTGTTTCATACCTGCCCTGCCATAGAATGATCTAGACCTTT AAGAGGACTAGAATCAGCCCTCTTTTTCTGGGCTTTCTGGGGCCAGG AATGACTAGGATTGATCTGCTTTCTCAAGCTTTGCCCCGGGCCAAC CAGGTCAGCCTGGGACCAGCCGTTGGGTTTACTATACCTGGAACA GATGGTTAATCTTA/- TTGGCTTGCTATAATGTAATTTCCATTTGGCTGGCAGTAGGGAAAGG AAGTACTTCTGTAAAGCTACACACTGATTTTCATCCAGGTGTTTAC ACATACCGGGTTTATGAAAGAGAGCTTGACCTCGCATTCCTGATT AGCATTTTGTAGTGTGAAAGTAAGGTATAGACACAGAGACAGGTAT AATCACAATAATG

LNPEP Region	rs3734015	194	CCCAGGATCATCAACCCATCAAATTTCACTTGAAGTATTTTCATTATG GCCATGTAAGCACAGGTTCCAACCTGAAGGAAGAGTGATTTTGCCCTA GATTGGAATGCCAGAGTACCAGGGGATATAAGGAGAAATATTTTATAG TAGAAATCTTTATTTGTAAGGTTTCCAATTCTGTGCTTCATGTGTCT GTATAGTCACCTTCCCTTCTTTCCCAAATGACATTTGAAGGCTTTGC TTTGAAAGGTTTGTAGAGGATAAAATTTAATGGCTACTTCTCGTAATAA AATTCAGTATGCACACCACAGTTCAGAGACTGAGTACTGTGCTACT TGACGTTGTGTTAGGTTTGTAGTCTCTAAGTTCCCCCTCTAGAGGTA AATGAGATGATTTATTTTGTTCAG
LNPEP Region	rs3797796	195	TCAAAGCCATTTTTTTGTCTTTCTCTCTTTTAATTTTGCTTAGTTCT ATTAGAGAAGCTTTTATAAATTTTCTTCTCTGAGGTATGATTAGAA TACATATTTATACTGGTAGATAAAGTAATTAAGGGATGTATTTCTTG TTTTTACACATAGCTTACATTTCTGGGGATAATAGGCATTATAGAA GGAGAACTAAAGRCAAGAAGTTTCAAGTTCCCATTGCAATTATACAT TTGTGTTCAATCCCAGATCTCACGCAAGAATTGAAATGCAGGGCCAG TATGCCATTTATTTTAAAGTATTACATAGAGGGGAAAAATAAAATAAA AATTTATTTATCTGAATAGAATTATGGATCTTGCTTGGTCTCTTTCTC CATTTAAGAAGGATCAAAAAGTTTC
LNPEP Region	rs38029	196	CGTCTGCCCTTTTTCTTGTGTTGATTTGTAAGAGTTCTGTATATATCCTA GATATGAATCTTTTGTGGTCATGTATATTTGCAAATATCTTCTCCC ACTCCATCTTGCTTTTTTTTACTCTCTTAATGATTTTTTTATTAATAT GAGTTTTAAATTTTAAATGTAATCTAGCTTATGAAATCTTTTCTTACC CCTAGATATCTTSTGTCTCTTCTGAAAACCTTATCATTTTATCCTT TACATTTAGATCTGTGATCCATCTGGAATTGATTTTTGTGGATGGTG TGAGGTAGACACCAAGATTCATCTTTTTCAGTATGGATATCCAGTTA TCCCCAGGACCAGTATATTTTATTCATAGAATTATGTTTGAGGTAA TTAGTATGATATCAACACCATTGG
LNPEP Region	rs38030	197	ATAACAGAAATTTATCTCTCATAGTTCTGGAAGCCAGAAGGCCAAA ATCAAGGTATTGGCAGAGTAAGGTTTGCTCCTTCTGAGGAAGAATCT GTTCCATTTCCCCTCTCCTAACCTTCAAGTGATTGCCAGTAATCCTTGG TATTCCCTGGGCATGTAGGTGACTAACCGTGGCCTTTGTCTCTGTCAA CACAGTGTCTCY/- CTGTGTTTCTGTGCCCCAAATTGCCCCATCTTATAGTTAAGGCCACC ATAATCCAGTATGACCTCATCTTAACTTGATTGTACCTGCAAAGACC CTATTCCCTAAATGAGGTATATTCATAGGTCCCAGGCAGACACAAAA TTTGAGGGGATACTATTC AACCTAGTACAGGTAGCAATAAATAAGAT TAGTGCATATCA
LNPEP Region	rs38031	198	TCATATGGGAGACTAACTAGTAAAATTGCTCCCCTGTAATTCGGTGGTG TAACTGCTCAGGAATTAGCCACAGCCATCTTCAAGTGTGAGATTTCC TTTGCTTCCAGGACTTCAAGTGCCATTCTTTCCATTGCTGCCTTTGT GTTTTAGTAAACTCTCAATGAGTATGCCATTGTTCTTCACTGATTT TTTTTTTTAAATARGATTTCAAGCATGTGATTTTTTTTCTCACATTCT TCATTTGTTCTTATTTGACAGTTATGAGTAGGATTTGAATTTCTTTT GTTCTCCAGTCATTTGGAATGGTTTTCTATCATAATGCTATTGAGAA GGTAAGGCCAGTGAAGACACCACATAACAATGCAGTTAGGTATGTCA AGTGGGATCCCCCTGCATTGCTTGTC
LNPEP Region	rs38032	199	CCTACTTTAATTTGTGGTTGGAAAATTCATAAGGTTGCCTACATTC CCTCATTTTGTGTCTGCTGCAGACTTCTCTAATGACTTACTACTGAC TTTGTTCCCACTAAGCTTTCTTGGGGGTCCCTCAACATGGCACCCCAT GAAGCCATTTCAAGTATCTTTGAAGGGATGTGCGAGCTAGAGCTCCTT CTGTGGATGTATYGTGTAGCAGTAGAGTGGAGCAATCCCAGGTCATAA GGAAGGATTTTGGTTTTGGAGGTGTTCTAATGGGAGAAGCAGAACCA ATGTGACTATCTTTAACTTAACATTTATTTGGTCATCTTTGGGACTA AAAACCTCTTGAGGAGTTTCACTGTGCTCCATATGTCTCAGGATGA AGGATGGTACAACAGACTGAGACTA

LNPEP Region	rs38033	200	TTTGGAGGTGTTCTAATGGGAGAAGCAGAACCAATGTGACTATCTTT AACTFAACATTTATTTGGTCATCTTTGGGACTAAAAACCTCTTGAGG AGTTTCACTGTGCTCCATATGTCCCTCAGGATGAAGGATGGTACAACA GACTGAGACTAGGAGCCATGCTCTTTGCAGAAATTCATACAGAGAGG TTATAATATGCTTGGCATCTTTTACCATTTATTTCCATTTTGAATTTTC AGTTTCTCAGTTTGTGTTTATTTGCCATTTATTCCTATAGTTACAGA ACTGCTTTTCCCCCTTTGCTTGTAGAAAGTCATCAGTCGTTCTAGATG ATGGACTTGTTCAGGATGAGTTTTCTGAGAGTGTGAAGATGAGCACT TACTTGGTTGCTTTTCATTGTGGGAG
LNPEP Region	rs38034	201	CTGTCTTTTCCCCCTTTGCTTGTAGAAAGTCATCAGTCGTTCTAGATGA TGGACTTGTTCAGGATGAGTTTTCTGAGAGTGTGAAGATGAGCACTT ACTTGGTTGCTTTCAATTGTGGGAGAGATGAAGAACCAGAGTCAGGAC GTAAATGGAACCCCTGGTATGTTGATGTGGTAATTGTCTGAAAGCCCTG TGTCACAAGAGGCTCAGAGGACCTCTTGCTTTAACGATTCCTGGTAT TTGCTGTGTGAAATAAATAAGCTTTTAGATCACACTCTGACATTTTA TACCAGAAATGCTACTTTTTTTGCTTAGCTGTTATTTACTGTTACTAG TTTAATAGCTGAAAGTCAATAATTTTCAAGTTTAAAAAATTTTACT TTTAAAGAGAATTTTAGTAAGACAC
LNPEP Region	rs38035	202	AAACAATTATTCTTGATGATAGAAATATGATAGAATGTCTTAGTTTTT TGTTTTTCGTATTTTTGAGCTCTACCAGGGAATATACGCTAGTTTTG GGTTTCCTTTCTAGACTAAAGAGCTTTATATTAATCACAGGATACCTT GGATCTTATCATTTTGGCTACTTCAAAAGGGTATATGTTTCCATTTAG AAAAGACTATCAAGTCTATCCCATACCTTTCAGAGATAAGGACAGAG ATAAGGATTTCTCTGGTGATTTATCAGTAATAATCTGATGCCTTTA ATGATGCTACTCAAAAAGTAAACTAAGTTTTTAATGGTAAGTGTAGA CTGTAATATTAAGCGCTAAATAATGGTTCACCTCACCTTTGGATTGAA AGACTTTATGTCAAGGATTTTTTCAG
LNPEP Region	rs38036	203	ATAAGGACAGAGATAAGGATTCTCTGGTGATTTATCAGTAATAATAC TGATATGCCTTTAAATGATGCTACTCAAAAAGTAAACTAAGTTTTTAAT GGTAAGTGTAGACTGTAATATTAAGCGCTAAATAATGGTTCACCTCAC CTTTGGATTGAAAGACTTTATGTCAAGGATTTTTTCAGAATCCTTTCA AAAGGATATTAATTAAGTGGCTTAAATCTGAAATAATTCATTAATCC ACTTCAGGTGTGCACTACATATTTAGCCTTTGATTTAGAGTTTGCA GCCTTGATAAAGCCTAAGAAGCCCAATCTAAAAGAGTCAGGTTTGCT GCTGCTTCAAGACTCAGCTGAATACTACGTTCTCCATGAAGCATTTT TTTCTTTCCCCCAGCTGGAATTAATC
LNPEP Region	rs38040	204	TCTGTTCACTCTGCTGATTTGTTGAATAAGATGTCCTTTCCCCACTTT ATGTTTTTGCTTTGAGAAATTGTTGACAGTTTTTAAATCATAATGAG AAACTAAAAATTGGAGTTAAGAGTTCACCAATGTGCTTTTTCCAAAT ATGAATTGTTCAAAAAGTTTCCATTTTCCACCTGTTGAGATCTTCAT TTTGAGGTTTTTTTCTTCTACTGTGTCTAATCTACATCCCACTTTTT CAGGPGAGTATAGAGGGCTTTTAAAAATCAATTAGAAAAAATAAAT ACTGTTTTGTAAAACCATTTGCTTTGAACATGGCTGTTTAACACTTG CCTTTTGATACTTCCCTGAATAAAATGTTTATAGTTTGTGCGCATCATA TATGTTTAATTTATTCATTTAGCCA
LNPEP Region	rs38042	205	TTATCTAGTATCCCACCTCTCTTAATTACACAGAATATTTTGGCCAA ATTCCCAATTCTGAAACAAGTAGTTACCATGTTGACAGGGGTTGACA ATGATATGGAACTACATATTCAGAAGACACTGAATTCGGGTTTAG AGGGTTTGGGTCAGTGGCAGACAGAACTCTGTTATGACTCTGTTCTG TTATATATAAATTAAGCTTAGAGCATTTTAAGCAGGTTTTCAAATCCT GAAATAACTGCTCTAAGTTTGGTATAATAACAGAACCCTCAAGTTTTTA AATTTTCTTTATTGACAGGTCCACTATGGTCTTCAAAAATCACACCA GTAGCTCTAATTGGAATAGATTTAATAATAGCTAACTGAACCTCCTGAT TTTCTTGTGTTTAATAGTACCTGT

LNPEP Region	rs38043	206	ATACGAGATTGAGATAAAAGGTTGCTTTGCATGTTCAAGCACCAGCA ACGATCCAGTGTTATCTGAAGTAGAGTAAGCAGAGGAGAAAGTAGTA GATGAAGTTAGAGGGACTGTAAGAGGCCAGATTATTATAGGGTCTGC TAAGCCATAGTAAGGACCTTGATTTTATTTCTAAGTGAAACGAAAAGC AATTTGATCAGG R AAGTACCGTGATATGGCTTATTTTGTAAAGATC ACTCTAGTCTTCAACAGTACATGGAGTAAAGAGGACTAGTTAGGAAG TTATTTGTAATAGATGGGTGGCGAGATAATGGTAGCCTGGACAAGGGT GGAACTTGTGAAGGTGATGGAGGTACAACCTGGACTTGGAGTGTGTTT TAAAGATTGATCCAGTAGAATTTGT
LNPEP Region	rs38044	207	TCCCAGCACTTTGGGAGGCCAAGGTGGGTGGATCACCTGAGGTCAGC AGTTCAAGAACAGTCTGTCCAACATGGTGAAACCCCGTCTCTACTAA AAATACAAAAATTAGCTGGGCGTGGTGGTGGTGGCTGTAATCCAGC TACTCAGGAGGCTGAAGCAGGAGAAATCGCTTGAACCCAGGAGCGGA GGTTGTAGTGAG Y GGAGGTTCGCACCACTGCACCTCCAGCCTGGGTGAC AAGAGTGAGACTTCATCTCAAAATAAAATAAAATAAAATAAAATACT TACAGTAGAGTGATGATTAGAAGATGGCTCAAGAGAAAAATGGAAAGA GAGCAAATGGAGATGGCAAATTTGAGGACAACCTCTTTTGAGGAGTTT ACTACAATGGGGGAACAAAAAACA
LNPEP Region	rs3849749	208	ACTCGGGAGGTTGAGGCAGGAGAATCACCTTGAATCCAGGAGGCGGAG TTGCAATGAGCTGAGATCACACCACTGGACTCCAGCCTGGTGACAGA GTGAGACTCTGTCTTAAACAAAAACAAAACAAAACAAAACAAAA ACATATAAAGATGCTCTTTACTATCCATTTCCATCACCCACCGTCAG TGGICCAGACAC W CTTTCTCCATGCTTCCGCTTAAGCTTCTCAGCAC CAAGTATTGTGTTGCTTCTGTCTCTCATCCCTCTCCATTTCCCTCTC CCTTGCCATGTGTGTGTGCATGTATGTATATTGTAGACATCAGTTT AGCTCCCCCTCAACACGGAAGAATCTATCATTTGGTGTGCATACTGG CAGTAGAGGGTGGGAGTTAAAAAGA
LNPEP Region	rs3849750	209	AGTTGCAATGAGCTGAGATCACACCACTGGACTCCAGCCTGGTGACA GAGTGAGACTCTGTCTTAAACAAAAACAAAACAAAACAAAACAAA AAACATATAAAGATGCTCTTTACTATCCATTTCCATCACCCACCGTC AGTGGTCCAGACACACTTCTCCATGCTTCCGCTTAAGCTTCTCAGC ACCAAGTATTGT R TTGCTTCTGTCTCTCATCCCTCTCCATTTCCCTC TCCCTTGCCATGTGTGTGTGCATGTATGTATATTGTAGACATCAGT TTAGCTCCCCCTCAACACGGAAGAATCTATCATTTGGTGTGCATACT GGCAGTAGAGGGTGGGAGTTAAAAAGAAAATTTGGCCAGCAATTACC AGATCATTTTAGGCCAGCAGTGTA
LNPEP Region	rs3909451	210	GTTGACCATAACCAGTTAATCTTATTTACAGAGGATGTGGAGAGTAAT GATTAATATGTTGAGCTGATGAAGTAGACAAGTGGCTGCTGTATGTA GAAGTAATGTTGGAACAAATAACGTCCCAGAATAGTTTCTGTAAG GCTGATTTTACTCTGAAATTTTAATTAATTTATAGTTAATATAACTA CCTCTGTATTT K TTGTAGTCTTTTGTGGGTAGAGTTGAGGAAGAGA TAGGAATGGGATTATTTTGACATGGCTCATGATCACCAAAATGTGAT CCTTGTCAGTTTACCTAAATATCAATGTAATTATGTTTATCTAATT TAATAATTTGCTGAAATCTTCCCTTATTTTACTTTTATGAAGCTT TTAGCCATTTATATTAGATGGTGAT
LNPEP Region	rs39602	211	TCATTTTGTTGCCCATTCAGAGAGCTTGTAAGCTTGGGCTCTGCCGC TTTTGCAAAAGCCAAGGTAAAGCCAGGATCGCTGCCAAGTTGTTTGC ACTCTTTGGAGTCTAGTTAGCTCAGGGCCTGACTGATATTTTTCATC CATCTTTTCTGAAGTGTCTTTGGGCAGTATGTAGTTATTTATTACAA AATTATATTCAC S TAAATGCCAACCATCTACAAAAACAATGAGTAAT TTTTCTACTTTGAAGATACACAGATGGGGACAAAACCCCTGTTTGG AATTCCTGTTCTATTCCTCAGTATCCAGAAAGTTACTGACACAGTAAA ACAAGGAAAGTTCTACCTAAGAGCCGCCATCACTTCAGGCCGCTGG TTTGTCAGCCATCTGTTGCTTCTTA

LNPEP Region	rs3985004	212	TTGACATGTATTAGAATTGACTTTATGTGACACAATGGTGGGCAAGA TATTTTCAGTAATTTATTATTTTAATACTACAGGGCCCTTTGGTGTG AGAAGAGAGTTGGTCAAAATCTAGGACCTTTAGGGGAAGATTGATGG GGGACTTTTCTTAAAAC TAGGA ACTAGCTGTGATATAATTGAATAAC TATTTGGACTTAGG/- TCAGAAGACAAATTTTAAGTACTGATTTTCTCACTGACTTGGTGA TTGGGCAAATCTGTCCCTTAGTATCAGTTTCTCACTTATAAACACA GAGTAATGATGATTACTTTATCTTTTGAGATGATTATAAGCATGATG TGACAAAAAATAACACAGGAATTTACACTGCTGGCCTAAAATGATCT GGTAATTGCTGGCCAAA
LNPEP Region	rs42983	213	GAGCAGGTGATCAGTTATATCAAATGCTATCAATAGGTTGATAAGAT GAGCCTGAGAATTCACATTTGTATGGCACCAGGAAGTTTACCAGTGA CCTTGATAAAAATACTTCCGGCCGGGCATGGTAGCTCACGCCGTGTA TCCCAGCACTTTGGGAGGCCAAGGTGGGTGGATCACCTGAGGTGAGC AGTTCAAGAACA ^S CTGTCCAACATGGTGAAACCCCGCTCTACTAA AAATACAAAATTAGCTGGGCGTGGTGGTGGTGCCTGTAATCCAGC TACTCAGGAGGCTGAAGCAGGAGAATCGCTTGAACCCAGGAGGCGGA GGTTGTAGTGAGTGGAGGTGCGACCACTGCACTCCAGCCTGGGTGAC AAGAGTGAGACTTCATCTCAAATA
LNPEP Region	rs430827	214	TACCTCATAGAAGAAAATATTTAAAGCTCTTTCTGACTTCATTTGTT TATATATGCCATCTTTTTTTTTTTGTTTTTAAAGAAACAAGATCTCA CTCTGTCACCCAGGCTGGAATGCAGTGGCATGATCATAGCTCACTGC AATTTTGAACCTTTAGGCTCAACTGATCCTCCCGCCTCATCTCCCG AGTAGCTAGGCC ^M ACAGGCATACATCACCATGCCTGGCTTAATTTTT TTGTAGAGACAGAGTCTCTCTATGTTGCCCATGCTGGCTTGAACCTC TGGCCTTAAGCAATCCTCCTGCCTTGGCCTCCTAAAGCACTGGGATT ACAGGTGTAAGCCACGATGCCAGCCTGTATATGTCAACTTAGTCTT AAGGAATGTTGTTTGAATTCTGTTT
LNPEP Region	rs4360063	215	TTGTTTTGGCTGGCGATCACCCCTGCTCAGGTTTCAGACCTTAGTTCTG TTTACCATCTGTGGCCAGTGGCTCCAATGTTAGTTTAGTTCTCCTA GCCTTTGTATGGTAGGCAGAATAATGGTCTCCAAAGATGTCCATTTT CTAATCCCTGAAGCCTTGGTAATATTTTAGGTTACATAATGAAGAGG AGTTAGGTTGCA ^R TTAGAGTTGCGGTTGCTAATCAGCTGACCTTAAA ATAAAGAGGTTATCCTGGATTATCTAGTTAGGCCCAGTGTACTCATA AGGTTTTTAAAGTGAGAAAGTGAGGCAGAAGAGTCAGTATCAGAGT GACAAAGTGTGAGAAAGATTACGCCTGCACCTTGTGGCTTTGATGATG GGAGGGGGGCCCCAAGCTAAGGAATG
LNPEP Region	rs4869314	216	CTCTATTTTAAACATTTTAACTTTATCCTTTATCGTCACCACAATA ATGAGCTGTTGTTCTTTAAAGCAGTGAACATAAATACTCTGTTACACA GAGAGCCATGCTCAACACTGTGCTTCGAGAACACATGGGCTGCTTCC TTTGGTTCAAATCTCCCCACTGGCGCATTTTAGGTGTTTGTATCAT GAGTCACCAGGA ^K CTCTAAAGCACTTAACTGAGTCTGGGGATTCTTA ATCTTTCTGCCAGTTGTTTGTAGGGAAGTGCTCTGTGAGCTCTACCT CTGAGGCTCCATGCTCCCTCTGGCCCTCCCTTTAATAGCTTCTCTTC CACGGAGATGCAGTCAAGTGCTGAAGCAGCAAACAGCACTGGAATTT TTGCCCCCACTTTTTTGTCTTCCCA
LNPEP Region	rs4869315	217	ATGAGCTGTTGTTCTTTAAAGCAGTGAACATAAATACTCTGTTACACA GAGAGCCATGCTCAACACTGTGCTTCGAGAACACATGGGCTGCTTCC TTTGGTTCAAATCTCCCCACTGGCGCATTTTAGGTGTTTGTATCAT GAGTCACCAGGAGCTCTAAAGCACTTAACTGAGTCTGGGGATTCTTA ATCTTTCTGCCA ^R TTGTTTGTAGGGAAGTGCTCTGTGAGCTCTACCT CTGAGGCTCCATGCTCCCTCTGGCCCTCCCTTTAATAGCTTCTCTTC CACGGAGATGCAGTCAAGTGCTGAAGCAGCAAACAGCACTGGAATTT TTGCCCCCACTTTTTTGTCTTCCCA

LNPEP Region	rs4869316	218	TAGCACCTAGCATATGTTGATCTTATAATAGTGATTAATAAGCAGTT AATGATTGATTAAAGAACTTATGGTCTGTCTTTGGGATTTCATGTAGA TAATAGGAAAGGCAAAGCAGAAAAATTCAGTTAATTCAGATGATTCT AATAATTATTAAAAATATTTTAAAAATTTCCAAGTCAAAGAAAAATAAT TTTTTATAGAAC S ATTAGACCCAGAGAACTCATACCTGTAATTAGAA GAACCCTAAGTCATTGTAGACAGAAGAGATCCTTTCTTTTTTACAAG CACTTGTGTCCCAGGGACAGTAATAATATTGTTTAATATTTCTGCAG CAGTTTACAGTTTAAAGACACTTTTCATGGCCGGGTACAATGGCTCAC GCCTGTAATCCCAAGACTTTGGGAC
LNPEP Region	rs5869737	219	TGCCACCCAACCTTTTAAGATCCAGCTGAGATTTACCTCCTCCTTAC AGACTGTTCCAGCCCTCATTTCGTTTGCCTGTCTGTCTAAATTCCTTAGC AGTGCACCTATAAATCTGTTCCACATAATAGTACCCCTCTTTTATTGTT TTTATTAGTTCAATAATGATAATGTGCTTAAGAACAAAAATTGTGTC TATTCTTTTTTT T/- ATGTGATAGCACCTAGCATATGTTGATCTTATAATAGTGATTAATAA GCAGTTAATGATTGATTAAAGAACTTATGGTCTGTCTTTGGGATTCA TGTAGATAATAGGAAAGGCAAAGCAGAAAAATTCAGTTAATTCAGAT GATTCTAATAATTATTAAAAATATTTTAAAAATTTCCAAGTCAAAGAA AATAATTTTTTA
LNPEP Region	rs5869740	220	GAAATGCCTATACCTGTGTGTATGTAATTTGCAAGCTCTTTTGAAAA TTTTTGGGAAGACGAAGTGGTTTTATTGTTTCTTTATTTTTGAACTG CCTCGCTCTGTACGCCAGGCTGGAGTGCAGTGGCACCATTCTGGCTC ATTGTAACCTCCACCTGCTGGGTTCAGCAATCCTCCCGCCTCAGCC TTCCAAGTAGCT G/- GGACTACAGGCATGCACCATCATGTCCGACTAATTTTTGTCTTGTGTT GTTGTTATTTTTTGTAGAGTCAGGGGTTCTGGCATGTTGCCTAGGCT CGTATTGAATCCTGAGCTCAATTGATCTGCCCACCTTGGCCTCCCG AAGTGTCTGGGATTACAGGTGTGAACCACCACACTCGGCCAAGACAAA GTGTTAGTAATT
LNPEP Region	rs6556942	221	GATICTCATAAGGAACACGCAACTTAGATCCCTCACATGCGCAGTTTC ACAATAGGATTTCATGCTCCTATGAGAATCTAATGACACCTCTGATCT GGCAGGAGGCGGAGCTCAGGCAGTCATGCTCTCTCGCCCACCGCTCA CCTCCTGCCATGCAGCCAGTTTCTAATAGGCCATTGACAGGTACTG GTCCGCAGCCCT R GGGTAGGGACCCCTGTTGTAGAGCATATAAAAA CTGAAGAAAGTTTCATAGCATATAAAGATTAGTGCTTGGGGTTTCTG ACAGTGACAAAACAATTTTTTCCCTTTGGAATTTAGGATATACTTCT TATCCTGTCTTTTTTCGCCTCTTGCCCTCAACTCCAATGCATTTTCC TTACATAAATTTAAAGGGACCATCA
LNPEP Region	rs6859160	222	TCTTGAAAATCCTGAGACATATTCAAATACATAGTTTTTACTTACAA AAATACCTTATAGGCCTGGTGCGGTGGCTCATGCTTGTAATCCCATCA CTTTGGGAGACCGAGGTGGGCAAATTGCCGTGAGGTCAGTCTGGCCAA CATGGTGAAAACCCATCTCTACTAAAAATACAAAAAAAAAAAAAAAAA AAATTAGCCAGG Y CTGGTGGATCACCTGTAATCCCAGCTACTCGGGA GGTTGAGGCAGGAGAATCACTTGAATCCAGGAGGCGGAGTTGCAATG AGCTGAGATCACACCCTGGACTCCAGCCTGGTGACAGAGTGAGACT CTGTCTTAAACAAAAACAAACAAACAAACAAACAAAAACATATAA AGATGCTCTTTACTATCCATTTC
LNPEP Region	rs6859168	223	TCCTGAGACATATTCAAATACATAGTTTTTACTTACAAAAATACTTA TAGGCCTGGTGCGGTGGCTCATGCTTGTAATCCCATCACTTTGGGAG ACCGAGGTGGGCAAATTGCCTGAGGTCAGTCTGGCCAACATGGTGAA AACCCTCTCTACTAAAAATACAAAAAAAAAAAAAAAAAAAAATAGCC AGGTCTGGTGG K CACCTGTAATCCCAGCTACTCGGGAGGTTGAGGC AGGAGAATCACTTGAATCCAGGAGGCGGAGTTGCAATGAGCTGAGAT CACACCCTGGACTCCAGCCTGGTGACAGAGTGAGACTCTGTCTTAA ACAAAAACAAACAAACAAACAAACAAACAAACAAACAAACAAACATATAAAGATGCTCT TTACTATCCATTTCATCACCCACC

LNPEP Region	rs6868302	224	CACCTTAGACATGGATGTCTATGCATAGACATGGATGTGCAGGAGGTG AATGGCACTTCAGAGGACAGGTTCCCTGTCAGCCTCTTTGGATTACCG TCCCAGCTCTACAACCTTCAGCCTGGGTGATCTGGAGCAAGTTACTA AATCATTATGTGTTTTTATTGCTTCACCTATAAAATGGCACCTGCTT CATAGAGTGGGCRCAAGTATTAAATTAGATTTTATACGTAAGCATTC AGCACAGTGCCTGGTAAACTGTCAAAAAATGGTGGCCGTTTACATTT TTTCTGCATAAAAAGTTTTGAAGGACTTCAGTTAATTCAGAACATAAA AGTGGGTTCATGAAATAAAAGTAGCTCTATACCTTGAAGGCCAAGAAAA TTTGAATCTAATTCATTTTTTCTA
LNPEP Region	rs6871162	225	CTTTGGCCGTTTCAGTCAGAGGGGTCCATTCCGGTCAGTTGAGGGGCCCT AGAATTTTATTTTTTGGTTTACAAAAATCATTCCAAAGATCCTCTTTAGA GGAAAAATTTATAGAGATTAGTGGGAATGATGAGGAGAACTCAATCT TGAGAGCTCAATCAAAAGGAGATGTTTAAATATCTTTTAAAGTTGGT ATTGGTAAAGTGMTTTTGAAGACAGAAAGAATGTAATACATGTCTGGT GTCTGCTTGTCTATAATTGTCTGGAAGGGCCCTCAATGATGAAATAAG GGAGGCTGCCATGACACTTGAGTCTTGGTGAGAGGAGCTAGTGTGTC CACATTTATCAAGATCACCTGCAGGAGTTTGGGCTGGCCCCCTCTTA TTAGTAGTTTCTCTGTTTTTTAAAC
LNPEP Region	rs6873441	226	AAAATACTTATAGGCCTGGTGCGGTGGCTCATGCTTGTAATCCCATC ACTTTGGGAGACCGAGGTGGGCAAAATTCCTGAGGTTCAGTCTGGCCA ACATGGTGAAAACCCATCTCTACTAAAAATACAAAAAATAAAAAA AAAATTAGCCAGGTCTGGTGGATCACCTGTAATCCAGCTACTCGGG AGGTTGAGGCAGRAGAATCACTTGAATCCAGGAGGCGGAGTTGCAAT GAGCTGAGATCACACCACTGGACTCCAGCCTGGTGACAGAGTGAGAC TCTGTCTTAAAAACAAAAACAAAAACAAAAACAAAAACATATA AAGATGCTCTTTACTATCCATTTCCATCACCCACCGTCAGTGGTCCA GACACACTTCTCCATGCTTCCGCT
LNPEP Region	rs6874656	227	GTGCTCATGCTTGTAAATCCCATCACTTTGGGAGACCGAGGTGGGCA AATTCCTGAGGTTCAGTCTGGCCAACATGGTGAAAACCCATCTCTAC TAAAAATACAAAAAATAAAAAAATAAAAAAATAAAAAAATAAAAAA CACCTGTAATCCCAGCTACTCGGGAGGTTGAGGCAGGAGAACTCACTT GAA'TCCAGGAGGYGGAGTTGCAATGAGCTGAGTTCACACCACTGGAC TCCAGCCTGGTGACAGAGTGAGACTCTGTCTTAAAAACAAAAACAAAC AAACAAACAAACAAAAAACATATAAAGATGCTCTTTACTATCCATTT CCA'TCACCCACCGTCAGTGGTCCAGACACACTTTCTCCATGCTTCCG CTTAAGCTTCTCAGCACCAAGTATT
LNPEP Region	rs6879678	228	CTTTGTGGCTTCATCTCCAGCCACACTGGACAGCCACCCCCAGTTTC TGACATGCACTGCTCTCTGTGTTCCTGGACCAAACTGAGGGTCAG GCTGCTATTTTTTGTGCCCCAAAAACGAGATGCAGATGAACTGGGAA GAGACTTTTTATTTCTATAACCAGTTATATAGGGAGAAGGCTTGGA ATTATTGCCAGAMCAACTCAAAATTACAAAGTTTTCAGAGCTTATA TACCTTCTAAACTATATGTTTACGTGTAAGTGTGCATTTCTCTAAAG ACATAAGTGATTAACTTCTTTTAAATCCATAACTAAGGTCCGAGTCTT GAAGACCTTCTCTTGAGCCTCAGTAAATTTACTTAAATCTAAATGGG TCCAGGTGCTGGGGTGATTACCCCTT
LNPEP Region	rs6887500	229	ATTGGAAGAGGAGAAATCAATGATGAAGATGAAAGAAATGTGGAGATT GGGGGTAAAGGAAGAAGCTGATAGGCAGAGATTTTAAAAATGGTCAT GCCTTGATCCTTGCAAGTCTTTGGTTCAGAAATGAGCTTCAGTTGGA GACCAGGACACTGTTGTATGAGGTTGAAGACAGAGTCTAGGTTGGAA GGGGACAGGTAGRTAGGTCTGGTTGGATTAATGGAATTTGGGGGCTCA GGGGACAAATGAGTTAAGATTGGCATTTGGGAGCCTTGCCAAGAGAT AGAAAACATTTGCCAGAAATTTAAGCATACTGTCTTTTTTATAGTCA GAAAATTCAGTCACTCGTAAGTTGGGACTGTTCACTTGTCTGAATGT TTTAGATTTAAAGAAAAATATAGC

LNPEP Region	rs716848	230	AAAGAAAGGAAGGAAGGAAGGAAAAAAGGAAGGAAGGAAGGAAAAAG AAAAGAGGGAGGGAGGGAGGAAGGAAGGAAAGGAAGGAAGGAAGGAGAAAAG AAAAGTAGATCTAACTTATTTTGGGCATGTGTATTAGTTTACTAGTG TTAGCAATGGCAAATCCGTCGGGTCTGCAGAACTCTATTTTGCCT TCTTGGAGGAAA ~~K~~ AATTTCTGCTGAGGGGCATAAGGCAGAGAGACTGA GGCAACTTTTAGAGCAGGAGTGAAAGTTTATCAAAAAGTTATAGAGC AGGAATGAAAGGAAGTAAAGTACACTTGCAAGAGGGCCAAGTGATACC TGAGAGATCCAAGTGCACGTGTTTGGCCCTTGACTTGGGGGTTTTTACA CATTGGCATGGTGCCAGGATTCTG
LNPEP Region	rs7700332	231	ATTGAACCTTTTCTCCTAGATTTTCTTTTTCCTCTCATTTAGT TCTTTTCTAGTCTTGATTTCCCCACGGAGAGTCTCATCTATTCACAT ATCTCATTTTTCCTTTTAAAAATACATCTTCCTGCTTAATGATGG GGATACAATTGAAAAATAATAAACACGCTCTTCTTCAGGGATTCTTT TTTATTTATAAT ~~R~~ GCTACTCTAAAGACTCACTAAATACAAATGCAATA TCGGACCACCTTAAGATTGCTTTCTAATGATTTTGTTTACTTAGGG TTCACATTTTCTTGTTCATTAAATGTCTAGTAATTTTTTATTACAT ATTGAATAGTGTCAATGGCACATGGTAGAGATGCTGAATTAAAAAA ACTCTGTAAAAATGTGATTTTCTC
LNPEP Region	rs7703341	232	AAAATACCTTGAAATACTTACTTGACATTATAGAAAATTTAGCCCTTCA CTCTGCTGATGTTTATAGTTAAGTGTGAGAAATACTTTTATACAGAA GACCTTGTATGGTTCCCTTTGTGTGAGTGGACAGAAATTTGTGAGCAA AGACCTGGAATCCAGCATATGAGAAATGTGCAATAATTTGTTCAAATGA ATAAGCTTCTCA ~~R~~ AATTTGGCCTTTGTATAATTAAAAATCAGAGTGCTG AAGTGTGTCATATTCCTCATTTCTTCTCATTTCTTGCAAGTCTCTCTCT CTCTCTCTCTATATATATATATACATATATACATATATACATATAT TACACATATATACATATATATACACATATATACATATATATACATATAT ACATATATACACATATATATACATA
LNPEP Region	rs7713127	233	AGAATACAACCTGGATTTTCAGATTTGCTTCTGCATTTCAGTCAGTTGT AATAGCACAAAGTCATGTAGCCTGTGGAAAACCTCTGCTGTACACTCAT GAGAGAAGTGGAGTGAAAAATGGCATATAACATATTATGATGAAAATAG TTTTGACTCTGAAGGCCCTCTGCAAGGGTATCAGGGATTTCTAGGTG TACCCATATCAC ~~R~~ CTTTGAGAACATTAATCTTGCGTTTTTCAGGAAC TGGAGAGGAATAGTTTAGGAGTCCACAGAAGGTAGAAAGTGGAGCTG TTGGAATTTGGGCAGCAAGTTTCTTAAGATAGATCTAGGTCACAGGAG GGGAATGTTCTGGCCAGGCATATTTGACTGGCCACATTATCAGATGC CTTGGTTATGTGCGGATTCTACCGT
LNPEP Region	rs7716222	234	TTCCATCATCTGGTGATTGCGTTTTCCATTGAGGATTGTTTACATTT TCTTGGTCCCTTTGTATTTCAAGTAGTTGTGGCTTGCACTCCTGGACAT TATGGGTGTTATATTGTGTAGACTCTTTTATCCTCTGAAGAATGTTG ATATTTTTGTTTTGGCTGGCGATCACCCCTGCTCAGGTTTACAGACCTTA GTTCTGTTTCA ~~M~~ ATCTGTGGCCAGTGGCTCCAATGTAGTTTATGTT CTCCTAGCCTTTGTATGGTAGGCAGAAATAATGGTCTCCAAAGATGTC CATTTCCTAATCCCTGAAGCCTTGGTAATATTTTAGGTTACATAATG AAGAGGAGTTAGGTTGCAATTAGAGTTGCGGTTGCTAATCAGCTGAC CTTAAAAATAAGAGGTTATCCTGGA
LNPEP Region	rs7719705	235	AGAGCCACAAAAACAATTTCCCAAGCCAATTAAATTCAACTTTTAAAA AGGAATTTCCCTAATATACCATAGAGTTGGTGAGAAGGCAATGAATGG GTCCCACAAGCTTTTCATGTAGCCTTATGGGAAGAGTAAAGGTTAAGC TGTTGTCATGGTTGTCAACTGGGCAAAGCCACTGAAAGGCAGGACTCT CTATTAGTTGAC ~~R~~ TAACAAAAATATTAATAACTAGTGTATGAATTAG TTGCAGTATGAGCTGAGGTATGAAAGCATGAATTTTAGACCTGACAC TATCCAGGAGGGAAAAAAGTGGATGTTTCTGTACTGATGTTAATCAA AGGTAAAAATCAAATGACATTTTGAGGAAAACAAACCTAAACAAC CATTAATGGCCACACAACCTAAATT

LNPEP Region	rs7722694	236	ACGCATGTGCTACCATGCCTGGCTAATTTTATATTTTAAAGTAGAG ATGAGGTTTCACCATGTTGGCCAGGCTGGTCTCAAACCTCTGATCTC AAGTGATCCGCCCACCTTGGCCTCCCAAAGTGCTGGGATTTTCAGGCG TGAGCCACCTGGCCTGGACTGTAATTGAGGATTTTCTGTGTCTATAT TCTCAACTGTTG ~~Y~~ TGGTGTGCTACAGAAAGAGGAGGAAATTTTTTTTT AATCTCTGAGGCGAGTAAAGGAAACCAGAATACTACAGGACACCTAA TTTTTTCAATCTTCATGAAAATGCAAGCTGTGAAATTTGAGGTTTGGT ATCGTGAAAGCCAGAGTCTGTACAGATAATTCGCAGCAATTAATGACC ACCCTTCTTAATAATCTTCCATCAG
LNPEP Region	rs7726445	237	GTAATCCTAGCACTTTGGGAGGCCAAGGCAGGAAGATTGCTTGAGGC CAGCAGTTCAAGACCAGCCTGGGCAACATAGTGAGAGCCTGTCTCTA CAAAAAAATTAAAAATTAAAAAATTTAGTCAGGTGTGATGGTA TGCACCTGTGGTCCCAGCTGCTTGAGAGGCTGAGGTGAAAGGATCAC TTGAGCCTGGGC ~~W~~ AAGTGGAAGTGAGCTGTGGTCATGCCACTGCACT GCAGCCTGGGCAAGAGAGTGAGACCCCTATCTCAAAAAAATTTT AAAAGAGATCAGAAAGGTCTTTTCTATAGAATGTTCCACACAAGAG ACAGCTTTGCAGGGCCATTTCAAATAGGTCTAAGAAATATATTTTG GGTAAAATACCTTTATTTCTTTCA
LNPEP Region	rs7731592	238	GGATTGATCTGCTTTCTCAAGCTTTGCCCGGGCCTAACCAAGGTCAG CCTGGGACCAGCCCGTGGGGTTTGACTATACCTGGAACAGATGGTTA ATCTATTGGCTTGCTATAATGTAATTTCCATTTGGCTGGCAGTAGGG AAAGGAAGGTACTTCCGTGAAGCTACACACTGATTTTCATCCAGGTG TTCACACATACCC ~~R~~ GGTTTATGAAAGAGAGCTTGACCCTCGCATTCC TGATTAGCAATTTGTGTAGTGTGAAAGTAAGGTATAGACACAGAGACA GGIATAATCACAAAATGGTTGGAGTCTTTTATTTGTGTCTTTTCTTA GAGCAAAATTAATAGAGGAGTTTGATTAGCACCTAAGACTTGCCTAA AACTGAGTTACTAATCTTTTCTTCA
LNPEP Region	rs7733312	239	TCCTTCCCTCCCTCCCTCCCTTCTTCTTTTCCATCCTCCCCCTCACCTT TCCTTTTCTGTAAACTTTTCCATAGCAAATAGAGTAATTCCAAATC ATTTTGTGGAACATTCTTATTAGTGTTTCATTACAGCTTCCCTTTCCAC TGAAATGAATTTATTGAGTACTTGGAGTATTTCAAACCCATAGCTTT GTACAGAGAAG ~~S~~ AGTGCTAAATAGGAAACCCCTCTCAGTGTTAGAGG GAAAGGAAGATGATGTGGAGGGAAGGAGTCTCTTACTCTGAAGCATT TTCAAATCAACATTAAAGAGTGAACCAACATTTACCTCCTTTCTTC TTTCATCTTCTTATTTTCATAGCTAGAGAGCTGCTGTGCGTTTGAGAC CTAAGTGGTGCATTAATCAATTT
LNPEP Region	rs7736466	240	TTTTGTTTTTTACTCCAGATGTGTTGATAGAGTTAATATAAGAAAT GTTTGTGTTGGCATAATGCAAAGGTTATTTTGTATTCTGAACCCATA GCAGTTTCTAACCGGTGTTCGTGAGTTTGTGCTTGCTTTTATCTTG AGGTTAAGGATTGCTCACCAAGCCTTTGATTACTAGGTACATTGCAG AATAAATAAAAT ~~S~~ GTGTGCTAGTGTATACTCTGTATTAATCTGTCCAC AGCAGCATTTGTCAGTGATCTCAAGGTTCTCTGTAGACATTAGTATTG GGTTATGGCATGCTAAAATAGAGATAATTGAGACTATAAAGTTCCAA GTTGAAGTTATCAATAACAACCCATAAATCTTCCCTTTCTTTTCC TTCTAAAATAAGACATATGGTAATC
LNPEP Region	rs9127	241	TCATCCCCACATGTGGCAAGACAAGTTGGCCCTTCTTACCCAGAG GTCTTTTGTGTGACTGCATCTTCTCCCTCCGTTCTCCATTGTGTGCT TTCCATTTTGTCTTTAGTGCCATATACTGTTAGGTGTTTTCTTCACTG GCATTCACAAATTTAAGCCATTGCTGCCTCATTAGCCTTGATTTTG TGTGCATATCAT ~~R~~ ATCCAGACCCTGTATGTTTCGCTTTAAGCATCTT ATATCACACTGTCTCTCATCTACCATATGGTAAATGTTAAACATCC ACATTTGTCTGCATCAGGGAAAAATGCATGGGCACACATCCTCCCTCC CTCCCTCTCTGCTCTCTCCCTTCTTCCAGGCCTCTTAGCATGTGTT GTTTTCCCATTTCTGATACTACTAC

LNPEP Region	rs9314181	242	TGAAACAGTTGTTATGGAGGCCTGCGTTAGTGAGATCTGGCTTGCCA CACTTGTGTTACCCACTCTTTCCAGAGTATACTTTCTTCCCTTCTTC ACCTTTTCAAATACTCATCTTTTATAGGCCCTCTTCAGGTTTTCTGCA TGTTTCCCTTATAATATCTTCAACCTCTAGTCAGAATTTGTTTCCCTTC CCTTTGTTCCCA ~~Y~~ TGCTTTATTTTCATTGTTAGGACATGACTTACAG CCTGATGTAAGTTTCTGTTTCATTGTATAAACCTCTGCCTTTCCCACT TTATTGCAGATCCTTTAGTAACTAGGATTGTAACATATTTATCTTAG TATACTTGGCAGGGTGCTTGTACAGTAGGTGCTCAGTAACTACTGG ATTGAATTTGTGTTTGTGTTTAGGTA
AVPR1A	rs1042615	243	AGCAGCGTACTGCTGGCTCTGCACCGGACGCCGCCGAAGACGTCCCCG CATGCACCTCTTCATCCGACACCTCAGCCTGGCCGACCTGGCCGTGG CATTTCTTCCAGGTGCTGCCGCAAATGTGCTGGGACATCACCTACCGC TTCCGCGGCCCGACTGGCTGTGCCGCGTGGTGAAGCACCTGCAGGT GTTCCGGCATGTT ~~Y~~ GCGTCCGGCTACATGCTGGTAGTCATGACAGCCG ACCGCTACATCGCGGTGTGCCACCCGCTCAAGACTCTGCAACAGCCC GCCGCCCGCTCGCGCCTCATGATCGCGGCCCGCTGGGTGCTGAGCTT CGTGCTGAGCACGCCGCAGTACTTCGTCTTCTCCATGATCGAGGTGA ACAATGTCACCAAGGCCCGCGACTG
AVPR1A	rs10747983	244	AACTGTGAAAAATAAAAAAAGGTGCTGCAACACATTTTCTTTGAC TGTAAGCTGTTATTTGGCATAATATCTCAGGTCTTCTCTTTAGTCAA GAAAAGGAAAACCTTCCCTTCCCGGAATACTTTTTCAGTTTCTCTTCT TCTGAAACAGACAGGCAGGTAGATTCCCTTCCAATCTGAAATATGTT TTCAGATATGT ~~G~~ RCGTCCATTTCTGGGTACATAACATTGAGAAAAT TACCAACCAGACAGATGAAACTTCTCAGCCTAAACCGCAGAGAATAA GACCATGTATTTGCCCTAGTGCAGAACTAGCACCCAGATCTCATGTTT CCCCAGCCCATTCTTCTACTGTCTCATCTCCCAATACATTTAAAGGA GAAAATACAACCTGGGTAGGGTGATA
AVPR1A	rs10784339	245	TTGAGATATGTGGCGTCCATTTCTGGGTACATAACATTGAGAAAATT TAGCAACCAGACAGATGAAACTTCTCAGCCTAAACCGCAGAGAATAA GACCATGTATTTGCCCTAGTGCAGAACTAGCACCCAGATCTCATGTTT CCCCAGCCCATTCTTCTACTGTCTCATCTCCCAATACATTTAAAGGA GAAAATACAACCT ~~S~~ GGTAGGGTGATATGCACCTTTTTTTTGTGAGCTGT TCTCAGAAATAACATTCAAATTGAATGTTTGTCTGGGGGTACATA TCAACATTTTGAAGCAAGATCTATAGGTCTGAGGTCTTACTTTGG AAATGGATTTTAGAAAAAATGGGTTCATCTTAGTTCCAAACCAAAAA GCTTTAGTTTTTTGAACATATCAAAGA
AVPR1A	rs10877962	246	AACCTCCCAAGTAGCTGGGACTATAGGCACACACCACCATGCCCAGC TAA'TTTTTTGTATTTTTTTTTTCTTTTATAGAGTAGAGATAGGGGTCT CCCCATGTTGCCCAGGCTGGATTATACATGAATTTTTAAAAATGAAA GTTACACTGAATGTGCCTGCCTGTCTGCTCCCTTTTCCCTTCCCTC CACCCCTTCCAC ~~Y~~ CGAGACAGCAAGATCAACCCCTCTTCTGCCTCTT CCTCCTCAGTCTACTCAACCTGAAGATGAGGGTGAAGACCTTTATGA TGATCCACTTGCACCTTAATGAATAGGAAGCACTTTCTATATTTTTTA AATAACGTTTTCTTTTCTCTAGCTTACTTTATTTGTAAGAATACAGTA TATCATATATAATATGCAAAATATG
AVPR1A	rs10877969	247	ATATGTATGCATCTGGCCATTTCTATGTATCATGTGTCAATCAATCAT CTATCTATCTGTCTATCTATCTATCTATCTATCTATCTATCTATCTA TCATCCATCTATCTGTCTCTCGCTGGTTGTGCTGGATGCCATGGGC CTGGAAAGCAGGAAAAAATGTTTCAATTGCAGATTGTAGAACCAGT CCCTTTGTTTAA ~~Y~~ CCATATAGTTTTTAAACATGTTTTTGACTTAATTT AACTGGTTTTATATACAAAGGAAAGCAGGACTATTACATATGAGGCA CTACTCATATGCCTCACTGGACCTGCTATTTAAATTAACCCCATAGAGA GTAATAATTTGTGGTCTTAAAAATGAAAAAGAAAACACAACAGAC AATATTTTATGTGGCACCTTGTGCT

AVPRIA	rs10877977	248	TTTACATGTCCATCCCTGTGGGCAGGAAAAGAGTGAAAAACAGCCTTA TGTGGATCGCATGAAATGGATTCCCTACAGGAAAAGAAATGCTCCTGTT GCTAGAAAAGGAGGGTATGCTAAGCTGGCAAAAATAACAGATATTTA CTTCACATATGAAAACCAACCTGTTGATCTCAGACTTGCAATGGATG GCTGAATTTTCATYCTAGCCTTTCTTTGCATAAGTGACCGGGGAAGAA GTACTGACTTTACTTTTATCATTTACAGTGATTTTTTTCTGTATAT GCTAGTTAATTAACTGAATAAAAAGGAATTCCTATATTATGATAATF TAGTCTCAGTAATAGCCAATAAATATTTCTGGAAAAGATACCCAGC CCCTGTGTGGGTGCTATTATTGAAT
AVPRIA	rs10877986	249	TCCCTGTCTTAGAAGAAAAGTTTTCAACTTTTTTACCATTAAGTATGA TGTTAGCTATAGGCTAGTGATCTATGGCCTTTATTGTGTGAGGTAC ATTCCCTTCTATACCTAATTTGTTGAGAATTTTATCATGAAAGTGTG TTGAATTTTGTCAACTTCTTTTTCTGCATCTATCAAGATGATCGATC ATATGGCTTTTAYTTTTCATTTCTGATAATATGGTGAATCACTTTATT GGTTTCTGTATGTGGAACCATCCTAGGCAAGTCAGATTTTGGATTTT CTCCTTTATGTTCCATTCTGTAAACATGTTAATGGGAACCGGAATTCA GATCAGAATAACAGCTTAGGAACCAAGCAGGTATATATATATGTGT GTGTGTGTGTGCGTGTGTGTGTATA
AVPRIA	rs11174811	250	TGTAACTGATCAAAAATACGTTTACAATGTCCAAGAGAAAAGTCCAG AGTACCTTAAGCAATCCTTTTCTACTCTTTTAATAAAATTTGGCTTT CCTTATACAAATCTGACTTTTAAACAACCTCGCAGTGGGGCAAAAA GATATTTTGGCCAGTCAACATTTCCCTCTCACCTTCAGCATCTCAGT TTTCATGCTTTTMTTGACCAATAATATGTGAGGAACCAAAAGGAGGC CACTGCCAGTTGTAAAGTTACCATTTTGAAATGCAAGGTGATTGATA GCTTCTAATAGAACTCTAAACTGGCCACAATGAGCAGGAGCTCATTA CACCCAGGCACCTGTACTCCTAGGAGGTACCATCCCATCTCCTGGA CACTGTTTAAAGGCTGCATTTTCTGA
AVPRIA	rs11832877	251	TTTTTGAGAATATTTTCTTTTTCCAAATTTATTACATACTCAGATA TACTCTTGAATCTCTCATTTCAACAAGTCCCCAAACTTTGTCCATGAA ACCTTTCTTCTCTTTCTTTTCTCTATACCCCATCATTTCTAAATTTACA TCACGTTAATCTTTTGGATTATATTTACATATTTAATTTCTCTCC ACTTTGCTCCAAATCTCAAATCTTTATAACAACCACAAGAACACGAAA CTCCTGTAACTAGCCAATGTAGTAATTAGGGTAGGATAGGCATGTGTC CTGTAGTAACAGAGCAATTTCTGACACCTCAGTGGCTTTAACAAAAAA TTATTTCTCACTCATGCAAAAGTCTAATGCAAGTTGAGCAGCTTTCCC CCAAGCAGTGACTCTGAGGTCCATG
AVPRIA	rs11835545	252	TTTTATTTTGATCTAGATGTCTGAGAGTATGAATGTTCTTAGTGCAA ATAATAAATGGAATGCTCTCGAGGATAAAATTTGAAAATAATTTCTAT CTTAAGATGTCTAACAAAATGAATAAAAATTTATAAACCTTTATGAAT GAGGTTGTACTCTCCAAGTGTCTTGTGTTAAGAACCATAGAAGGACT TCCCTTTTAGAARTGCTTTGGATATTTCTAATACATTTAATGCCAGGG CATAAGCTAGTGGTTGTTAAGCTTTTCTCTCCCTCCCACAGCACCAA GAGCCTAACATTCACCCATTTGTAGCAGTTGTTTTAGAACAGTGAT TGCCAAGGAGGGGAAAAATGAGGAAGCATAGCAGAATTTCTGGGGAA CTGTAGAAAAGAGAGAGCATATTGGG
AVPRIA	rs11836346	253	TTCCACAGCTTTTGTGAACACAGAATAGTCCCATTGAAAAGAAAATCT TTCCGAATTTGATAAATGAATAAGTATCTGATTTGTTTAAATGTATTT CGTTAGAAAATATTTTCATCGTTTTTGTCTCATTACTTACTTAATAATG AGTTAAACATTTTCATAAATGTCTTTATAACTTACAAACAGAATCTGG GAGTGCTGAATTRTGATAAAGGAACCTGCTCAAGTTAGAAATATTACT TTTACTTTTCTTTGAACGTGTTATAAATTTATACAGAAAAAATAATACA TGGTATATATGGACCATAAGTAGCAGGAGCTGTAATCCAGGTTTTCG ATACATTATCTTATTTAATCCCTCACGAATCTAATGAGATGGATTAA CACTATTTTACACATAAGGATGCGG

AVPRIA	rs16856	254	TGATGCCAACACTATAAATTGCCAACCCCATTTGAGAAAGGAAAGAAAC ATTTGCCCTGACATCTTCCCTCCAGGCAGGGCTGGCCATGCCACTAG TAGCAAAGAGGAGGGATGTGTTGAGTCATCTAGTAAGTCCCTGTGAA GAGTGGATCCTGGCCCATCTGAACATCTGACCAGAACTAGTGGCAG CAGTTGTAGAAC K TGGTATATGCATGTGCTTCTCTTTTATGGAATC GGAATCAGGGTGCCCCAGAAAGAAAACGAGCCCAATTTTAAAGGGGT TAATTGGGTATCGTCTTGATTCTTTGTAAAGATTGGTTAGGTATTTCAG GAATCAGGCTGACCAGGCACAAGTACCTACCAACCTTTGTAAAAATAT TCTACACTCTACAATATCATTCACA
AVPRIA	rs2030106	255	CACCACCACGCCCCGGCTAATTCTTCATATTTTTAGTAGAGACGGGGT TTCACCGTGTTAGCCAGGATGGTCTCAAACCTCTGACCTAAAGTGAT CAGCCAGTCTCGTCTCCCAAAGTGCTGGGATTACAGGCATGAGCCA CCACACCCAGCAAAGTGGAACAGAAATAGACAGCCGTAATGGTTCCAT GTATATTTGGGT R CTTACTATACAATAAAGAGGTCTCCACTAAAACA AGGGAGAAGGATGCCATAAAGGAGTTGGGAAATGCAGAAAATTATGC TAGATTTCATCTTCTTATATCACATCTTAGTAGTAGACTCCAAATAAA TTAATGAAGTAAATGTGGAAGGTAAATTACAAACCTGATACAAGGAA AATGTTATTAGAGAACCTATATGAC
AVPRIA	rs2201895	256	GAGCTGCCTAAGGCTGTGGGAGCCACCTCTTGCAATCAATGTGCCCT GGATGTGAGACATGGAGTCAAAGGAGATCATTTTGAATTTAATAT TTGACTGCCCTGCTGGAATTTGGACTTGCATGGTGCCCTTAGCCCCCT TCATTTTGGCCAATTTCTCCCATTTGGAATGGGTGCATTTATCCAAT GCCTGTACTCCC R TTGTATCGAGGAAGTAACCTAACCTTCCCTTTGATT TTACAGGCTCATAGGCAGAAAGGGACTTGCCTTACCTCAGATGAGACT TTGACTGTGCACTTTTGAGTTAATGCTGAAATTAGTTAAGACTTTA GGGACTTTTGGGAAAGCATGATTGGTTTGAATGTGAGGACATGA AATTTGGGAGGGGACCAGGGTGGAA
AVPRIA	rs3021529	257	TCTTTCCTCTCTTTGAGATTGCCCTCTTCTTACTCCTGAGCACAGGA GCCGGGCGGGTTTTCTGTCCCTTGCCCTGGACAGCACTGCCGCGATG GCCGCTGTCCGGCAGCTGCTCTTTGTCCACCCAAAAAGATGTCCCA CGACTCAGTAGTAACCAGACGCTCCCCACGGACCACTGCGGCCAAAT TTCCGCCATCCC Y GCTGTGGGAATCAGGCTTTTCCCGCAGAAAACCC CAGGAATCTAGAGAAAACCTCTTAAGTCCCTAGTCTCCATAGAGAAA ACCAGGAGACACTCCCCCAACCCCGCTGTGAATACAGGCACAGCA GCCACTGGGGCTGCAAAAGTGATGAGTGCGTCTTCCCGTCGCAAAACA TAGGGTAATAAATAGCATGCATCAA
AVPRIA	rs34462214	258	AACATTTCAGTATGAATTTAACTTAAATATTTCTTACTGACTATAATA CTAGCGATAATGAAAAATACAATATAAACACTTTATTTTGGTTTGC TATTTCTTATCTTGCTTGATCTTAGAAGCCTCTTCATATTTGCCATC AAATAAAGAAATTTCAGTCTAATTATTGCTTTAGCAGAATTTACACTC AAGTAATAAAAA Y TTCAATTGTGCATAGATATGTTGGTAATTTTCAT TCTTTGTGAATACCATCTTACCCATGGCTCCTGATCACCTTTGATAG CAGCATCTTAGCACTAAGTATGATTAAATAATAACCTGTAAATTGTTT TCTGGCATAACAAGAGTGAGAAGATCCAAGTTTATATTTAATAATCA AGGAAAAGTCAGTGTATTATGATTA
AVPRIA	rs36014760	259	TGTCCTTAAAGGGTACTGTCCAATATAAGCCATAACTAAATTAATT AATTCATTATTTGAGTTAGAGTAGCATCTCAGTAACCCAGCACTCGA AGACTGTGAGTCTTTTAAACAACCTTTGATAGTTCAAAAACATAAG CTTTTGGTTTGGAACTAAGATGAACCCATTTTCTTAAATCCATT TCCAAAGTAAGA A/- CCTCAGAACCTATAGATCTTTGCTTCAAAAATGTTGATATGTACCCCCA AGCAAAACAATTCAATTTGAATGTTATTTCTGAGAACAGCTCACAAA AAAAAGTGCATATCACCCACCCAGTTGTATTTCTCCTTTTAAATG TATTGGGAGATGAGACAGTAGAAAAATGGGCTGGGGAAACATGAGATC TGGGTGCTAGTT

AVPR1A	rs7294536	260	TTCCAATTAAAGCAAAATATTTCCCAATTTACATATGTGCAATGAGAA GAGTTTTATGGTTAAATATGTTGGAGAAGTGCTGTGTATGCATCCCCA CCCTCTCCTGGTGATTTATACATAAAAAAGGACCTGAGAAAC TTCAGA AAAGAAACTTACTTAACCTTGTTTCATCAATGTTTTC CAAGGTATTTT TACCATGGAAAC ~~C~~ CCCCATTTTTTTTACTTTCCCCATGGAATGGTGAT GAACATGTCACAAGACAAGGTGACAGAGCAGGAGCATCACCATCCTG CCA'TTTTAAAGTTACCTTGATCAAAAACCACTAAATCCAAAGGGC ATCAGCCTAATGGCTAAGGCCAGAATGACCATGAGCCACAAATAACA TCTCTTACCAGAAACATTTCCAAACC
AVPR1A	rs7302323	261	TTATGCAGTCTTGTAGGACACGTTAAAGATATTTGGGCTTGATCTACA AGAAAGGGAAAAATGTTGAAGGAATTTTAAACAAGGGAAGGGCATAATC ATT'TTTGTATCTTTTAAAAGAGAATACTTTGGCTTTATGTGCAAAATG AATGGAGGAGGGTGAGAACAGATAGAGACTCAGTTAAGAGACCATAG CAGAGGACCCGAWAAGCTAGAGTATGGTAGGGAAGAAGACATGCAGA GTCATGGTCTTGAGGATGAGTTTGGGAGTATTGGAATAATGAAGTTT ACATCTCTATTGCCGAAATGAGGATTAGTCGTGACCACTCAAGGCAG GAGCCAGCCCCACTTATGAGGGAGAGAAGGCAGCAGAGTCTGGGGAC AGGCTCCTAGACACCTTCTGGATCA
AVPR1A	rs7308008	262	AACAACATAAAATGAATTTTTTTCCAAATAGAAATGTAATTGATTTCTGC CCCGTAGGAAAAGAAAAC TCCAAGCATTATGTTTTATGAACCAATAGA AAAATAATAATCAATCTTACATCTTTTAGCAAAATCATTTCAGAAATT CTTGACTGCCTGTGTGTTACTCTTCTTCAGATTCTCCCCGTAACAGG TCTTAACATCTC ~~R~~ TTGGTTCCATCCTTAATTAATAAGCTGAATAAAA CTGTAGCATGTGTTCAATTTTACATTTGTCAGGAGAGTCATGACTTTAT CTTTATAAAATTTATACATAGCAGCCCTGCGTGGTCTCAGGGGTCTG CCTCTATCTTTGCCACATCCCATGCTGAGGTCCATAGCTATTTCTAGC TGGTCCCTCACTAGTCCCTCTGTTCTA
AVPR1A	rs7959001	263	TTCTGGTTAAATGATTTTTTAATAAGACGTTAATCTCTTTGTACAATA AGAGTGCTTATACCCTTTTTCATAATAATTTGTGTAAAGACTTATGATT ACACTAGGCACAGGAAGGTGTTTTCAATAAAACAAAGTGTCCTTTCCA GTTCCCTGCTTTGAAGTAGGGTCTTCAATCTTCCCATCTCCATTGTT CAGTGCATATGT ~~W~~ TCACTTAGGATAAGCTAAGTTATGTCTAAAGTAAC AAGCAAAACAACAAATCTCAGTGGCTTAGAGCAATCAAGATCTATTTTC TTATTCATGCTACTATTTCATCATGCATAGCTGGGGCTTTAC TCCATG TGC TTCTCATTCAGGAACCTAGGTGAGGGGGCTTGATCATCTGGAAT GTCACCAGTCACTGTAGCAGGGAGA
AVPR1A	rs7972829	264	AATPATAGATACTGAAATCTGAATTTTATACAATGTTTCATGTGTGTCAG AAATATTCATTTTGATTTTTCTCAATTATTTAAAAATGTAAAAACTA TTC TTAGCTCATAGGACAAACTAAAACATGGATGAGCTAGATTTGGC TTGTGCATCATAGTTTGCCAATTCCCTGTTCTAAAGTATGTTAAACAAA TCCACATATCTT ~~R~~ AATATTACTATTTTTTCATAATAGGTGAGAGCCTA TTTTTAACTCCCGTTATGCTGATAAAATAAGCTACTGATTTTACCATT ATGTTAATTAACAAAATATCTATTGTCAATCAGAAGAAAAGGTCACC AATATTCTTATAGTAGTCATCTCTGGTGGGTGGGGCTTTTCTGATAA AATTC TAGCTGCTTCCCCATTCCCT

An “allele” is defined as any one or more alternative forms of a given gene. In a diploid cell or organism the members of an allelic pair (i.e. the two alleles of a given gene) occupy corresponding positions (loci) on a pair of homologous chromosomes and if these alleles are genetically identical the cell or organism is said to be “homozygous”, but if genetically different the cell or organism is said to be “heterozygous” with respect to the particular gene.

A “gene” is an ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific functional product and may include untranslated and

untranscribed sequences in proximity to the coding regions (5' and 3' to the coding sequence). Such non-coding sequences may contain regulatory sequences needed for transcription and translation of the sequence or introns etc. or may as yet to have any function attributed to them beyond the occurrence of the SNP of interest.

5

A "genotype" is defined as the genetic constitution of an organism, usually in respect to one gene or a few genes or a region of a gene relevant to a particular context (i.e. the genetic loci responsible for a particular phenotype).

- 10 **TABLE 1E.** Genotype correlations for SNPs in vasopressin pathway associated genes with values representing an ability to recover from an inflammatory condition and an indication of responsiveness to treatment of an inflammatory condition with a vasopressin receptor agonist.

POLYMORPHISM	Genotype	Patient Outcome Score*	Responsiveness To Treatment'
rs18059	TT	1	R
rs18059	CT	1	R
rs18059	CC	2	PR
rs27711	GG	1	R
rs27711	AG	1	N/A
rs27711	AA	2	PR
rs38041	GG	1	N/A
rs38041	AG	1	N/A
rs38041	AA	2	N/A
rs10051637	GG	1	PR
rs10051637	AG	1	R
rs10051637	AA	2	R
rs1410713	AA	1	R
rs1410713	AC	2	R
rs1410713	CC	2	PR
rs857240	CC	1	R
rs857240	CT	2	PR
rs857240	TT	2	N/A
rs857242	CC	1	R
rs857242	AC	2	PR
rs857242	AA	2	N/A
rs10877970	TT	1	N/A
rs10877970	CT	2	N/A
rs10877970	CC	2	N/A
rs3803107	TT	1	N/A
rs3803107	CT	2	N/A
rs3803107	CC	2	N/A
rs1495027	CC	1	PR
rs1495027	CT	2	R
rs1495027	TT	2	R

* good = 2; poor = 1.

' Responsive (R); Poor Response (PR).

A "phenotype" is defined as the observable characters of an organism. In gene association studies, the genetic model at a given locus can change depending on the selection pressures (i.e., the environment), the population studied, or the outcome variable (i.e., the phenotype). For example, the model at rs1410713 changed between the risk of death claims (AA versus AC/CC) and the vasopressin IRP claims (AA/AC versus CC). This is a case of the same outcome variable (survival) following a different genetic model in different environments (i.e., no vasopressin treatment versus vasopressin treatment).

A similar observation would be seen in a gene association study with the hemoglobin, beta gene (HBB) with mortality as the primary outcome variable. A mutation in the HBB gene, which normally produces the beta chain subunit of hemoglobin (B allele), results in an abnormal beta chain called hemoglobin S (S allele; Allison A (1955) Cold Spring Harbor Symp. Quant. Biol. 20:239-255). Hemoglobin S results in abnormal sickle-shaped red blood cells which lead to anemia and other serious complications including death. In the absence of malaria, a gene association study with the HBB gene would suggest a codominant model (survival(BB) > survival(BS) > survival(SS)). However, in the presence of malaria, a gene association study with the HBB gene would suggest a heterozygote advantage model (survival(BB) < survival(BS) > survival(SS)).

A "single nucleotide polymorphism" (SNP) occurs at a polymorphic site occupied by a single nucleotide, which is the site of variation between allelic sequences. The site is usually preceded by and followed by highly conserved sequences of the allele (e.g., sequences that vary in less than 1/100 or 1/1000 members of the populations). A single nucleotide polymorphism usually arises due to substitution of one nucleotide for another at the polymorphic site. A "transition" is the replacement of one purine by another purine or one pyrimidine by another pyrimidine. A "transversion" is the replacement of a purine by a pyrimidine or vice versa. Single nucleotide polymorphisms can also arise from a deletion (represented by "-" or "del") of a nucleotide or an insertion (represented by "+" or "ins" or "I") of a nucleotide relative to a reference allele.

Furthermore, a person of skill in the art would appreciate that an insertion or deletion within a given sequence could alter the relative position and therefore the position number of another polymorphism within the sequence. Furthermore, although an insertion or deletion may by some definitions not qualify as a SNP as it may involve the deletion of or insertion of more than a single

nucleotide at a given position, as used herein such polymorphisms are also called SNPs as they generally result from an insertion or deletion at a single site within a given sequence.

A "systemic inflammatory response syndrome" or (SIRS) is defined as including both septic (i.e. sepsis or septic shock) and non-septic systemic inflammatory response (i.e. post operative).

"SIRS" is further defined according to ACCP (American College of Chest Physicians) guidelines as the presence of two or more of A) temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$, B) heart rate > 90 beats per minute, C) respiratory rate > 20 breaths per minute, or $\text{PaCO}_2 < 32$ mm Hg or the need for mechanical ventilation, and D) white blood cell count $> 12,000$ per mm^3 or $< 4,000$ mm^3 . In the following description, the presence of two, three, or four of the "SIRS" criteria were scored each day over the 28 day observation period.

"Sepsis" is defined as the presence of at least two "SIRS" criteria and known or suspected source of infection. Septic shock was defined as sepsis plus one new organ failure by Brussels criteria plus need for vasopressor medication or vasopressin receptor agonist.

Subject outcome or prognosis as used herein refers the ability of a subject to recover from an inflammatory condition and may be used to determine the efficacy of a treatment regimen, for example the administration of a vasopressin receptor agonist. An inflammatory condition, may be selected from the group consisting of: sepsis, septicemia, pneumonia, septic shock, systemic inflammatory response syndrome (SIRS), Acute Respiratory Distress Syndrome (ARDS), acute lung injury, aspiration pneumonitis, infection, pancreatitis, bacteremia, peritonitis, abdominal abscess, inflammation due to trauma, inflammation due to surgery, chronic inflammatory disease, ischemia, ischemia-reperfusion injury of an organ or tissue, tissue damage due to disease, tissue damage due to chemotherapy or radiotherapy, and reactions to ingested, inhaled, infused, injected, or delivered substances, glomerulonephritis, bowel infection, opportunistic infections, and for subjects undergoing major surgery or dialysis, subjects who are immunocompromised, subjects on immunosuppressive agents, subjects with HIV/AIDS, subjects with suspected endocarditis, subjects with fever, subjects with fever of unknown origin, subjects with cystic fibrosis, subjects with diabetes mellitus, subjects with chronic renal failure, subjects with acute renal failure, oliguria, subjects with acute renal dysfunction, glomerulo-nephritis, interstitial-nephritis, acute tubular necrosis (ATN), subjects with bronchiectasis, subjects with chronic obstructive lung disease, chronic bronchitis, emphysema, or asthma, subjects with febrile neutropenia, subjects with meningitis, subjects with septic arthritis, subjects with urinary tract infection, subjects with

necrotizing fasciitis, subjects with other suspected Group A streptococcus infection, subjects who have had a splenectomy, subjects with recurrent or suspected enterococcus infection, other medical and surgical conditions associated with increased risk of infection, Gram positive sepsis, Gram negative sepsis, culture negative sepsis, fungal sepsis, meningococemia, post-pump syndrome,

5 cardiac stun syndrome, myocardial infarction, stroke, congestive heart failure, hepatitis, epiglottitis, E. coli 0157:H7, malaria, gas gangrene, toxic shock syndrome, pre-eclampsia, eclampsia, HELLP syndrome, mycobacterial tuberculosis, Pneumocystis carinii pneumonia, pneumonia, Leishmaniasis, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, Dengue hemorrhagic fever, pelvic inflammatory disease, Legionella, Lyme disease, Influenza A,

10 Epstein-Barr virus, encephalitis, inflammatory diseases and autoimmunity including Rheumatoid arthritis, osteoarthritis, progressive systemic sclerosis, systemic lupus erythematosus, inflammatory bowel disease, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, systemic vasculitis, Wegener's granulomatosis, transplants including heart, liver, lung kidney bone marrow, graft-versus-host disease, transplant rejection, sickle cell anemia,

15 nephrotic syndrome, toxicity of agents such as OKT3, cytokine therapy, and cirrhosis.

Assessing subject outcome, prognosis, or response of a subject to vasopressin receptor agonist administration may be accomplished by various methods. For Example, an "APACHE II" score is defined as Acute Physiology And Chronic Health Evaluation and herein was calculated on a daily

20 basis from raw clinical and laboratory variables. Vincent *et al.* (Vincent JL, Ferreira F, Moreno R. 2000 Crit Care Clin. 16:353-366) summarize APACHE score as follows "First developed in 1981 by Knaus *et al.*, the APACHE score has become the most commonly used survival prediction model in ICUs worldwide. The APACHE II score, a revised and simplified version of the original prototype, uses a point score based on initial values of 12 routine physiologic measures, age, and

25 previous health status to provide a general measure of severity of disease. The values recorded are the worst values taken during the subject's first 24 hours in the ICU. The score is applied to one of 34 admission diagnoses to estimate a disease-specific probability of mortality (APACHE II predicted risk of death). The maximum possible APACHE II score is 71, and high scores have been well correlated with mortality. The APACHE II score has been widely used to stratify and

30 compare various groups of critically ill subjects, including subjects with sepsis, by severity of illness on entry into clinical trials".

A "Brussels score" score is a method for evaluating organ dysfunction as compared to a baseline. If the Brussels score is 0 (i.e. moderate, severe, or extreme), then organ failure was recorded as

present on that particular day (see TABLE 2A below). In the following description, to correct for deaths during the observation period, days alive and free of organ failure (DAF) were calculated as previously described. For example, acute lung injury was calculated as follows. Acute lung injury is defined as present when a subject meets all of these four criteria. 1) Need for mechanical ventilation, 2) Bilateral pulmonary infiltrates on chest X-ray consistent with acute lung injury, 3) $\text{PaO}_2/\text{FiO}_2$ ratio is less than 300mmHg, 4) No clinical evidence of congestive heart failure or if a pulmonary artery catheter is in place for clinical purposes, a pulmonary capillary wedge pressure less than 18 mm Hg (1). The severity of acute lung injury is assessed by measuring days alive and free of acute lung injury over a 28-day observation period. Acute lung injury is recorded as present on each day that the person has moderate, severe or extreme dysfunction as defined in the Brussels score. Days alive and free of acute lung injury is calculated as the number of days after onset of acute lung injury that a subject is alive and free of acute lung injury over a defined observation period (28 days). Thus, a lower score for days alive and free of acute lung injury indicates more severe acute lung injury. The reason that days alive and free of acute lung injury is preferable to simply presence or absence of acute lung injury, is that acute lung injury has a high acute mortality and early death (within 28 days) precludes calculation of the presence or absence of acute lung injury in dead subjects. The cardiovascular, renal, neurologic, hepatic and coagulation dysfunction were similarly defined as present on each day that the person had moderate, severe or extreme dysfunction as defined by the Brussels score. Days alive and free of steroids are days that a person is alive and is not being treated with exogenous corticosteroids (e.g. hydrocortisone, prednisone, methylprednisolone). Days alive and free of pressors are days that a person is alive and not being treated with intravenous vasopressors (e.g. dopamine, norepinephrine, epinephrine or phenylephrine). Days alive and free of an International Normalized Ratio (INR) > 1.5 are days that a person is alive and does not have an INR > 1.5.

TABLE 2A Brussels Organ Dysfunction Scoring System

ORGANS	Free of Organ Dysfunction		Clinically Significant Organ Dysfunction		
	Normal	Mild	Moderate	Severe	Extreme
DAF ORGAN DYSFUNCTION SCORE	1		0		
<u>Cardiovascular</u> Systolic BP (mmHg)	>90	≤90 Responsive to fluid	≤90 Unresponsive to fluid	≤90 plus pH ≤7.3	≤90 plus pH ≤7.2

<u>Pulmonary</u> P _a O ₂ /F _I O ₂ (mmHg)	>400	400-301	300-201 Acute lung injury	200-101 ARDS	≤100 Severe ARDS
<u>Renal</u> Creatinine (mg/dl)	<1.5	1.5-1.9	2.0-3.4	3.5-4.9	≥5.0
<u>Hepatic</u> Bilirubin (mg/dL)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	≥12
<u>Hematologic</u> Platelets (x10 ⁵ /mm ³)	>120	120-81	80-51	50-21	≤20
<u>Neurologic</u> (Glasgow Score)	15	14-13	12-10	9-6	≤5
Round Table Conference on Clinical Trials for the Treatment of Sepsis Brussels, March 12-14, 1994.					

2. General Methods

One aspect of the invention may involve the identification of subjects or the selection of subjects that are either at risk of developing and inflammatory condition or the identification of subjects who already have an inflammatory condition. For example, subjects who have undergone major surgery or scheduled for or contemplating major surgery may be considered as being at risk of developing an inflammatory condition. Furthermore, subjects may be determined as having an inflammatory condition using diagnostic methods and clinical evaluations known in the medical arts. An inflammatory condition, may be selected from the group consisting of: sepsis, septicemia, pneumonia, septic shock, systemic inflammatory response syndrome (SIRS), Acute Respiratory Distress Syndrome (ARDS), acute lung injury, aspiration pneumonitis, infection, pancreatitis, bacteremia, peritonitis, abdominal abscess, inflammation due to trauma, inflammation due to surgery, chronic inflammatory disease, ischemia, ischemia-reperfusion injury of an organ or tissue, tissue damage due to disease, tissue damage due to chemotherapy or radiotherapy, and reactions to ingested, inhaled, infused, injected, or delivered substances, glomerulonephritis, bowel infection, opportunistic infections, and for subjects undergoing major surgery or dialysis, subjects who are immunocompromised, subjects on immunosuppressive agents, subjects with HIV/AIDS, subjects with suspected endocarditis, subjects with fever, subjects with fever of unknown origin, subjects with cystic fibrosis, subjects with diabetes mellitus, subjects with chronic renal failure, subjects with acute renal failure, oliguria, subjects with acute renal dysfunction, glomerulonephritis, interstitial-nephritis, acute tubular necrosis (ATN), subjects with bronchiectasis, subjects with chronic obstructive lung disease, chronic bronchitis, emphysema, or asthma, subjects with febrile neutropenia, subjects with meningitis, subjects with septic arthritis, subjects with urinary tract infection, subjects with necrotizing fasciitis, subjects with other suspected Group A streptococcus

infection, subjects who have had a splenectomy, subjects with recurrent or suspected enterococcus infection, other medical and surgical conditions associated with increased risk of infection, Gram positive sepsis, Gram negative sepsis, culture negative sepsis, fungal sepsis, meningococemia, post-pump syndrome, cardiac stun syndrome, myocardial infarction, stroke, congestive heart failure, hepatitis, epiglottitis, E. coli 0157:H7, malaria, gas gangrene, toxic shock syndrome, pre-eclampsia, eclampsia, HELLP syndrome, mycobacterial tuberculosis, Pneumocystis carinii pneumonia, pneumonia, Leishmaniasis, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, Dengue hemorrhagic fever, pelvic inflammatory disease, Legionella, Lyme disease, Influenza A, Epstein-Barr virus, encephalitis, inflammatory diseases and autoimmunity including rheumatoid arthritis, osteoarthritis, progressive systemic sclerosis, systemic lupus erythematosus, inflammatory bowel disease, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, systemic vasculitis, Wegener's granulomatosis, transplants including heart, liver, lung kidney bone marrow, graft-versus-host disease, transplant rejection, sickle cell anemia, nephrotic syndrome, toxicity of agents such as OKT3, cytokine therapy, and cirrhosis.

Once a subject is identified as being at risk for developing or having an inflammatory condition or is to be administered vasopressin receptor agonist, then genetic sequence information may be obtained from the subject. Or alternatively genetic sequence information may already have been obtained from the subject. For example, a subject may have already provided a biological sample for other purposes or may have even had their genetic sequence determined in whole or in part and stored for future use. Genetic sequence information may be obtained in numerous different ways and may involve the collection of a biological sample that contains genetic material, particularly, genetic material containing the sequence or sequences of interest. Many methods are known in the art for collecting biological samples and extracting genetic material from those samples. Genetic material can be extracted from blood, tissue, hair and other biological material. There are many methods known to isolate DNA and RNA from biological material. Typically, DNA may be isolated from a biological sample when first the sample is lysed and then the DNA is separated from the lysate according to any one of a variety of multi-step protocols, which can take varying lengths of time. DNA isolation methods may involve the use of phenol (Sambrook, J. *et al.*, "Molecular Cloning", Vol. 2, pp. 9.14-9.23. Cold Spring Harbor Laboratory Press (1989) and Ausubel, Frederick M. *et al.*, "Current Protocols in Molecular Biology", Vol. 1, pp. 2.2.1-2.4.5, John Wiley & Sons, Inc. (1994)). Typically, a biological sample is lysed in a detergent solution and the protein component of the lysate is digested with proteinase for 12-18 hours. Next, the lysate is extracted with phenol to remove most of the cellular components, and the remaining

aqueous phase is processed further to isolate DNA. In another method, described in Van Ness *et al.* (U.S. Pat. # 5,130,423), non-corrosive phenol derivatives are used for the isolation of nucleic acids. The resulting preparation is a mix of RNA and DNA.

- 5 Other methods for DNA isolation utilize non-corrosive chaotropic agents. These methods, which are based on the use of guanidine salts, urea and sodium iodide, involve lysis of a biological sample in a chaotropic aqueous solution and subsequent precipitation of the crude DNA fraction with a lower alcohol. The final purification of the precipitated, crude DNA fraction can be achieved by any one of several methods, including column chromatography (Analects, (1994) Vol
10 22, No. 4, Pharmacia Biotech), or exposure of the crude DNA to a polyanion-containing protein as described in Koller (U.S. Pat. # 5,128,247).

Yet another method of DNA isolation, which is described by Botwell, D. D. L. (Anal. Biochem. (1987) 162:463-465) involves lysing cells in 6M guanidine hydrochloride, precipitating DNA from
15 the lysate at acid pH by adding 2.5 volumes of ethanol, and washing the DNA with ethanol.

Numerous other methods are known in the art to isolate both RNA and DNA, such as the one described by CHOMCZYNSKI (U.S. Pat. # 5,945,515), whereby genetic material can be extracted efficiently in as little as twenty minutes. EVANS and HUGH (U.S. Pat. # 5,989,431) describe
20 methods for isolating DNA using a hollow membrane filter.

Once a subject's genetic material has been obtained from the subject it may then be further be amplified by Reverse Transcription Polymerase Chain Reaction (RT-PCR), Polymerase Chain Reaction (PCR), Transcription Mediated Amplification (TMA), Ligase chain reaction (LCR),
25 Nucleic Acid Sequence Based Amplification (NASBA) or other methods known in the art, and then further analyzed to detect or determine the presence or absence of one or more polymorphisms or mutations in the sequence of interest, provided that the genetic material obtained contains the sequence of interest. Particularly, a person may be interested in determining the presence or absence of a mutation in a vasopressin pathway associated gene sequence, as
30 described in TABLES 1A-D. The sequence of interest may also include other mutations, or may also contain some of the sequence surrounding the mutation of interest.

Detection or determination of a nucleotide identity, or the presence of one or more single nucleotide polymorphism(s) (SNP typing), may be accomplished by any one of a number methods

or assays known in the art. Many DNA typing methodologies are useful for use in the detection of SNPs. The majority of SNP genotyping reactions or assays can be assigned to one of four broad groups (sequence-specific hybridization, primer extension, oligonucleotide ligation and invasive cleavage). Furthermore, there are numerous methods for analyzing/detecting the products of each type of reaction (for example, fluorescence, luminescence, mass measurement, electrophoresis, etc.). Furthermore, reactions can occur in solution or on a solid support such as a glass slide, a chip, a bead, etc.

In general, sequence-specific hybridization involves a hybridization probe, which is capable of distinguishing between two DNA targets differing at one nucleotide position by hybridization. Usually probes are designed with the polymorphic base in a central position in the probe sequence, whereby under optimized assay conditions only the perfectly matched probe target hybrids are stable and hybrids with a one base mismatch are unstable. A strategy which couples detection and sequence discrimination is the use of a "molecular beacon", whereby the hybridization probe (molecular beacon) has 3' and 5' reporter and quencher molecules and 3' and 5' sequences which are complementary such that absent an adequate binding target for the intervening sequence the probe will form a hairpin loop. The hairpin loop keeps the reporter and quencher in close proximity resulting in quenching of the fluorophor (reporter) which reduces fluorescence emissions. However, when the molecular beacon hybridizes to the target the fluorophor and the quencher are sufficiently separated to allow fluorescence to be emitted from the fluorophor.

Similarly, primer extension reactions (i.e. mini sequencing, nucleotide-specific extensions, or simple PCR amplification) are useful in sequence discrimination reactions. For example, in mini sequencing a primer anneals to its target DNA immediately upstream of the SNP and is extended with a single nucleotide complementary to the polymorphic site. Where the nucleotide is not complementary, no extension occurs.

Oligonucleotide ligation assays require two sequence-specific probes and one common ligation probe per SNP. The common ligation probe hybridizes adjacent to a sequence-specific probe and when there is a perfect match of the appropriate sequence-specific probe, the ligase joins both the sequence-specific and the common probes. Where there is not a perfect match the ligase is unable to join the sequence-specific and common probes. Probes used in hybridization can include double-stranded DNA, single-stranded DNA and RNA oligonucleotides, and peptide nucleic acids. Hybridization methods for the identification of single nucleotide polymorphisms or other

mutations involving a few nucleotides are described in the U.S. Pat. 6,270,961; 6,025,136; and 6,872,530. Suitable hybridization probes for use in accordance with the invention include oligonucleotides and PNAs from about 10 to about 400 nucleotides, alternatively from about 20 to about 200 nucleotides, or from about 30 to about 100 nucleotides in length.

5

Alternatively, an invasive cleavage method requires an oligonucleotide called an Invader™ probe and sequence-specific probes to anneal to the target DNA with an overlap of one nucleotide.

When the sequence-specific probe is complementary to the polymorphic base, overlaps of the 3' end of the invader oligonucleotide form a structure that is recognized and cleaved by a Flap
10 endonuclease releasing the 5' arm of the allele specific probe.

5' exonuclease activity or TaqMan™ assay (Applied Biosystems) is based on the 5' nuclease activity of Taq polymerase that displaces and cleaves the oligonucleotide probes hybridized to the target DNA generating a fluorescent signal. It is necessary to have two probes that differ at the
15 polymorphic site wherein one probe is complementary to the 'normal' sequence and the other to the mutation of interest. These probes have different fluorescent dyes attached to the 5' end and a quencher attached to the 3' end when the probes are intact the quencher interacts with the fluorophor by fluorescence resonance energy transfer (FRET) to quench the fluorescence of the probe. During the PCR annealing step the hybridization probes hybridize to target DNA. In the
20 extension step the 5' fluorescent dye is cleaved by the 5' nuclease activity of Taq polymerase, leading to an increase in fluorescence of the reporter dye. Mismatched probes are displaced without fragmentation. The presence of a mutation in a sample is determined by measuring the signal intensity of the two different dyes.

25

The Illumina Golden Gate™ Assay uses a combined oligonucleotide ligation assay/ allele-specific hybridization approach (SHEN R *et al Mutat Res* 2005573:70-82). The first series of steps involve the hybridization of three oligonucleotides to a set of specific target SNPs; two of these are fluorescently-labelled allele-specific oligonucleotides (ASOs) and the third a locus-specific oligonucleotide (LSO) binding 1-20 bp downstream of the ASOs. A second series of steps involve
30 the use of a stringent polymerase with high 3' specificity that extends only oligonucleotides specifically matching an allele at a target SNP. The polymerase extends until it reaches the LSO. Locus-specificity is ensured by requiring the hybridization of both the ASO and LSO in order that extension can proceed. After PCR amplification with universal primers, these allele-specific oligonucleotide extension products are hybridized to an array which has multiple discretely tagged

addresses (in this case 1536 addresses) which match an address embedded in each LSO. Fluorescent signals produced by each hybridization product are detected by a bead array reader from which genotypes at each SNP locus may be ascertained.

- 5 It will be appreciated that numerous other methods for sequence discrimination and detection are known in the art and some of which are described in further detail below. It will also be appreciated that reactions such as arrayed primer extension mini sequencing, tag microarrays and sequence-specific extension could be performed on a microarray. One such array based genotyping platform is the microsphere based tag-it high throughput genotyping array
- 10 (BORTOLIN S. *et al.* Clinical Chemistry (2004) 50(11): 2028-36). This method amplifies genomic DNA by PCR followed by sequence-specific primer extension with universally tagged genotyping primers. The products are then sorted on a Tag-It array and detected using the Luminex xMAP system.
- 15 Mutation detection methods may include but are not limited to the following:
Restriction Fragment Length Polymorphism (RFLP) strategy – An RFLP gel-based analysis can be used to indicate the presence or absence of a specific mutation at polymorphic sites within a gene. Briefly, a short segment of DNA (typically several hundred base pairs) is amplified by PCR. Where possible, a specific restriction endonuclease is chosen that cuts the short DNA segment
- 20 when one polymorphism is present but does not cut the short DNA segment when the polymorphism is not present, or vice versa. After incubation of the PCR amplified DNA with this restriction endonuclease, the reaction products are then separated using gel electrophoresis. Thus, when the gel is examined the appearance of two lower molecular weight bands (lower molecular weight molecules travel farther down the gel during electrophoresis) indicates that the DNA
- 25 sample had a polymorphism was present that permitted cleavage by the specific restriction endonuclease. In contrast, if only one higher molecular weight band is observed (at the molecular weight of the PCR product) then the initial DNA sample had the polymorphism that could not be cleaved by the chosen restriction endonuclease. Finally, if both the higher molecular weight band and the two lower molecular weight bands are visible then the DNA sample contained both
- 30 polymorphisms, and therefore the DNA sample, and by extension the subject providing the DNA sample, was heterozygous for this polymorphism;

For example the Maxam-Gilbert technique for sequencing (MAXAM AM. and GILBERT W. Proc. Natl. Acad. Sci. USA (1977) 74(4):560-564) involves the specific chemical cleavage of

terminally labelled DNA. In this technique four samples of the same labeled DNA are each subjected to a different chemical reaction to effect preferential cleavage of the DNA molecule at one or two nucleotides of a specific base identity. The conditions are adjusted to obtain only partial cleavage, DNA fragments are thus generated in each sample whose lengths are dependent upon the position within the DNA base sequence of the nucleotide(s) which are subject to such cleavage. After partial cleavage is performed, each sample contains DNA fragments of different lengths, each of which ends with the same one or two of the four nucleotides. In particular, in one sample each fragment ends with a C, in another sample each fragment ends with a C or a T, in a third sample each ends with a G, and in a fourth sample each ends with an A or a G. When the products of these four reactions are resolved by size, by electrophoresis on a polyacrylamide gel, the DNA sequence can be read from the pattern of radioactive bands. This technique permits the sequencing of at least 100 bases from the point of labeling. Another method is the dideoxy method of sequencing was published by SANGER *et al.* (Proc. Natl. Acad. Sci. USA (1977) 74(12):5463-5467). The Sanger method relies on enzymatic activity of a DNA polymerase to synthesize sequence-dependent fragments of various lengths. The lengths of the fragments are determined by the random incorporation of dideoxynucleotide base-specific terminators. These fragments can then be separated in a gel as in the Maxam-Gilbert procedure, visualized, and the sequence determined. Numerous improvements have been made to refine the above methods and to automate the sequencing procedures. Similarly, RNA sequencing methods are also known. For example, reverse transcriptase with dideoxynucleotides have been used to sequence encephalomyocarditis virus RNA (ZIMMERN D. and KAESBERG P. Proc. Natl. Acad. Sci. USA (1978) 75(9):4257-4261). MILLS DR. and KRAMER FR. (Proc. Natl. Acad. Sci. USA (1979) 76(5):2232-2235) describe the use of Q β replicase and the nucleotide analog inosine for sequencing RNA in a chain-termination mechanism. Direct chemical methods for sequencing RNA are also known (PEATTIE DA. Proc. Natl. Acad. Sci. USA (1979) 76(4):1760-1764). Other methods include those of Donis-Keller *et al.* (1977, Nucl. Acids Res. 4:2527-2538), SIMONCSITS A. *et al.* (Nature (1977) 269(5631):833-836), AXELROD VD. *et al.* (Nucl. Acids Res. (1978) 5(10):3549-3563), and KRAMER FR. and MILLS DR. (Proc. Natl. Acad. Sci. USA (1978) 75(11):5334-5338). Nucleic acid sequences can also be read by stimulating the natural fluoresce of a cleaved nucleotide with a laser while the single nucleotide is contained in a fluorescence enhancing matrix (U.S. Pat. # 5,674,743); In a mini sequencing reaction, a primer that anneals to target DNA adjacent to a SNP is extended by DNA polymerase with a single nucleotide that is complementary to the polymorphic site. This method is based on the high accuracy of nucleotide incorporation by DNA polymerases. There are different technologies for analyzing the

primer extension products. For example, the use of labeled or unlabeled nucleotides, ddNTP combined with dNTP or only ddNTP in the mini sequencing reaction depends on the method chosen for detecting the products;

- 5 Probes used in hybridization can include double-stranded DNA, single-stranded DNA and RNA oligonucleotides, and peptide nucleic acids. Hybridization methods for the identification of single nucleotide polymorphisms or other mutations involving a few nucleotides are described in the U.S. Pat. 6,270,961; 6,025,136; and 6,872,530. Suitable hybridization probes for use in accordance with the invention include oligonucleotides and PNAs from about 10 to about 400 nucleotides,
10 alternatively from about 20 to about 200 nucleotides, or from about 30 to about 100 nucleotides in length.

- A template-directed dye-terminator incorporation with fluorescent polarization-detection (TDI-FP) method is described by FREEMAN BD. *et al.* (J Mol Diagnostics (2002) 4(4):209-215) for large
15 scale screening;

- Oligonucleotide ligation assay (OLA) is based on ligation of probe and detector oligonucleotides annealed to a polymerase chain reaction amplicon strand with detection by an enzyme immunoassay (VILLAHERMOSA ML. J Hum Virol (2001) 4(5):238-48; ROMPPANEN EL. Scand J Clin Lab Invest (2001) 61(2):123-9; IANNONE MA. *et al.* Cytometry (2000) 39(2):131-40);
20

- Ligation-Rolling Circle Amplification (L-RCA) has also been successfully used for genotyping single nucleotide polymorphisms as described in QI X. *et al.* Nucleic Acids Res (2001) 29(22):E116;
25

5' nuclease assay has also been successfully used for genotyping single nucleotide polymorphisms (AYDIN A. *et al.* Biotechniques (2001) (4):920-2, 924, 926-8.);

- 30 Polymerase proofreading methods are used to determine SNPs identities, as described in WO 0181631;

Detection of single base pair DNA mutations by enzyme-amplified electronic transduction is described in PATOLSKY F *et al.* Nat Biotech. (2001) 19(3):253-257;

Gene chip technologies are also known for single nucleotide polymorphism discrimination whereby numerous polymorphisms may be tested for simultaneously on a single array (EP 1120646 and GILLES PN. *et al.* Nat. Biotechnology (1999) 17(4):365-70);

5

Matrix assisted laser desorption ionization time of flight (MALDI-TOF) mass spectroscopy is also useful in the genotyping single nucleotide polymorphisms through the analysis of microsequencing products (HAFF LA. and SMIRNOV IP. Nucleic Acids Res. (1997) 25(18):3749-50; HAFF LA. and SMIRNOV IP. Genome Res. (1997) 7:378-388; SUN X. *et al.* Nucleic Acids Res. (2000) 28 e68; BRAUN A. *et al.* Clin. Chem. (1997) 43:1151-1158; LITTLE DP. *et al.* Eur. J. Clin. Chem. Clin. Biochem. (1997) 35:545-548; FEI Z. *et al.* Nucleic Acids Res. (2000) 26:2827-2828; and BLONDAL T. *et al.* Nucleic Acids Res. (2003) 31(24):e155).

10

Sequence-specific PCR methods have also been successfully used for genotyping single nucleotide polymorphisms (HAWKINS JR. *et al.* Hum Mutat (2002) 19(5):543-553). Alternatively, a Single-Stranded Conformational Polymorphism (SSCP) assay or a Cleavase Fragment Length Polymorphism (CFLP) assay may be used to detect mutations as described herein.

15

Alternatively, if a subject's sequence data is already known, then obtaining may involve retrieval of the subjects nucleic acid sequence data (for example from a database), followed by determining or detecting the identity of a nucleic acid or genotype at a polymorphic site by reading the subject's nucleic acid sequence at the one or more polymorphic sites.

20

Once the identity of a polymorphism(s) is determined or detected an indication may be obtained as to subject response to vasopressin receptor agonist administration based on the genotype (the nucleotide at the position) of the polymorphism of interest. In the present invention, polymorphisms in vasopressin pathway associated gene sequences, are used to predict a subject's response to vasopressin receptor agonist treatment. Methods for predicting a subject's response to vasopressin receptor agonist treatment may be useful in making decisions regarding the administration of vasopressin receptor agonist.

25

30

Methods of treatment of an inflammatory condition in a subject having an improved response genotype in a vasopressin pathway associated gene are described herein. An improved response may include an improvement subsequent to administration of said therapeutic agent, whereby the

subject has an increased likelihood of survival, reduced likelihood of organ damage or organ dysfunction (Brussels score), an improved APACHE II score, days alive and free of pressors, inotropes, and reduced systemic dysfunction (cardiovascular, respiratory, ventilation, central nervous system, coagulation [INR > 1.5], renal and/or hepatic).

5

As described above genetic sequence information or genotype information may be obtained from a subject wherein the sequence information contains one or more polymorphic sites in a vasopressin pathway associated gene sequence. Also, as previously described the sequence identity of one or more polymorphisms in a vasopressin pathway associated gene sequence of one or more subjects may then be detected or determined. Furthermore, subject response to administration of vasopressin receptor agonist may be assessed as described above. For example, the APACHE II scoring system or the Brussels score may be used to assess a subject's response to treatment by comparing subject scores before and after treatment. Once subject response has been assessed, subject response may be correlated with the sequence identity of one or more polymorphism(s). The correlation of subject response may further include statistical analysis of subject outcome scores and polymorphism(s) for a number of subjects.

10

15

20

25

Methods of treatment of an inflammatory condition in a subject having one or more of the risk genotypes in AVP, AVPR1A LNPEP or LRAP (or a SNP in linkage disequilibrium thereto) associated with improved response to a therapeutic agent are described herein. An improved response may include an improvement subsequent to administration of said therapeutic agent, whereby the subject has an increased likelihood of survival, reduced likelihood of organ damage or organ dysfunction (Brussels score), an improved APACHE II score, days alive and free of pressors, inotropes, and reduced systemic dysfunction (cardiovascular, respiratory, ventilation, central nervous system, coagulation [INR > 1.5], renal and/or hepatic).

30

As described above genetic sequence information or genotype information may be obtained from a subject wherein the sequence information contains one or more single nucleotide polymorphic sites in AVP, AVPR1A LNPEP or LRAP sequences. Also, as previously described the sequence identity of one or more single nucleotide polymorphisms in the AVP, AVPR1A or LNPEP sequences of one or more subjects may then be detected or determined. Furthermore, subject outcome or prognosis may be assessed as described above, for example the APACHE II scoring system or the Brussels score may be used to assess subject outcome or prognosis by comparing subject scores before and after treatment. Once subject outcome or prognosis has been assessed,

subject outcome or prognosis may be correlated with the sequence identity of one or more single nucleotide polymorphism(s). The correlation of subject outcome or prognosis may further include statistical analysis of subject outcome scores and polymorphism(s) for a number of subjects.

3. Analytical Methods

Patient Cohort Selection

a. Intensive Care Unit (ICU) Cohort Inclusion Criteria

All subjects admitted to the ICU of St. Paul's Hospital (SPH) were screened for study inclusion.

SPH ICU is a mixed medical-surgical ICU in a tertiary care, university-affiliated teaching hospital. Subjects were included in the study if they met at least two out of four SIRS criteria: 1) fever ($> 38^{\circ}\text{C}$) or hypothermia ($< 36^{\circ}\text{C}$), 2) tachycardia (> 90 beats/minute), 3) tachypnea (> 20 breaths/minute), $\text{PaCO}_2 < 32$ mm Hg, or need for mechanical ventilation, and 4) leukocytosis (total leukocyte count $> 12,000 \text{ mm}^3$) or leukopenia ($< 4,000 \text{ mm}^3$). Subjects were included in the analysis if they met the diagnostic criteria for septic shock (sepsis *and* cardiovascular dysfunction (as defined by Brussels scoring system) *and* one other organ dysfunction) on admission to the ICU. Subjects were excluded if blood could not be obtained for genotype analysis. Baseline characteristics (age, gender, admission APACHE II score (KNAUS WA. *et al.* Crit. Care Med. (1985) 13:818-829), together with medical vs. surgical diagnosis KNAUS WA. *et al.* Chest (1991) 100:1619-1636.) were recorded on admission to the ICU. The full cohort meeting these criteria included 1072 Caucasian subjects and 153 Asian subjects.

The Institutional Review Board at Providence Health Care and the University of British Columbia approved this study.

b. Biological Plausibility (BP) Cohort Inclusion Criteria

An independent cohort of Caucasian subjects ($N = 102$) scheduled for first time elective coronary artery bypass grafting that required cardiopulmonary bypass is referred to as the "Biological Plausibility" (BP) cohort. Significant SNP-biomarker associations identified in this cohort may provide insight into biological processes underlying SNP-phenotype associations observed in the ICU cohort or subsets of the ICU cohort.

For the BP cohort, individuals were included in the analysis if they were met diagnostic criteria for systemic inflammatory response syndrome (SIRS). Subjects were excluded from the study if they

had undergone 1) urgent or emergency cardiopulmonary bypass surgery or 2) valve or repeat cardiac surgery. Subjects with urgent or emergency cardiopulmonary bypass surgery were excluded because they may have had an inflammatory response due to other triggers (i.e. shock). Subjects with valve surgery or repeat surgery were excluded because they could have had different pre-operative pathophysiology or longer total surgical and cardiopulmonary bypass time than subjects having elective cardiopulmonary bypass surgery.

The Institutional Review Board at Providence Health Care and the University of British Columbia approved this study.

Clinical Phenotype

The primary outcome variable evaluated in this study was 28-day mortality. Various organ dysfunctions were considered as secondary outcome variables. Baseline demographics recorded were age, gender, admission APACHE II score (KNAUS WA. *et al.* Crit Care Med (1985) 13:818-829), and medical or surgical diagnosis on admission to the ICU (based on the APACHE III diagnostic codes) (KNAUS WA. *et al.* Chest (1991) 100:1619-1636) (**TABLE 2B**).

TABLE 2B. Baseline characteristics key.

Baseline Key	
AGE	Given In Years
GENDER	Percentage of Male Subjects
APACHE II	APACHE II score
% SURGICAL	The % of Subjects with a SURGICAL ICU admitting diagnosis
SEP.ADMIT	Sepsis upon admission
SEP.ANY	Sepsis anytime during admission
SS.ADMIT	Septic shock upon admission
SS.ANY	Septic shock anytime during admission

After meeting the inclusion criteria, data were recorded for each 24-hour period (8 am to 8 am) for 28-days after ICU admission or until hospital discharge to evaluate organ dysfunction, the intensity of SIRS (Systemic Inflammatory Response Syndrome) and sepsis. Raw clinical and laboratory variables were recorded using the worst or most abnormal variable for each 24-hour period with the exception of Glasgow Coma Score, for which the best possible score for each 24-hour period was recorded. Missing data on the date of admission was assigned a normal value and missing data after day one was substituted by carrying forward the value from the previous day. When data collection for each patient was complete, all patient identifiers were removed from all records and the patient file was assigned a unique random number linked with the blood samples. The

completed raw data file was used to calculate descriptive and severity of illness scores using standard definitions as described below.

Organ dysfunction was first evaluated at baseline and then daily using the Brussels score (SIBBALD WJ. and VINCENT JL. *Chest* (1995) 107(2):522-7) (see TABLE 2A in General Methods Section). If the Brussels score was moderate, severe, or extreme dysfunction then organ dysfunction was recorded as present on that day. To correct for deaths during the observation period, we calculated the days alive and free of organ dysfunction (RUSSELL JA. *et al.* *Crit Care Med* (2000) 28(10):3405-11 and BERNARD GR. *et al.* *Chest* (1997) 112(1):164-72) (TABLE 2C). For example, the severity of cardiovascular dysfunction was assessed by measuring days alive and free of cardiovascular dysfunction over a 28-day observation period. Days alive and free of cardiovascular dysfunction was calculated as the number of days after inclusion that a patient was alive and free of cardiovascular dysfunction over 28-days. Thus, a lower score for days alive and free of cardiovascular dysfunction indicates more cardiovascular dysfunction. The reason that days alive and free of cardiovascular dysfunction is preferable to simply presence or absence of cardiovascular dysfunction is that severe sepsis has a high acute mortality so that early death (within 28-days) precludes calculation of the presence or absence of cardiovascular dysfunction in dead subjects. Organ dysfunction has been evaluated in this way in observational studies (Russell JA. *et al.* *Crit Care Med* (2000) 28(10):3405-11) and in randomized controlled trials of new therapy in sepsis, acute respiratory distress syndrome (BERNARD GR. *et al.* *N Engl J Med* (1997) 336(13):912-8) and in critical care (HEBERT PC. *et al.* *N Engl J Med* (1999) 340(6):409-17).

To further evaluate cardiovascular, respiratory, and renal function we also recorded, during each 24-hour period, vasopressor support, mechanical ventilation, and renal support, respectively.

Vasopressor use was defined as dopamine > 5 µg/kg/min or any dose of norepinephrine, epinephrine, vasopressin, or phenylephrine. Mechanical ventilation was defined as need for intubation and positive airway pressure (i.e. T- piece and mask ventilation were not considered ventilation). Renal support was defined as hemodialysis, peritoneal dialysis, or any continuous renal support mode (e.g. continuous veno-venous hemodialysis).

As a cumulative measure of the severity of SIRS, the presence of two, three or four of the SIRS criteria was scored each day over the 28-day observation period SIRS was considered present when subjects met at least two of four SIRS criteria. The SIRS criteria were 1) fever (>38 °C) or hypothermia (<36 °C), 2) tachycardia (>90 beats/min in the absence of beta-blockers, 3) tachypnea

(>20 breaths/min) or need for mechanical ventilation, and 4) leukocytosis (total leukocyte count > 12,000/ μ L or <4,000/ μ L).

TABLE 2C. Primary and secondary outcome variables for the ICU cohort and subsets

Survival and Days alive and free (DAF) of organ dysfunction Key	
SURVIVAL	28-Day Survival
ALI.DAF	Days alive and free of acute Lung Injury
PRESS.DAF	Days alive and free of any vasopressors
PRESS2.DAF	Days alive and free of more than 2ug/min of vasopressors
PRESS5.DAF	Days alive and free of more than 5ug/min of vasopressors
PRESS15.DAF	Days alive and free of more than 15ug/min of vasopressors
INO.DAF	Days alive and free of inotropes
SIRS2.DAF	Days alive and free of 2 of 4 SIRS criteria
SIRS3.DAF	Days alive and free of 3 of 4 SIRS criteria
SIRS4.DAF	Days alive and free of 4 of 4 SIRS criteria
STER.DAF	Days alive and free of steroids
CVS.DAF	Days alive and free of cardiovascular dysfunction
RESP.DAF	Days alive and free of respiratory dysfunction
PF300.DAF	Days alive and free of PaO ₂ /FiO ₂ less than 300mHg
VENT.DAF	Days alive and free of mechanical ventilators
CNS.DAF	Days alive and free of neurological dysfunction
COAG.DAF	Days alive and free of coagulation dysfunction
INR.DAF	Days alive and free of international normalized ratio > 1.5
ACRF.DAF	Days alive and free of acute renal failure
ANYREN.DAF	Days alive and free of any type of renal dysfunction
RENSUP.DAF	Days alive and free of renal support
ACHEP.DAF	Days alive and free of acute hepatic dysfunction
ANYHEP.DAF	Days alive and free of any type of hepatic dysfunction
AFFD.DAF	Days alive and free of acute Failure
FFD.DAF	Days alive and free of acute or chronic failure

Baseline characteristics for the Biological Plausibility cohort included age in years, % males %smokers, % diabetes, % hypertension, ejection fraction, bypass time, clamp time and aprotinin.

- 5 Outcome variables measured in the Biological Plausibility cohort included Granulocyte colony stimulating factor (GCSF), Interleukin 10 (IL10), Interleukin receptor 1a (IL1ra), Interleukin 6 (IL6), Interleukin 8 (IL8) and Monocyte Chemoattractant Protein 1 (MCP1). A key for the variables evaluated in the Biological Plausibility cohort is provided in TABLE 2D.

10 TABLE 2D. Biological plausibility key.

Biological Plausibility Key	
H.TENSE	Hypertensive (% hypertension)
EJEC.FRAC	Ejection Fraction
BYPASS	Bypass Time (hours)
CLAMP	Clamp Time (hours)
APROTININ	Aprotinin Use
GCSF	Granulocyte Colony Stimulating Factor (pg/mL)
IL10	Interleukin 10 (pg/mL)
IL1ra	Interleukin receptor 1a (pg/mL)

IL6	Interleukin 6 (pg/mL)
IL8	Interleukin 8 (pg/mL)
MCP	Monocyte Chemoattractant Protein (pg/mL)
X.diff	DELTA for protein X preoperatively and 3 hours postoperatively
X.0	protein X levels preoperatively
X.3	protein X levels 3 hours postoperatively

Selection of SNPs for Genotyping

Publicly available genotype data was queried from the International HapMap Project

(www.hapmap.org) and Perlegen Sciences, Inc. (www.perlegen.com) to select a set of tag SNPs

(tSNPs) in the LNPEP, AVP and AVPR1A regions each having a minor allele frequency (MAF) greater than 0.05. These tSNPs were chosen using several statistical methods, including pairwise linkage disequilibrium (LD) measures (DEVLIN B. and RISCH N. *Genomics* (1995) 29:311-322), haplotype (STEPHENS M. *et al.* *Am J Hum Genet.* (2001) 68:978-989; and EXCOFFIER L. and SLATKIN M. *Mol. Biol. Evol.* (1995) 12(5):921-927) and haplotype block (HAWLEY ME. and KIDD KK. *J. Heredity.* (1995) 86:409-411) patterns, as well as phylogenetic (cladistic) distance metrics (HAWLEY ME. and KIDD KK. (1995)). When these methods did not yield a parsimonious conclusion, as was the case for AVP, SNPs closest in physical distance to the given gene of interest were selected. Each polymorphism was genotyped in the ICU Cohort and the Biological Plausibility Cohort.

Sample Analysis

Sample Preparation

Discarded whole blood samples, stored at 4°C, were collected from the hospital laboratory. DNA was extracted from buffy coat using the QIAamp DNA Midi kit (Qiagen, Mississauga, ON, Canada). After extraction, the DNA samples were transferred to 1.5 mL cryotubes, bar coded and cross-referenced with a unique patient number and stored at -80°C.

ABI Genotyping

Single nucleotide polymorphisms in AVP, LNPEP and AVPR1A were genotyped using the 5' nuclease, Taqman™ (Applied Biosystems; Foster City, CA) polymerase chain reaction (PCR) method. TABLE 2E provides a complete list of the 10 SNPs genotyped for this study.

TABLE 2E: List of tSNPs genotyped in ICU and Biological Plausibility Cohorts

Gene	tSNPs			
LNPEP	rs10051637	rs38041	rs27711	rs18059
AVP	rs1410713	rs857240	rs857242	
AVPR1A	rs3803107	rs10877970	rs1495027	

Illumina Genotyping

Single nucleotide polymorphisms in AVP, LNPEP and AVPR1A were genotyped using the Illumina Golden Gate™ assay from 250 ng of DNA extracted from buffy coat. A list of these
5 SNPs can be found labeled as cohort 'I' in TABLE 1B found in the General Methods section.

Sequencing of LNPEP region

Sequencing of a 157.1 kb region including the LNPEP and LRAP genes was undertaken using DNA extracted from six CEPH (i.e., Centre d'Etudes du Polymorphisme Humain) individuals
10 obtained through the Coriell Institute for Medical Research using the Applied Biosystems 3730 platform. Ascertained polymorphisms were investigated for NCBI rs Id annotation using the UCSC genome browser (<http://genome.ucsc.edu>). If a polymorphism was found to not have an rs Id assigned, it was given a numeric id prefixed by 'sirius' (i.e. siriusx).

Linkage Disequilibrium Analysis

Included in this patent are SNPs found to be associated with 28-day survival or response to vasopressin as well as SNPs determined to be in LD with the former. LD SNPs were ascertained using either Haploview (BARRETT JC. *et al.* Bioinformatics (2005) 21(2):263-5
(<http://www.broad.mit.edu/mpg/haploview/>)) or the LD function in the Genetics Package in R (R
20 Core Development Group, 2005 - R Development Core Team (www.R-project.org). A R^2 threshold of 0.5 was required in order that a SNP be considered in LD with those claimed herein. All LD SNPs are shown in table 1B.

The AVP, AVPR1A, LNPEP and LRAP genes are central to the action of vasopressin given that
25 vasopressin induces vasoconstriction by signaling through the AVPR1A receptor and that vasopressin activity is inhibited when cleaved by LNPEP. Similar protein homology between LNPEP and LRAP suggest that these two genes arose through an ancient gene duplication event (DANCHIN E *et al.*, *Immunol Rev* (2004) 198:216-332). This homology and the observation of an extended linkage disequilibrium (LD) block throughout the LRAP and LNPEP region (HapMap
30 Phase II data; www.hapmap.org) supports the inclusion of LRAP in the vasopressin pathway.

Furthermore, variability in response to infused (*i.e.*, administered) vasopressin most likely occurs as a result of polymorphisms in the AVP, AVPR1A, LNPEP and LRAP genes because the proteins that these genes encode are central to the actions of native and infused vasopressin (AVP).

5 Statistical Analysis

A description of the statistical analysis used is provided for each example in the following sections.

10 EXAMPLES

EXAMPLE 1: RESPONSE TO VASOPRESSIN IN SEPTIC SHOCK

METHODS

15 Cohort Selection

To investigate whether genotype predicts response to vasopressin, a subset of Caucasian subjects with septic shock and treated with vasopressin (N = 103) were compared to a control group of Caucasian subjects with septic shock who had not been administered vasopressin (N = 103).

Vasopressin-treated and control subjects were matched based on age, gender, admission APACHE II score, medical versus surgical diagnosis and days alive and free of 3 of 4 systematic inflammatory response syndrome (SIRS) criteria. The baseline characteristics of these groups are presented in Table 3.1.

TABLE 3.1

25 Baseline characteristics of cases (Caucasian ICU septic shock subjects treated with vasopressin) and controls (Caucasian ICU subjects with septic shock, matched (see text for details) and not treated with vasopressin). For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

ALL	Control (N=103)	Cases (Vasopressin-treated) (N=103)	Combined (N=206)	Test Statistic
AGE	44 56 71.5	47 60 68.5	44.25 58.5 70	F=0.14 d.f.=1,204 P=0.713
GENDER	69% (71/103)	78% (80/103)	73% (151/206)	X ² =2.01 d.f.=1 P=0.156
APACHE II	24 29 34	25 30 37	24.25 29 34	F=0.38 d.f.=1,204 P=0.537
% SURGICAL	44% (45/103)	44% (45/103)	44% (90/206)	X ² =0 d.f.=1 P=1

30 Data Analysis

All data analysis was carried out using statistical packages available in R (R Core Development Group, 2005 - R Development Core Team (www.R-project.org). R: A language and environment

for statistical computing, Vienna, Austria, 2005). Chi-square and Kruskal-Wallis (KW) test statistics were used in conjunction with Cox proportional hazards (CPH) regression to identify significant SNP-phenotype associations, as well as to identify significantly different baseline characteristics (age, gender, admitting APACHE II score, and medical vs. surgical admitting diagnosis) requiring post-hoc, multivariate adjustment. The control population was selected by matching, using the MatchIt package in R, by age, gender, APACHE II score, medical vs. surgical diagnosis, and days alive and free of 3 of 4 SIRS criteria. There were no differences in baseline characteristics between vasopressin-treated cases and controls.

Using 28-day survival as the outcome variable and a chi-squared test of significance, SNP-phenotype comparisons were undertaken within and between treatment groups. We considered a by-genotype effect to be significant when two criteria were fulfilled. First, we expected an increase in 28-day survival for vasopressin-treated subjects compared to controls. Second, we required a p-value < 0.1 for this difference in 28-day survival. When both criteria were met, we considered the allele or genotype predicting increased 28-day survival with vasopressin treatment to be an “improved response genotype” (IRG). Only IRG polymorphisms were evaluated for organ dysfunction results and were compared between vasopressin-treated subjects and matched controls using a Kruskal-Wallis test.

Results

1.1 Leucyl/Cystinyl Amino peptidase (LNPEP)

1.1.1 Adverse Response to Vasopressin Treatment of subjects who have the CC Genotype of LNPEP rs18059 and Improved Response to Vasopressin Treatment of subjects who have the TT Genotype of LNPEP rs18059

It was unknown whether SNPs within the LNPEP gene and those regions immediately upstream and downstream would be associated with the response to vasopressin. It was found that LNPEP rs18059 can be used to predict response (28-day survival) to vasopressin in subjects with septic shock. Of 103 vasopressin-treated and 103 matched-control subjects with septic shock, 73 and 81 were respectively genotyped for LNPEP rs18059. Baseline characteristics for subjects with genotypes are shown in Table 3.2 and Table 3.3.

TABLE 3.2

Baseline characteristics of a group of vasopressin-treated Caucasian septic-shock subjects by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs18059. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

VASOPRESSIN	CC (N=27)	CT (N=33)	TT (N=13)	Combined (N=73)	Test Statistic
AGE	44 60 69.5	48 64 72	39 57 66	47 60 68	F=0.7 d.f.=2,70 P=0.5
GENDER	67% (18/27)	85% (28/33)	77% (10/13)	77% (56/73)	X ² =2.75 d.f.=2 P=0.253
APACHE II	25 32 40	23 30 37	26 29 34	25 30 37	F=0.39 d.f.=2,70 P=0.678
% SURGICAL	48% (13/27)	39% (13/33)	31% (4/13)	41% (30/73)	X ² =1.17 d.f.=2 P=0.558

TABLE 3.3

Baseline characteristics of a vasopressin untreated matched control group of Caucasian ICU septic shock subjects by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs18059. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

CONTROL	CC (N=18)	CT (N=43)	TT (N=20)	Combined (N=81)	Test Statistic
AGE	39.25 46.5 62.75	44 52 66.5	48.75 67 74	44 56 71.5	F=2.58 d.f.=2,78 P=0.0824
GENDER	83% (15/18)	67% (29/43)	50% (10/20)	67% (54/81)	Chi =4.76 d.f.=2 P=0.0925
APACHE II	23.25 26.5 32.5	26.5 31 37	25 29 34	24 29 34	F=2.24 d.f.=2,78 P=0.113
% SURGICAL	22% (4/18)	33% (14/43)	50% (10/20)	35% (28/81)	Chi=3.4 d.f.=2 P=0.183

Table 3.4 and Table 3.5 show 28-day survival and organ dysfunction data by LNPEP rs18059 genotype for vasopressin-treated and control subjects respectively. Table 3.6 shows the differences in survival and measures of organ dysfunction between by LNPEP rs18059 genotype between vasopressin-treated and control subjects.

In general, Table 3.6 shows that vasopressin-treated subjects with LNPEP rs18059 CC had lower survival and more organ dysfunction than controls as evidenced by negative values for the LNPEP rs18059 CC subjects in the DELTA column. In contrast, vasopressin-treated subjects with the LNPEP rs18059 TT genotype had increased survival and improved organ function (shown by greater DAF) compared to controls as demonstrated by the generally positive values in DELTA column. There was a small increase in survival of subjects with the LNPEP rs18059 CT genotype in vasopressin-treated subjects (36 %) compared to controls (28 %).

TABLE 3.4

A response association of leucyl/cystinyl aminopeptidase (LNPEP) rs18059 in a group of Caucasian ICU septic shock subjects treated with vasopressin. For 28-day survival, data is given as % (N survived / N total). N, number of subjects. For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile.

VASOPRESSIN-TREATED	CC (N=27)	CT (N=33)	TT (N=13)	Combined (N=73)	Test Statistic
SURVIVAL	44% (12/27)	36% (12/33)	38% (5/13)	40% (29/73)	Chisquare=0.42 d.f.=2 P=0.812
DAYS ALIVE	7.5 19 28	3 13 28	2 8 28	3 13 28	F=0.71 d.f.=2,70 P=0.496

ALI.DAF	2 8 16	1 3 19	1 4 12	1 6 17	F=0.23 d.f.=2,70 P=0.798
PRESS.DAF	0 5 19	0 3 18	0 0 22	0 3 19	F=0.21 d.f.=2,70 P=0.812
PRESS2.DAF	0 5 20.5	0 3 18	0 0 22	0 3 20	F=0.16 d.f.=2,70 P=0.855
PRESS5.DAF	0 11 20.5	0 3 19	0 0 23	0 3 21	F=0.12 d.f.=2,70 P=0.887
PRESS15.DAF	1 12 23	0 6 22	0 0 25	0 7 23	F=0.51 d.f.=2,70 P=0.6
INO.DAF	6 12 28	2 12 26	2 8 22	2 12 26	F=1.24 d.f.=2,70 P=0.296
SIRS2.DAF	0 0 3.5	0 0 2	0 0 1	0 0 2	F=0.12 d.f.=2,70 P=0.883
SIRS3.DAF	1.5 4 13.5	0 4 9	0 2 14	1 4 11	F=0.41 d.f.=2,70 P=0.667
SIRS4.DAF	5.5 14 21.5	2 8 23	2 5 20	2 10 23	F=0.51 d.f.=2,70 P=0.6
STER.DAF	0 3 17.5	1 6 20	1 2 7	1 4 19	F=0.19 d.f.=2,70 P=0.824
CVS.DAF	0 2 14.5	0 0 13	0 0 21	0 1 14	F=0.38 d.f.=2,70 P=0.684
RESP.DAF	0 2 7	0 0 5	0 0 8	0 0 8	F=0.56 d.f.=2,70 P=0.573
PF300.DAF	0 0 2	0 0 0	0 0 0	0 0 1	F=3.61 d.f.=2,70 P=0.0321
VENT.DAF	0 0 7	0 0 5	0 0 8	0 0 8	F=0.35 d.f.=2,70 P=0.707
CNS.DAF	6.5 14 27	2 6 24	2 7 24	2 11 25	F=1.29 d.f.=2,70 P=0.281
COAG.DAF	2 11 26.5	1 5 26	1 7 26	1 8 26	F=0.53 d.f.=2,70 P=0.588
INR.DAF	5.5 15 26.5	1 8 27	1 5 27	2 8 27	F=0.29 d.f.=2,70 P=0.746
ACRF.DAF	2.5 8 27	0 2 13	0 2 26	0 5 19	F=2.32 d.f.=2,70 P=0.106
ANYREN.DAF	2.5 8 24	0 2 13	0 2 26	0 5 18	F=1.8 d.f.=2,70 P=0.173
RENSUP.DAF	1 6 27.5	2 5 23	1 3 28	1 5 27	F=0.23 d.f.=2,70 P=0.796
ACHEP.DAF	1.5 11 24.5	2 9 24	2 3 28	2 9 27	F=0.1 d.f.=2,70 P=0.906
ANYHEP.DAF	1.5 11 24.5	2 9 24	2 3 28	2 9 27	F=0.07 d.f.=2,70 P=0.937

TABLE 3.5

A response association of leucyl/cystinyl aminopeptidase (LNPEP) rs18059 in a matched control group of Caucasian ICU septic shock subjects not treated with vasopressin. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.. For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile.

CONTROL	CC (N=18)	CT (N=43)	TT (N=20)	Combined (N=81)	Test Statistic
SURVIVAL	67% (12/18)	28% (12/43)	15% (3/20)	33% (27/81)	Chisquare=12.59 d.f.=2 P=0.00184
DAYS ALIVE	14.25 28 28	2 6 28	2.5 5 7.25	3 8 2	F=7.24 d.f.=2,78 P=0.00130
ALI.DAF	3.25 12.5 21.75	1 2 9	1 3.5 7	1 5 14	F=3.04 d.f.=2,78 P=0.0537
PRESS.DAF	9.25 24.5 26	0 3 17.5	0 0 4.25	0 4 22	F=7.98 d.f.=2,78 P<0.001
PRESS2.DAF	9.5 24.5 26	0 3 17.5	0 0 4.25	0 4 22	F=8.05 d.f.=2,78 P<0.001
PRESS5.DAF	10 25.5 27	0 4 19.5	0 0.5 5	0 4 23	F=7.69 d.f.=2,78 P<0.001
PRESS15.DAF	14.25 26.5 28	0 5 22	0 2 6.25	0 5 26	F=7.52 d.f.=2,78 P=0.00103
INO.DAF	14.25 26.5 28	2 5 20.5	0.75 3 7.25	2 6 28	F=5.54 d.f.=2,78 P=0.00561
SIRS2.DAF	0 0.5 10.75	0 0 1.5	0 0 0	0 0 1	F=2.28 d.f.=2,78 P=0.109
SIRS3.DAF	2 4.5 16.5	0 2 6	0.75 1 2	0 2 7	F=2.81 d.f.=2,78 P=0.0664
SIRS4.DAF	9.25 16 26.75	1 5 19.5	1.75 3.5 6.25	2 6 22	F=6.37 d.f.=2,78 P=0.00273
STER.DAF	2.75 17 27.5	1 4 1	1 3.5 7	1 5 21	F=1.78 d.f.=2,78 P=0.175
CVS.DAF	4.75 21.5 24.75	0 2 15.5	0 0 4	0 2 19	F=6.7 d.f.=2,78 P=0.00206
RESP.DAF	1.25 8.5 19.75	0 1 7.5	0 0.5 3.25	0 1 10	F=3.45 d.f.=2,78 P=0.0365
PF300.DAF	0 0 2	0 0 1	0 0 1	0 0 1	F=0.52 d.f.=2,78 P=0.598
VENT.DAF	0 8.5 19.75	0 0 7	0 0 1.5	0 0 10	F=3.53 d.f.=2,78 P=0.0342
CNS.DAF	11 25.5 27	0.5 4 23	0.75 4 7	1 7 25	F=8.55 d.f.=2,78 P<0.001
COAG.DAF	14.25 28 28	1 3 21	0.75 5 7.25	1 6 25	F=9 d.f.=2,78 P<0.001
INR.DAF	14 24.5 28	0 3 16.5	0 3 5.5	0 4 22	F=8.74 d.f.=2,78 P<0.001
ACRF.DAF	9.25 22.5 27	0 4 10.5	0 0.5 4	0 4 20	F=8.63 d.f.=2,78 P<0.001

ANYREN.DAF	9.25 22.5 27	0 2 10.5	0 0 4	0 3 20	F=9.64 d.f.=2,78 P<0.001
RENSUP.DAF	5.5 23 28	1 2 9.5	1 2.5 7.25	1 4 18	F=5.85 d.f.=2,78 P=0.00431
ACHEP.DAF	14.25 28 28	1 4 20	1 5 7.25	1 6 28	F=6.46 d.f.=2,78 P=0.00254
ANYHEP.DAF	14.25 28 28	1 4 20	1 5 7.25	1 6 28	F=6.73 d.f.=2,78 P=0.00201

TABLE 3.6

Difference in response association of leucyl/cystinyl aminopeptidase (LNPEP) rs18059 between cases (vasopressin-treated group) (Treat) and controls (vasopressin untreated matched control) (Cont) of Caucasian ICU subjects diagnosed with septic shock. For all variables besides 28-day survival, data is presented as medians. For 28-day survival, data is presented as % (N survived / N total). N, number of subjects.

	rs18059 CC			rs18059 CT			rs18059 TT		
	(N=27)	(N=18)		(N=33)	(N=43)		(N=13)	(N=20)	
	Treat	Cont	DELTA	Treat	Cont	DELTA	Treat	Cont	DELTA
SURVIVAL	44% (12)	67% (12)	-23%	36% (12)	28% (12)	8%	38% (5)	15% (3)	23%
DAYS ALIVE	19	28	-9	13	6	7	8	5	3
ALI.DAF	8	12.5	-4.5	3	2	1	4	3.5	0.5
PRESS.DAF	5	24.5	-19.5	3	3	0	0	0	0
PRESS2.DAF	5	24.5	-19.5	3	3	0	0	0	0
PRESS5.DAF	11	25.5	-14.5	3	4	-1	0	0.5	-0.5
PRESS15.DAF	12	26.5	-14.5	6	5	1	0	2	-2
INO.DAF	12	26.5	-14.5	12	5	7	8	3	5
SIRS2.DAF	0	0.5	-0.5	0	0	0	0	0	0
SIRS3.DAF	4	4.5	-0.5	4	2	2	2	1	1
SIRS4.DAF	14	16	-2	8	5	3	5	3.5	1.5
STER.DAF	3	17	-14	6	4	2	2	3.5	-1.5
CVS.DAF	2	21.5	-19.5	0	2	-2	0	0	0
RESP.DAF	2	8.5	-6.5	0	1	-1	0	0.5	-0.5
PF300.DAF	0	0	0	0	0	0	0	0	0
VENT.DAF	0	8.5	-8.5	0	0	0	0	0	0
CNS.DAF	14	25.5	-11.5	6	4	2	7	4	3
COAG.DAF	11	28	-17	5	3	2	7	5	2
INR.DAF	15	24.5	-9.5	8	3	5	5	3	2
ACRF.DAF	8	22.5	-14.5	2	4	-2	2	0.5	1.5
ANYREN.DAF	8	22.5	-14.5	2	2	0	2	0	2
RENSUP.DAF	6	23	-17	5	2	3	3	2.5	0.5
ACHEP.DAF	11	28	-17	9	4	5	3	5	-2
ANYHEP.DAF	11	28	-17	9	4	5	3	5	-2

A logistic regression approach was used to test for a statistically significant interaction between genotype and vasopressin use as predicted by 28-day survival. **TABLE 3.7** shows that there is a statistically significant interaction between LNPEP rs18059 genotype, vasopressin treatment and survival ($P = 0.0391$), confirming that treatment with vasopressin decreases 28-day survival in LNPEP rs18059 CC subjects. In contrast, 28-day survival for vasopressin-treated subjects with the LNPEP rs18059 TT genotype is improved compared with controls. Following adjustment for age, admission APACHE II score, gender, medical, surgical diagnosis and 3 of 4 systematic

inflammatory response syndrome (SIRS) criteria, there was still a statistically significant interaction of the LNPEP rs18059 genotype, treatment with vasopressin and survival ($P = 0.0555$)

TABLE 3.7

5 Interaction between vasopressin use vs. no vasopressin use (controls) and CC or CT genotype vs. TT genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs18059 on 28-day survival.

	Estimate	Std. Error	z value	Pr(> z)
Vasopressin vs. controls + genotype interaction	-2.1809	1.057	-2.063	0.03908
Vasopressin vs. controls + genotype interaction - Adjusted	-2.2301	1.165	-1.914	0.05559

1.1.2 Adverse Response to Vasopressin Treatment of Subjects Who Have the AA Genotype of LNPEP rs27711 and Improved Response to Vasopressin Treatment of Subjects Who Have the GG Genotype of LNPEP rs27711

It was unknown whether SNPs within the LNPEP gene and those regions immediately upstream and downstream are associated with the response to vasopressin. It was found that LNPEP rs27711 can be used to predict response to vasopressin in subjects with septic shock using 28-day survival and measures of organ dysfunction as outcome variables. Of 103 vasopressin-treated and 103 matched-control subjects with septic shock, 70 and 81 were respectively genotyped for LNPEP rs27711. Baseline characteristics for subjects with genotypes are shown in Table 3.8 and Table 3.9. LNPEP rs27711 is in linkage disequilibrium with, for example, LNPEP rs18059 and LNPEP rs10051637, which were also genotyped in this cohort.

TABLE 3.8

Baseline characteristics of vasopressin-treated Caucasian septic-shock subjects by LNPEP rs27711 genotype. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

VASOPRESSIN	AA (N=21)	AG (N=28)	GG (N=21)	Combined (N=70)	Test Statistic
AGE	43 58 71	50.25 63.5 72	39 60 68	47 60 68.5	$F=0.32$ d.f.=2,67 $P=0.728$
GENDER	71% (15/21)	75% (21/28)	81% (17/21)	76% (53/70)	$\chi^2=0.53$ d.f.=2 $P=0.767$
APACHE II	25 33 41	23.75 29.5 36.25	26 29 36	25 30 37	$F=0.68$ d.f.=2,67 $P=0.512$
% SURGICAL	43% (9/21)	46% (13/28)	29% (6/21)	40% (28/70)	$\chi^2=1.7$ d.f.=2 $P=0.428$

TABLE 3.9

Baseline characteristics of a group of Caucasian septic-shock control subjects by LNPEP rs27711 genotype. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

CONTROL	AA (N=10)	AG (N=45)	GG (N=26)	Combined (N=81)	Test Statistic
---------	--------------	--------------	--------------	--------------------	-------------------

AGE	39.25 45.5 58.5	43 52 67	49 66 74	44 56 71.5	F=3.59 d.f.=2,78 P=0.0322
GENDER	80% (8/10)	67% (30/45)	62% (16/26)	67% (54/81)	X ² =1.11 d.f.=2 P=0.575
APACHE II	23.25 26 32.5	26 30 34	27 30.5 38	24 29 34	F=1.26 d.f.=2,78 P=0.29
% SURGICAL	20% (2/10)	36% (16/45)	38% (10/26)	35% (28/81)	X ² =1.13 d.f.=2 P=0.568

Tables 3.10, 3.11 and 3.12 contain 28-day survival and organ dysfunction data for septic-shock subjects genotyped for LNPEP rs27711. In general, vasopressin-treated subjects with the LNPEP rs27711 AA genotype had a dramatically decreased survival (43 %) compared to controls (60 %) as demonstrated by the negative values in the LNPEP rs27711 AA DELTA column in Table 3.12. In general, vasopressin-treated subjects with the LNPEP rs27711 AA genotype also had increased organ dysfunction as demonstrated by fewer DAF of organ dysfunction compared with controls. In contrast, vasopressin –treated subjects with the LNPEP rs27711 GG genotype had an increased survival (33 %) compared to controls (19 %) as demonstrated by the positive values in the LNPEP rs27711 GG DELTA column in Table 3.12.

TABLE 3.10

A response association of leucyl/cystinyl aminopeptidase (LNPEP) rs27711 in a group of Caucasian ICU septic shock subjects who were treated with vasopressin. For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

VASOPRESSIN	AA (N=21)	AG (N=28)	GG (N=21)	Combined (N=70)	Test Statistic
SURVIVAL	43% (9)	36% (10)	33% (7)	37% (26)	Chisquare=0.45 d.f.=2 P=0.799
DAYS ALIVE	7 12 28	3 17.5 28	2 8 28	3 12.5 28	F=0.49 d.f.=2,67 P=0.615
ALL.DAF	2 6 12	2 9 21	1 2 12	1 5.5 17	F=1.65 d.f.=2,67 P=0.201
PRESS.DAF	0 1 19	0 4 16.25	0 0 21	0 1 18	F=0.03 d.f.=2,67 P=0.97
PRESS2.DAF	0 1 20	0 4 16.25	0 0 21	0 1 18	F=0.04 d.f.=2,67 P=0.96
PRESS5.DAF	0 2 20	0 7.5 18	0 0 21	0 1.5 19.75	F=0.09 d.f.=2,67 P=0.91
PRESS15.DAF	1 7 23	0 11.5 21.25	0 2 21	0 5 22	F=0.4 d.f.=2,67 P=0.672
INO.DAF	7 12 28	2 14 26	2 5 22	2 12 26	F=0.99 d.f.=2,67 P=0.375
SIRS2.DAF	0 0 3	0 1 2	0 0 1	0 0 2.75	F=0.24 d.f.=2,67 P=0.787
SIRS3.DAF	1 4 7	1 7 12.5	0 2 8	1 4 11	F=1.13 d.f.=2,67 P=0.33
SIRS4.DAF	5 10 19	2 15 24	2 5 20	2 10 21.5	F=0.5 d.f.=2,67 P=0.61
STER.DAF	0 2 12	1 10 24.25	1 3 10	1 4 18.25	F=0.98 d.f.=2,67 P=0.382
CVS.DAF	0 1 14	0 0.5 13	0 0 14	0 0 13.75	F=0.1 d.f.=2,67 P=0.903
RESP.DAF	0 1 4	0 0 5	0 0 8	0 0 5	F=0.21 d.f.=2,67 P=0.812
PE300.DAF	0 0 2	0 0 1.25	0 0 0	0 0 1	F=3 d.f.=2,67 P=0.0565
VENT.DAF	0 0 3	0 0 2.75	0 0 8	0 0 4.5	F=0.01 d.f.=2,67 P=0.991
CNS.DAF	6 11 27	2 13 24	2 7 24	2 11 24	F=0.67 d.f.=2,67 P=0.513
COAG.DAF	2 8 25	1 13.5 27.25	1 6 26	1 8 26	F=0.18 d.f.=2,67 P=0.84
INR.DAF	4 11 26	1.75 11.5 27	1 5 26	2 8 26.75	F=0.29 d.f.=2,67 P=0.747
ACRE.DAF	2 6 24	0 2 18.25	0 4 14	0 5 19	F=0.5 d.f.=2,67 P=0.607
ANYREN.DAF	2 6 24	0 2 16.5	0 4 14	0 5 17.5	F=0.47 d.f.=2,67 P=0.629
RENSUP.DAF	1 3 27	2 7.5 23.5	2 5 23	1 5.5 24.5	F=0.5 d.f.=2,67 P=0.607
ACHEP.DAF	1 7 24	3 14 24.75	2 4 28	2 9 24.75	F=0.78 d.f.=2,67 P=0.462

ANYHEP.DAF	1 7 24	3 14 24.75	2 4 28	2 9 24.75	F=0.77 d.f.=2,67 P=0.466
------------	------------	----------------	------------	---------------	--------------------------

TABLE 3.11

A response association of leucyl/cystinyl aminopeptidase (LNPEP) rs27711 in a matched control group of Caucasian ICU septic shock subjects who were not treated with vasopressin. For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

CONTROL	AA (N=10)	AG (N=45)	GG (N=26)	Combined (N=81)	Test Statistic
SURVIVAL	60% (6)	36% (16)	19% (5)	33% (27)	Chisquare=5.63 d.f.=2 P=0.06
DAYS ALIVE	14.25 28 28	2 8 28	3 5.5 8.75	3 8 28	F=5.09 d.f.=2,78 P=0.00839
ALI.DAF	7 9.5 19.25	1 2 18	1 5 8	1 5 15	F=2.04 d.f.=2,78 P=0.136
PRESS.DAF	10.75 23 26.75	0 4 22	0 1.5 5.75	0 4 22	F=4.35 d.f.=2,78 P=0.0161
PRESS2.DAF	11.5 23 26.75	0 4 2	0 1.5 5.75	0 4 22	F=4.41 d.f.=2,78 P=0.0154
PRESS5.DAF	13 25 27	0 4 23	0 1.5 6.5	0 4 23	F=4.67 d.f.=2,78 P=0.0122
PRESS15.DAF	14.25 26.5 28	1 6 25	0 2.5 7	1 6 26	F=5.11 d.f.=2,78 P=0.00823
INO.DAF	14.25 28 28	2 6 25	1 3.5 8	2 6 28	F=3.76 d.f.=2,78 P=0.0276
SIRS2.DAF	0 1 4	0 0 2	0 0 1	0 0 1	F=1.59 d.f.=2,78 P=0.211
SIRS3.DAF	2 3.5 6.5	0 2 9	0.25 1 2	0 2 7	F=1.19 d.f.=2,78 P=0.308
SIRS4.DAF	9.25 10.5 23	1 7 22	2 4 7	2 7 22	F=3.72 d.f.=2,78 P=0.0286
STER.DAF	8.5 17 26.25	1 4 24	1 4.5 7.75	1 5 21	F=1.37 d.f.=2,78 P=0.26
CVS.DAF	7.5 21.5 23.75	0 2 18	0 0 4	0 3 19	F=4.48 d.f.=2,78 P=0.0144
RESP.DAF	4.75 11 20.75	0 1 9	0 1 3.75	0 1 10	F=3.5 d.f.=2,78 P=0.035
PF300.DAF	0 1.5 2	0 0 1	0 0 1	0 0 1	F=2.04 d.f.=2,78 P=0.137
VENT.DAF	4 10 20	0 0 9	0 0 2.75	0 0 10	F=3.16 d.f.=2,78 P=0.048
CNS.DAF	11 24.5 26	1 7 25	0 4 8.5	1 7 25	F=4.78 d.f.=2,78 P=0.011
COAG.DAF	14.25 28 28	1 4 24	1 5 8	1 6 25	F=6.32 d.f.=2,78 P=0.00287
INR.DAF	14 26.5 28	1 4 22	0 3 6.5	0 5 22	F=7.51 d.f.=2,78 P=0.00104
ACRF.DAF	11 20 27.75	1 5 20	0 0.5 4.75	0 4 20	F=8.6 d.f.=2,78 P<0.001
ANYREN.DAF	11 20 27.75	0 3 20	0 0 4.75	0 4 20	F=8.38 d.f.=2,78 P<0.001
RENSUP.DAF	11 21.5 28	1 3 18	1 3 8	1 4 18	F=3.51 d.f.=2,78 P=0.0346
ACHEP.DAF	14.25 28 28	1 6 22	1.25 5 7.75	1 6 28	F=3.65 d.f.=2,78 P=0.0304
ANYHEP.DAF	14.25 28 28	1 5 22	1.25 5 7.75	1 6 28	F=3.64 d.f.=2,78 P=0.0309

TABLE 3.12

Difference in response association of leucyl/cystinyl aminopeptidase (LNPEP) rs27711 between cases (vasopressin-treated group) (Treat) and controls (vasopressin untreated matched control) (Cont) of Caucasian ICU subjects diagnosed with septic shock. For all variables besides 28-day survival, data is presented as medians. For 28-day survival, data is presented as % (N survived / N total). N, number of subjects.

	AA (N=21)	AA (N=10)		AG (N=28)	AG (N=45)		GG (N=21)	GG (N=26)	
	Treat	Cont	DELTA	Treat	Cont	DELTA	Treat	Cont	DELTA
SURVIVAL	43% (9)	60% (6)	-18%	36% (10)	36% (16)	0%	33% (7)	19% (5)	14%
DAYS ALIVE	12	28	-16	17.5	8	9.5	8	5.5	2.5
ALI.DAF	6	9.5	-3.5	9	2	7	2	5	-3
PRESS.DAF	1	23	-22	4	4	0	0	1.5	-1.5
PRESS2.DAF	1	23	-22	4	4	0	0	1.5	-1.5
PRESS5.DAF	2	25	-23	7.5	4	3.5	0	1.5	-1.5
PRESS15.DAF	7	26.5	-19.5	11.5	6	5.5	2	2.5	-0.5

INO.DAF	12	28	-16	14	6	8	5	3.5	1.5
SIRS2.DAF	0	1	-1	1	0	1	0	0	0
SIRS3.DAF	4	3.5	0.5	7	2	5	2	1	1
SIRS4.DAF	10	10.5	-0.5	15	7	8	5	4	1
STER.DAF	2	17	-15	10	4	6	3	4.5	-1.5
CVS.DAF	1	21.5	-20.5	0.5	2	-1.5	0	0	0
RESP.DAF	1	11	-10	0	1	-1	0	1	-1
PF300.DAF	0	1.5	-1.5	0	0	0	0	0	0
VENT.DAF	0	10	-10	0	0	0	0	0	0
CNS.DAF	11	24.5	-13.5	13	7	6	7	4	3
COAG.DAF	8	28	-20	13.5	4	9.5	6	5	1
INR.DAF	11	26.5	-15.5	11.5	4	7.5	5	3	2
ACRF.DAF	6	20	-14	2	5	-3	4	0.5	3.5
ANYREN.DAF	6	20	-14	2	3	-1	4	0	4
RENSUP.DAF	3	21.5	-18.5	7.5	3	4.5	5	3	2
ACHEP.DAF	7	28	-21	14	6	8	4	5	-1
ANYHEP.DAF	7	28	-21	14	5	9	4	5	-1

1.1.3 Adverse Response to Vasopressin Treatment of subjects who have the GG Genotype of LNPEP rs10051637

It was unknown whether SNPs within the LNPEP gene and those regions immediately upstream and downstream are associated with the response to vasopressin. It was found that LNPEP rs10051637 can be used to predict response to vasopressin in subjects with septic shock using 28-day survival and measures of organ dysfunction as outcome variables. Of 103 vasopressin-treated and 103 matched-control subjects with septic shock, 72 and 81 were respectively genotyped for LNPEP rs10051637. Baseline characteristics for subjects with genotypes are shown in Table 3.13 and Table 3.14. LNPEP rs10051637 is in linkage disequilibrium with, for example LNPEP rs18059 and LNPEP G9419812A, which were also genotyped in this cohort.

TABLE 3.13

Baseline characteristics of a group of vasopressin-treated Caucasian septic shock subjects leucyl/cystinyl aminopeptidase (LNPEP) rs10051637 genotype. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

VASOPRESSIN	AA (N=19)	AG (N=29)	GG (N=24)	Combined (N=72)	Test Statistic
AGE	38 60 68	54 65 72	42.75 55 68.75	47 60 68.5	F=0.89 d.f.=2,69 P=0.417
GENDER	79% (15/19)	79% (23/29)	71% (17/24)	76% (55/72)	X ² =0.62 d.f.=2 P=0.735
APACHE II	25.5 28 35	23 30 37	25 32.5 40.25	25 30 37	F=0.49 d.f.=2,69 P=0.616
% SURGICAL	26% (5/19)	48% (14/29)	38% (9/24)	39% (28/72)	X ² =2.36 d.f.=2 P=0.308

TABLE 3.14

Baseline characteristics of a matched-control group of Caucasian septic-shock subjects by leucyl/cystinyl aminopeptidase (LNPEP) rs10051637 genotype. For age and APACHE II score,

data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

CONTROL	AA (N=25)	AG (N=46)	GG (N=10)	Combined (N=81)	Test Statistic
AGE	49 67 74	43.25 52 66.5	39.25 45.5 58.5	44 56 71.5	F=3.91 d.f.=2,78 P=0.024
GENDER	60% (15/25)	67% (31/46)	80% (8/10)	67% (54/81)	X ² =1.31 d.f.=2 P=0.519
APACHE II	27 29 38	26 30 34	23.25 26 32.5	24 29 34	F=1.04 d.f.=2,78 P=0.359
% SURGICAL	40% (10/25)	35% (16/46)	20% (2/10)	35% (28/81)	X ² =1.27 d.f.=2 P=0.531

Tables 3.15, 3.16 and Tables 3.17 contain 28-day survival and organ dysfunction data for

septic-shock subjects genotyped for LNPEP rs10051637. Vasopressin-treated subjects with the LNPEP rs10051637 GG genotype had a dramatically decreased survival (46 %) compared to controls (60 %) as demonstrated by the negative values in the LNPEP rs10051637 GG DELTA column in Table 3.17. Vasopressin-treated subjects with the LNPEP rs10051637 GG genotype were also observed to have more organ dysfunction as demonstrated by fewer DAF of organ dysfunction. In contrast, vasopressin-treated subjects with the LNPEP rs10051637 AG and AA genotypes had increased survival (26 %) compared to controls (20 %).

TABLE 3.15

A response association of leucyl/cystinyl aminopeptidase (LNPEP) rs10051637 and use of vasopressin in a group of vasopressin-treated Caucasian ICU septic-shock subjects. For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

VASOPRESSIN	AA (N=19)	AG (N=29)	GG (N=24)	Combined (N=72)	Test Statistic
SURVIVAL	26% (5/19)	38% (11/29)	46% (11/24)	38% (27/72)	Chisquare=1.73 d.f.=2 P=0.422
DAYS ALIVE	2 6 25.5	3 20 28	7 15.5 28	3 12.5 28	F=1.08 d.f.=2,69 P=0.345
ALL.DAF	1 2 6	2 10 24	1.75 6.5 13	1 5.5 17	F=2.68 d.f.=2,69 P=0.0754
PRESS.DAF	0 0 17.5	0 5 17	0 6.5 19.5	0 1 18	F=0.43 d.f.=2,69 P=0.651
PRESS2.DAF	0 0 19	0 5 17	0 6.5 21	0 1 18	F=0.44 d.f.=2,69 P=0.646
PRESS5.DAF	0 0 19.5	0 8 18	0 8 21.25	0 1.5 20	F=0.48 d.f.=2,69 P=0.619
PRESS15.DAF	0 1 20.5	0 12 21	0.75 12 23.25	0 5 22.25	F=1.02 d.f.=2,69 P=0.364
INO.DAF	1.5 4 17.5	2 15 26	6.5 12 28	2 12 26	F=2.31 d.f.=2,69 P=0.107
SIRS2.DAF	0 0 1	0 1 2	0 0 3.25	0 0 2	F=0.51 d.f.=2,69 P=0.605
SIRS3.DAF	0 1 6	1 7 11	1 3.5 8.5	0.75 3.5 11	F=1.54 d.f.=2,69 P=0.221
SIRS4.DAF	1.5 4 18	2 16 24	4.5 10.5 20	2 10 22.25	F=1 d.f.=2,69 P=0.372
STER.DAF	1 2 6	1 9 16	0 2.5 20.25	1 3.5 16	F=0.8 d.f.=2,69 P=0.455
CVS.DAF	0 0 9	0 1 13	0 1.5 16.25	0 0 14	F=0.58 d.f.=2,69 P=0.56
RESP.DAF	0 0 1	0 0 5	0 1 7.5	0 0 5.25	F=0.93 d.f.=2,69 P=0.401
PF300.DAF	0 0 0	0 0 1	0 0 2	0 0 1	F=5.18 d.f.=2,69 P=0.0079
VENT.DAF	0 0 0	0 0 5	0 0 7.5	0 0 5.25	F=0.36 d.f.=2,69 P=0.697
CNS.DAF	2 5 19	2 13 24	6 11.5 27.25	2 11 24.25	F=1.35 d.f.=2,69 P=0.265
COAG.DAF	1 5 16.5	1 12 26	1.75 9 25.75	1 7.5 26	F=0.41 d.f.=2,69 P=0.666
INR.DAF	1 5 23.5	2 13 27	3.5 13 27	1.75 8 27	F=0.81 d.f.=2,69 P=0.448
ACRF.DAF	0 3 12	0 2 16	1.75 6 27	0 4.5 19	F=1.21 d.f.=2,69 P=0.303
ANYREN.DAF	0 3 12	0 2 13	1.75 6 24.75	0 4.5 16.5	F=1.16 d.f.=2,69 P=0.318

RENSUP.DAF	2 4 16.5	2 6 20	0.75 4.5 28	1 4.5 23.5	F=0.1 d.f.=2,69 P=0.908
ACHEP.DAF	2 3 21	3 15 27	1 8.5 24.25	2 9 25.5	F=1.19 d.f.=2,69 P=0.309
ANYHEP.DAF	2 3 21	3 15 27	1 8.5 24.25	2 9 25.5	F=1.25 d.f.=2,69 P=0.293

TABLE 3.16

A response association of leucyl/cystinyl aminopeptidase (LNPEP) rs10051637 and use of vasopressin in a matched control group of Caucasian ICU septic shock subjects who were not treated with vasopressin. For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

CONTROL	AA (N=25)	AG (N=46)	GG (N=10)	Combined (N=81)	Test Statistic
SURVIVAL	20% (5/25)	35% (16/46)	60% (6/10)	33% (27/81)	Chisquare=5.24 d.f.=2 P=0.0727
DAYS ALIVE	3 5 8	2 8 28	14.25 28 28	3 8 28	F=5.18 d.f.=2,78 P=0.0077
ALI.DAF	1 5 8	1 2.5 17.25	7 9.5 19.25	1 5 15	F=2.04 d.f.=2,78 P=0.137
PRESS.DAF	0 2 6	0 3.5 21.25	10.75 23 26.75	0 4 22	F=4.27 d.f.=2,78 P=0.0174
PRESS2.DAF	0 2 6	0 3.5 21.25	11.5 23 26.75	0 4 22	F=4.32 d.f.=2,78 P=0.0166
PRESS5.DAF	0 2 7	0.25 4 22.5	13 25 27	0 4 23	F=4.52 d.f.=2,78 P=0.0138
PRESS15.DAF	0 3 7	1 5.5 25	14.25 26.5 28	1 6 26	F=4.9 d.f.=2,78 P=0.0099
INO.DAF	1 3 8	2 6 24.5	14.25 28 28	2 6 28	F=3.9 d.f.=2,78 P=0.0243
SIRS2.DAF	0 0 1	0 0 1.75	0 1 4	0 0 1	F=1.57 d.f.=2,78 P=0.214
SIRS3.DAF	1 1 2	0 2 9	2 3.5 6.5	0 2 7	F=0.94 d.f.=2,78 P=0.395
SIRS4.DAF	2 4 7	1.25 6.5 22	9.25 10.5 23	2 7 22	F=3.59 d.f.=2,78 P=0.0322
STER.DAF	1 5 8	1 4 21.75	8.5 17 26.25	1 5 21	F=1.37 d.f.=2,78 P=0.261
CVS.DAF	0 0 4	0 2 18	7.5 21.5 23.75	0 3 19	F=4.27 d.f.=2,78 P=0.0174
RESP.DAF	0 1 4	0 1 9	4.75 11 20.75	0 1 10	F=3.46 d.f.=2,78 P=0.0364
PF300.DAF	0 0 1	0 0 0.75	0 1.5 2	0 0 1	F=2.26 d.f.=2,78 P=0.111
VENT.DAF	0 0 3	0 0 9	4 10 20	0 0 10	F=3.1 d.f.=2,78 P=0.0506
CNS.DAF	0 3 7	1 7 25	11 24.5 26	1 7 25	F=4.96 d.f.=2,78 P=0.00942
COAG.DAF	1 5 8	1 4 24	14.25 28 28	1 6 25	F=6.03 d.f.=2,78 P=0.00367
INR.DAF	0 3 7	1 4 21.75	14 26.5 28	0 5 22	F=7.54 d.f.=2,78 P=0.00101
ACRF.DAF	0 0 4	1 5 20	11 20 27.75	0 4 20	F=9.11 d.f.=2,78 P<0.001
ANYREN.DAF	0 0 4	0 3.5 19.5	11 20 27.75	0 4 20	F=8.82 d.f.=2,78 P<0.001
RENSUP.DAF	1 3 8	1 3.5 17.5	11 21.5 28	1 4 18	F=3.62 d.f.=2,78 P=0.0313
ACHEP.DAF	1 5 8	1 5.5 22	14.25 28 28	1 6 28	F=3.54 d.f.=2,78 P=0.0339
ANYHEP.DAF	1 5 8	1 4.5 22	14.25 28 28	1 6 28	F=3.55 d.f.=2,78 P=0.0334

TABLE 3.17

Difference in response association of leucyl/cystinyl aminopeptidase (LNPEP) rs10051637 and use of vasopressin between cases (vasopressin-treated group) and controls (vasopressin untreated matched control) of Caucasian ICU subjects diagnosed with septic shock.

	rs10051637 GG (N=24)			rs10051637 AG (N=29)			rs10051637 AA (N=19)		
	Treat	Cont	DELTA	Treat	Cont	DELTA	Treat	Cont	DELTA
SURVIVAL	46% (11)	60% (6)	-14%	38% (11)	35% (16)	3%	26% (5)	20% (5)	6%
DAYS ALIVE	15.5	28	-12.5	20	8	12	6	5	1
ALI.DAF	6.5	9.5	-3	10	2.5	7.5	2	5	-3
PRESS.DAF	6.5	23	-16.5	5	3.5	1.5	0	2	-2
PRESS2.DAF	6.5	23	-16.5	5	3.5	1.5	0	2	-2
PRESS5.DAF	8	25	-17	8	4	4	0	2	-2
PRESS15.DAF	12	26.5	-14.5	12	5.5	6.5	1	3	-2

INO.DAF	12	28	-16	15	6	9	4	3	1
SIRS2.DAF	0	1	-1	1	0	1	0	0	0
SIRS3.DAF	3.5	3.5	0	7	2	5	1	1	0
SIRS4.DAF	10.5	10.5	0	16	6.5	9.5	4	4	0
STER.DAF	2.5	17	-14.5	9	4	5	2	5	-3
CVS.DAF	1.5	21.5	-20	1	2	-1	0	0	0
RESP.DAF	1	11	-10	0	1	-1	0	1	-1
PF300.DAF	0	1.5	-1.5	0	0	0	0	0	0
VENT.DAF	0	10	-10	0	0	0	0	0	0
CNS.DAF	11.5	24.5	-13	13	7	6	5	3	2
COAG.DAF	9	28	-19	12	4	8	5	5	0
INR.DAF	13	26.5	-13.5	13	4	9	5	3	2
ACRF.DAF	6	20	-14	2	5	-3	3	0	3
ANYREN.DAF	6	20	-14	2	3.5	-1.5	3	0	3
RENSUP.DAF	4.5	21.5	-17	6	3.5	2.5	4	3	1
ACHEP.DAF	8.5	28	-19.5	15	5.5	9.5	3	5	-2
ANYHEP.DAF	8.5	28	-19.5	15	4.5	10.5	3	5	-2

1.2 Arginine Vasopressin (AVP)

1.2.1 Improved Response to Vasopressin Treatment of subjects who have the AA or AC Genotype of AVP rs1410713

- 5 It is unknown whether SNPs within the AVP gene and those regions immediately upstream and downstream are associated with the response to vasopressin. AVP rs1410713 can be used to predict response to vasopressin in subjects with septic shock using 28-day survival and measures of organ dysfunction as outcome variables. Of 103 vasopressin-treated and 103 matched-control subjects with septic shock, 72 and 81 were respectively genotyped for AVP rs1410713. Baseline
- 10 characteristics for subjects with genotypes are shown in Table 3.18 and Table 3.19.

TABLE 3.18

15 Baseline characteristics of a group of vasopressin-treated Caucasian septic-shock subjects by arginine vasopressin (AVP) rs1410713 genotype. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N = number of subjects.

VASOPRESSIN	AA (N=8)	AC (N=30)	CC (N=34)	Combined (N=72)	Test Statistic
AGE	50 66.5 69	39.25 57.5 67.5	54 63.5 71	47 60 68.5	F=1.23 d.f.=2,69 P=0.300
GENDER	75% (6/8)	63% (19/30)	88% (30/34)	76% (55/72)	X ² =5.49 d.f.=2 P=0.0643
APACHE II	26 28.5 34.75	20 26 30.75	28 32 40.75	25 30 37	F=5.4 d.f.=2,69 P=0.00664
% SURGICAL	38% (3/8)	43% (13/30)	41% (14/34)	42% (30/72)	X ² =0.09 d.f.=2 P=0.954

TABLE 3.19

20 Baseline characteristics of a group of Caucasian septic-shock control subjects by arginine vasopressin (AVP) rs1410713 genotype. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

CONTROL	AA	AC	CC	Combined	Test
---------	----	----	----	----------	------

	(N=6)	(N=35)	(N=40)	(N=81)	Statistic
AGE	46 53 59.25	42 52 68	45.75 61 71.25	44 56 71.5	F=0.72 d.f.=2,78 P=0.491
GENDER	67% (4/6)	71% (25/35)	62% (25/40)	67% (54/81)	X ² =0.67 d.f.=2 P=0.715
APACHE II	29.5 31.5 32.75	22 27 34	26.75 30.5 34.75	24 29 34	F=1.11 d.f.=2,78 P=0.334
% SURGICAL	17% (1/6)	46% (16/35)	25% (10/40)	33% (27/81)	X ² =4.41 d.f.=2 P=0.11

Tables 3.20, 3.21 and 3.22 contain 28-day survival and organ dysfunction data for septic-shock subjects genotyped for AVP rs1410713. Vasopressin –treated subjects with the AVP

rs1410713 AA genotype had a dramatically increased survival (38 %) compared to controls (0 %)

as demonstrated by the positive values in the AVP rs1410713 AA DELTA column in Table 3.22.

Furthermore, vasopressin-treated subjects with the AVP rs1410713 AA genotype were observed to have less organ dysfunction as demonstrated by more DAF of organ dysfunction. Vasopressin-treated subjects with AVP rs1410713 AC genotype were also observed to have increased 28-day survival (47%) compared with that of control subjects (37%).

TABLE 3.20

A response association of arginine vasopressin (AVP) rs1410713 in a group of Caucasian ICU septic shock subjects who were treated with vasopressin. For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

VASOPRESSIN	AA (N=8)	AC (N=30)	CC (N=34)	Combined (N=72)	Test Statistic
SURVIVAL	38% (3/8)	47% (14/30)	32% (11/34)	39% (28/72)	Chisquare=1.38 d.f.=2 P=0.501
DAYS ALIVE	5.75 11 28	9.25 22.5 28	2 9 28	3 14 28	F=1.78 d.f.=2,69 P=0.176
ALI.DAF	0.75 5.5 20	2 8.5 18.5	1 3.5 16	1 6 17.25	F=0.18 d.f.=2,69 P=0.834
PRESS.DAF	0 2 11.25	0 13.5 18.75	0 0 17	0 2 18.25	F=1.49 d.f.=2,69 P=0.232
PRESS2.DAF	0 2 12	0 14.5 20.25	0 0 17	0 2 18.5	F=1.82 d.f.=2,69 P=0.170
PRESS5.DAF	0.75 2 12.75	0 15.5 22	0 0 18.5	0 2.5 20.25	F=1.99 d.f.=2,69 P=0.144
PRESS15.DAF	1 5 17.25	2.25 18.5 24.75	0 1 21.75	0 6.5 23.25	F=2.5 d.f.=2,69 P=0.0892
INO.DAF	4.25 10 28	3 19.5 28	1.25 9 21.75	2 12 26	F=1.57 d.f.=2,69 P=0.215
SIRS2.DAF	0 0 1.25	0 1 3	0 0 1	0 0 2.25	F=0.74 d.f.=2,69 P=0.48
SIRS3.DAF	2.25 4.5 16.5	2 5.5 11	0.25 2 7.75	0.75 4 11.25	F=0.8 d.f.=2,69 P=0.455
SIRS4.DAF	4 9 22.75	6.5 16 23.75	2 5.5 19.75	2 10 23	F=1.04 d.f.=2,69 P=0.359
STER.DAF	2 5.5 28	2 9.5 22	0 2 15	1 4 16.75	F=2.14 d.f.=2,69 P=0.126
CVS.DAF	0 1.5 11.25	0 5.5 14	0 0 8	0 0.5 14	F=1.54 d.f.=2,69 P=0.221
RESP.DAF	0 0 4.25	0 2 5.75	0 0 8	0 0 6.5	F=0.81 d.f.=2,69 P=0.449
PE300.DAF	0 0 0.5	0 0 1.75	0 0 0	0 0 1	F=1.75 d.f.=2,69 P=0.181
VENT.DAF	0 0 3.75	0 0 5.75	0 0 8	0 0 6.5	F=0.31 d.f.=2,69 P=0.731
CNS.DAF	5 9.5 28	3.75 19 26.25	2 7 23	2 11 24.25	F=1.59 d.f.=2,69 P=0.211
COAG.DAF	4.25 6 21.25	1 13.5 26	1 7 26	1 8 26	F=0.14 d.f.=2,69 P=0.867
INR.DAF	3.75 7 25	6.25 19.5 27.75	0.25 6.5 23.75	2 9 2	F=2.88 d.f.=2,69 P=0.063
ACRF.DAF	0 1.5 2.75	0 8.5 22.5	1 5 23	0 5 19.25	F=1.4 d.f.=2,69 P=0.254
ANYREN.DAF	0 1.5 2.75	0 8.5 17.5	1 5 19.75	0 5 18.25	F=1.34 d.f.=2,69 P=0.269
RENSUP.DAF	1 2 10.0	3 11 26	1 2 26.75	1 5.5 25.5	F=1.39 d.f.=2,69 P=0.256
ACHEP.DAF	4.25 10 23.25	3.25 15.5 28	1 3 24.75	2 9.5 27.25	F=1.98 d.f.=2,69 P=0.146
ANYHEP.DAF	4.25 10 23.25	3.25 15 28	1 3 24.75	2 9.5 27.25	F=2.14 d.f.=2,69 P=0.126

TABLE 3.21

A response association of arginine vasopressin (AVP) rs1410713 in a matched control group of Caucasian ICU septic shock subjects who were not treated with vasopressin. For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

CONTROL	AA (N=6)	AC (N=35)	CC (N=40)	Combined (N=81)	Test Statistic
SURVIVAL	0% (0/6)	37% (13/35)	35% (14/40)	33% (27/81)	Chisquare=3.28 d.f.=2 P=0.194
DAYS ALIVE	1.75 4.5 5.75	3.5 10 28	1.75 8.5 28	3 8 28	F=2.06 d.f.=2,78 P=0.134
ALI.DAF	1 1 3.25	2 7 16.5	1 4.5 18.5	1 5 15	F=2.06 d.f.=2,78 P=0.135
PRESS.DAF	0 1.5 4.5	0 4 22	0 4.5 24.25	0 4 22	F=0.95 d.f.=2,78 P=0.393
PRESS2.DAF	0 1.5 4.5	0 4 22	0 4.5 24.25	0 4 22	F=0.95 d.f.=2,78 P=0.392
PRESS5.DAF	0.5 2.5 4.5	0 4 24	0 6 25.25	0 4 23	F=0.75 d.f.=2,78 P=0.475
PRESS15.DAF	0.75 3.5 4.75	1 6 26.5	0 7 26	1 6 26	F=1.13 d.f.=2,78 P=0.328
INO.DAF	1.25 3.5 5.75	2.5 8 28	1 6.5 25.75	2 6 28	F=1.1 d.f.=2,78 P=0.337
SIRS2.DAF	0 0 0	0 0 2	0 0 1	0 0 1	F=1.22 d.f.=2,78 P=0.301
SIRS3.DAF	0.25 1 1.75	0 2 8.5	1 2 6.75	0 2 7	F=0.93 d.f.=2,78 P=0.4
SIRS4.DAF	1 2 3.75	2.5 8 22	1 7 22.25	2 7 22	F=2.7 d.f.=2,78 P=0.0736
STER.DAF	1.75 4.5 5.75	1 6 28	1 4.5 12.75	1 5 21	F=1.19 d.f.=2,78 P=0.31
CVS.DAF	0 1 2.0	0 3 18.5	0 3 20	0 3 19	F=0.9 d.f.=2,78 P=0.409
RESP.DAF	0.25 1 2.	0 2 11.5	0 1 10	0 1 10	F=0.65 d.f.=2,78 P=0.526
PE300.DAF	0 0.5 1.75	0 0 3	0 0 0	0 0 1	F=2.99 d.f.=2,78 P=0.0559
VENT.DAF	0 0 0.75	0 1 10.5	0 0 10	0 0 10	F=1.05 d.f.=2,78 P=0.353
CNS.DAF	0.25 1 1	3 7 24.5	1 8.5 26	1 7 25	F=3.55 d.f.=2,78 P=0.0336
COAG.DAF	1 2.5 5.5	2.5 8 27.5	1 6.5 24.25	1 6 25	F=1.56 d.f.=2,78 P=0.217
INR.DAF	0 0.5 3.25	2.5 7 24.5	0 6 23.5	1 5 22	F=2.59 d.f.=2,78 P=0.0812
ACRF.DAF	0 0 3	1 4 21.5	0 5 21.75	0 4 20	F=2.19 d.f.=2,78 P=0.118
ANYREN.DAF	0 0 0	1 4 21.5	0 4.5 20.25	0 4 20	F=3.47 d.f.=2,78 P=0.0359
RENSUP.DAF	1 2.5 4.75	2 5 25.5	1 3.5 18.25	1 4 18	F=1.42 d.f.=2,78 P=0.247
ACHEP.DAF	1.5 3.5 5.5	2.5 6 26	1 7.5 28	1 6 28	F=1.2 d.f.=2,78 P=0.307
ANYHEP.DAF	1.5 3.5 5.5	2 6 26	1 7.5 28	1 6 28	F=0.99 d.f.=2,78 P=0.377

5

TABLE 3.22

Difference in response association of arginine vasopressin (AVP) rs1410713 between cases (vasopressin-treated group) (Treat) and controls (vasopressin untreated matched control) (Cont) of Caucasian ICU subjects diagnosed with septic shock. For all variables besides 28-day survival, data is presented as medians. For 28-day survival, data is presented as % (N survived / N total). N, number of subjects.

10

	AVP rs1410713 CC (N=34)			AVP rs1410713 AC (N=30)			AVP rs1410713 AA (N=8)		
	Treat	Cont	Treat-Cont	Treat	Cont	Treat-Cont	Treat	Cont	Treat-Cont
SURVIVAL	32% (11)	35% (14)	-3%	47% (14)	37% (13)	10%	38% (3)	0% (0)	38%
DAYS ALIVE	9	8.5	0.5	22.5	10	12.5	11	4.5	6.5
ALI.DAF	3.5	4.5	-1	8.5	7	1.5	5.5	1	4.5
PRESS.DAF	0	4.5	-4.5	13.5	4	9.5	2	1.5	0.5
PRESS2.DAF	0	4.5	-4.5	14.5	4	10.5	2	1.5	0.5
PRESS5.DAF	0	6	-6	15.5	4	11.5	2	2.5	-0.5
PRESS15.DAF	1	7	-6	18.5	6	12.5	5	3.5	1.5
INO.DAF	9	6.5	2.5	19.5	8	11.5	10	3.5	6.5
SIRS2.DAF	0	0	0	1	0	1	0	0	0
SIRS3.DAF	2	2	0	5.5	2	3.5	4.5	1	3.5

SIRS4.DAF	5.5	7	-1.5	16	8	8	9	2	7
STER.DAF	2	4.5	-2.5	9.5	6	3.5	5.5	4.5	1
CVS.DAF	0	3	-3	5.5	3	2.5	1.5	1	0.5
RESP.DAF	0	1	-1	2	2	0	0	1	-1
PE300.DAF	0	0	0	0	0	0	0	0.5	-0.5
VENT.DAF	0	0	0	0	1	-1	0	0	0
CNS.DAF	7	8.5	-1.5	19	7	12	9.5	1	8.5
COAG.DAF	7	6.5	0.5	13.5	8	5.5	6	2.5	3.5
INR.DAF	6.5	6	0.5	19.5	7	12.5	7	0.5	6.5
ACRF.DAF	5	5	0	8.5	4	4.5	1.5	0	1.5
ANYREN.DAF	5	4.5	0.5	8.5	4	4.5	1.5	0	1.5
RENSUP.DAF	2	3.5	-1.5	11	5	6	2	2.5	-0.5
ACHEP.DAF	3	7.5	-4.5	15.5	6	9.5	10	3.5	6.5
ANYHEP.DAF	3	7.5	-4.5	15	6	9	10	3.5	6.5

1.2.2 Adverse Response to Vasopressin Treatment of subjects who have the CT Genotype of AVP rs857240 and Improved Response to Vasopressin Treatment of subjects who have the CC Genotype of AVP rs857240

It was unknown whether SNPs within the AVP gene and those regions immediately upstream and downstream are associated with the response to vasopressin. It was found that AVP rs857240 can be used to predict response to vasopressin in subjects with septic shock using 28-day survival and measures of organ dysfunction as respective primary and secondary outcome variables. Of 103 vasopressin-treated and 103 matched-control subjects with septic shock, 73 and 83 were respectively genotyped for LNPEP rs857240. Baseline characteristics for subjects with genotypes are shown in Table 3.23 and Table 3.24

TABLE 3.23

Baseline characteristics of a group of vasopressin-treated Caucasian septic shock subjects by arginine vasopressin (AVP) rs857240 genotype. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

VASOPRESSIN	CC (N=56)	CT (N=17)	Combined (N=73)	Test Statistic
AGE	46.75 61.5 68.75	39 56 68	47 60 68.5	F=0.33 d.f.=1,71 P=0.569
GENDER	73% (41/56)	88% (15/17)	77% (56/73)	X ² =1.65 d.f.=1 P=0.199
APACHE II	25 30.5 36.25	24 28 39	25 30 37	F=0.09 d.f.=1,71 P=0.761
% SURGICAL	41% (23/56)	35% (6/17)	40% (29/73)	X ² =0.18 d.f.=1 P=0.67

TABLE 3.24

Baseline characteristics of Caucasian septic shock control subjects by arginine vasopressin (AVP) rs857240 genotype. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

CONTROL	CC (N=69)	CT (N=14)	Combined (N=83)	Test Statistic
AGE	44 55 68	36.75 53.5 71	44 56 71.5	F=0.12 d.f.=1,81 P=0.731

GENDER	65% (45/69)	79% (11/14)	67% (56/83)	$\chi^2=0.95$ d.f.=1 P=0.331
APACHE II	25 29 34	27 32 34	24 29 34	F=0.59 d.f.=1.81 P=0.446
% SURGICAL	35% (24/69)	29% (4/14)	34% (28/83)	$\chi^2=0.2$ d.f.=1 P=0.654

Tables 3.25, 3.26 and 3.27 contain 28-day survival and organ dysfunction data for septic-shock subjects genotyped for AVP rs857240. Vasopressin –treated subjects with the AVP rs857240 CT genotype had dramatically decreased survival if vasopressin-treated (29 %) compared to controls (43 %) as demonstrated by the negative values in the AVP rs857240 CT DELTA column in Table 3.27. Furthermore, vasopressin-treated subjects with the AVP rs857240 CT genotype were observed to have more organ dysfunction than AVP rs857240 CT control subjects as demonstrated by more DAF of organ dysfunction. In contrast, vasopressin-treated subjects with the AVP rs857240 CC genotype had increased survival (41 %) compared to controls (30 %) as demonstrated by the positive values in the AVP rs857240 CC DELTA column in Table 3.27. Furthermore, vasopressin-treated subjects AVP rs857240 CC subjects were observed to have less organ dysfunction than AVP rs857240 CC control subjects.

TABLE 3.25

A response association of arginine vasopressin (AVP) rs857240 in a group of Caucasian ICU septic shock subjects who were treated with vasopressin. For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects. Note: TT genotype frequency = 0.

VASOPRESSIN	CC (N=56)	CT (N=17)	Combined (N=73)	Test Statistic
SURVIVAL	41% (23/56)	29% (5/17)	38% (28/73)	Chisquare=0.75 d.f.=1 P=0.387
DAYS ALIVE	5.75 19.5 28	2 5 28	3 13 28	F=2.96 d.f.=1.71 P=0.0899
ALI.DAF	2 6 17	1 3 9	1 6 17	F=1.26 d.f.=1.71 P=0.265
PRESS.DAF	0 7.5 19	0 0 5	0 1 19	F=2.66 d.f.=1.71 P=0.108
PRESS2.DAF	0 8 20.25	0 0 5	0 1 20	F=2.1 d.f.=1.71 P=0.151
PRESS5.DAF	0 10.5 21.25	0 0 7	0 2 21	F=2.54 d.f.=1.71 P=0.116
PRESS15.DAF	0 14 24	0 1 11	0 6 23	F=3.01 d.f.=1.71 P=0.087
INO.DAF	2 13.5 28	1 4 22	2 12 26	F=2.51 d.f.=1.71 P=0.118
SIRS2.DAF	0 0 2.25	0 0 1	0 0 2	F=0.18 d.f.=1.71 P=0.671
SIRS3.DAF	1 4 11.5	0 2 7	1 4 11	F=1.56 d.f.=1.71 P=0.216
SIRS4.DAF	3 15 22.25	2 3 20	2 10 22	F=1.52 d.f.=1.71 P=0.221
STER.DAF	1 5 21	0 3 11	1 4 19	F=0.58 d.f.=1.71 P=0.448
CVS.DAF	0 2.5 14.25	0 0 3	0 0 14	F=1.97 d.f.=1.71 P=0.165
RESP.DAF	0 0 8	0 0 2	0 0 8	F=0.19 d.f.=1.71 P=0.661
PH300.DAF	0 0 1.25	0 0 0	0 0 1	F=1.43 d.f.=1.71 P=0.235
VENT.DAF	0 0 8	0 0 2	0 0 8	F=0 d.f.=1.71 P=0.946
CNS.DAF	3 13 25	2 5 21	2 11 24	F=2.4 d.f.=1.71 P=0.126
COAG.DAF	1.75 9.5 26	1 3 18	1 8 26	F=1.56 d.f.=1.71 P=0.216
INR.DAF	2 14 27	1 4 20	2 8 27	F=1.95 d.f.=1.71 P=0.167
ACRF.DAF	0 6 19.25	0 3 5	0 5 19	F=0.62 d.f.=1.71 P=0.435
ANYREN.DAF	0 6 19	0 3 5	0 5 18	F=0.98 d.f.=1.71 P=0.325
RENSUP.DAF	1.75 7.5 27.25	1 2 5	1 5 2	F=2.74 d.f.=1.71 P=0.102
ACHEP.DAF	2 11.5 27.25	2 3 16	2 9 25	F=1.41 d.f.=1.71 P=0.239

ANYHEP.DAF	2 11.5 27.25	1 3 15	2 9 25	F=1.7 d.f.=1,71 P=0.197
------------	------------------	------------	------------	-------------------------

TABLE 3.26

A response association of arginine vasopressin (AVP) rs857240 a matched control group of Caucasian ICU septic shock subjects who were not treated with vasopressin. For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects. Note: TT genotype frequency = 0.

CONTROL	CC (N=69)	CT (N=14)	Combined (N=83)	Test Statistic
SURVIVAL	30% (21/69)	43% (6/14)	33% (27/83)	Chisquare=0.82 d.f.=1 P=0.366
DAYS ALIVE	3 7 28	2 16.5 28	3 8 28	F=0.16 d.f.=1,81 P=0.694
ALL.DAF	1 5 11	1.25 2 21.75	1 5 14.5	F=0 d.f.=1,81 P=0.995
PRESS.DAF	0 3 19	0 12.5 23.75	0 4 22	F=0.49 d.f.=1,81 P=0.487
PRESS2.DAF	0 3 19	0 12.5 23.75	0 4 22	F=0.45 d.f.=1,81 P=0.503
PRESS5.DAF	0 4 21	0 12.5 24.5	0 4 23	F=0.43 d.f.=1,81 P=0.516
PRESS15.DAF	1 5 26	0 15 25.75	0.5 5 26	F=0.05 d.f.=1,81 P=0.817
INO.DAF	1 5 25	2 13 28	2 6 28	F=0.4 d.f.=1,81 P=0.53
SIRS2.DAF	0 0 1	0 0 1.75	0 0 1	F=0.11 d.f.=1,81 P=0.744
SIRS3.DAF	0 2 6	0.25 2 16	0 2 6.5	F=0.41 d.f.=1,81 P=0.524
SIRS4.DAF	2 6 17	1.25 14 24.75	2 6 21.5	F=0.16 d.f.=1,81 P=0.694
STER.DAF	1 5 19	1 2 18.25	1 5 20	F=0.19 d.f.=1,81 P=0.666
CVS.DAF	0 2 18	0 8 22	0 2 18.5	F=0.64 d.f.=1,81 P=0.425
RESP.DAF	0 1 9	0 3 18.25	0 1 9.5	F=0.87 d.f.=1,81 P=0.354
PF300.DAF	0 0 2	0 0 1	0 0 1	F=0.06 d.f.=1,81 P=0.81
VENT.DAF	0 0 9	0 3 18.25	0 0 9.5	F=1.63 d.f.=1,81 P=0.205
CNS.DAF	1 6 24	1.25 15 25.75	1 7 25	F=0.47 d.f.=1,81 P=0.497
COAG.DAF	1 6 24	1.25 7.5 28	1 6 24.5	F=0.34 d.f.=1,81 P=0.563
INR.DAF	1 4 14	0 15.5 24.25	0 4 21.5	F=0.03 d.f.=1,81 P=0.855
ACRE.DAF	0 4 15	1.25 9 26.75	0 4 20	F=1.6 d.f.=1,81 P=0.21
ANYREN.DAF	0 3 15	1 9 24.75	0 3 19	F=1.39 d.f.=1,81 P=0.242
RENSUP.DAF	1 4 15	1.25 5.5 26.25	1 4 17	F=0.52 d.f.=1,81 P=0.475
ACHEP.DAF	1 6 22	1.25 16.5 28	1 6 26	F=0.65 d.f.=1,81 P=0.424
ANYHEP.DAF	1 5 22	1.25 16.5 28	1 6 26	F=1.01 d.f.=1,81 P=0.319

TABLE 3.27

Difference in response association of arginine vasopressin (AVP) rs857240 between cases (vasopressin-treated group) (Treat) and controls (vasopressin untreated matched control) (Cont) of Caucasian ICU subjects diagnosed with septic shock. For all variables besides 28-day survival, data is presented as medians. For 28-day survival, data is presented as % (N survived / N total). N, number of subjects. Note: TT genotype frequency = 0.

	rs857240 CT (N=17)			rs857240 CC (N=56)		
	Treat	Cont	Treat-Cont	Treat	Cont	Treat-Cont
SURVIVAL	29% (5/17)	43% (6/14)	-14%	41% (23/56)	30% (21/69)	11%
DAYS ALIVE	5	16.5	-11.5	19.5	7	12.5
ALL.DAF	3	2	1	6	5	1
PRESS.DAF	0	12.5	-12.5	7.5	3	4.5
PRESS2.DAF	0	12.5	-12.5	8	3	5
PRESS5.DAF	0	12.5	-12.5	10.5	4	6.5
PRESS15.DAF	1	15	-14	14	5	9
INO.DAF	4	13	-9	13.5	5	8.5
SIRS2.DAF	0	0	0	0	0	0

SIRS3.DAF	2	2	0	4	2	2
SIRS4.DAF	3	14	-11	15	6	9
STER.DAF	3	2	1	5	5	0
CVS.DAF	0	8	-8	2.5	2	0.5
RESP.DAF	0	3	-3	0	1	-1
PF300.DAF	0	0	0	0	0	0
VENT.DAF	0	3	-3	0	0	0
CNS.DAF	5	15	-10	13	6	7
COAG.DAF	3	7.5	-4.5	9.5	6	3.5
INR.DAF	4	15.5	-11.5	14	4	10
ACRF.DAF	3	9	-6	6	4	2
ANYREN.DAF	3	9	-6	6	3	3
RENSUP.DAF	2	5.5	-3.5	7.5	4	3.5
ACHEP.DAF	3	16.5	-13.5	11.5	6	5.5
ANYHEP.DAF	3	16.5	-13.5	11.5	5	6.5

1.2.3 Adverse Response to Vasopressin Treatment of subjects who have the AC Genotype of AVP rs857242 and Improved Response to Vasopressin Treatment of subjects who have the CC Genotype of AVP rs857242

It was unknown whether SNPs within the AVP gene and those regions immediately upstream and downstream are associated with the response to vasopressin. It was found that AVP rs857242 can be used to predict response to vasopressin in subjects with septic shock using 28-day survival and measures of organ dysfunction as respective primary and secondary outcome variables. Of 103 vasopressin-treated and 103 matched-control subjects with septic shock, 75 and 81 were respectively genotyped for AVP rs857242. Baseline characteristics for subjects with genotypes are shown in Table 3.28 and Table 3.29.

TABLE 3.28

Baseline characteristics of a group of vasopressin-treated Caucasian ICU septic shock subjects by genotype of arginine vasopressin (AVP) rs 857242. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

VASOPRESSIN	AC (N=16)	CC (N=59)	Combined (N=75)	Test Statistic
AGE	39.75 60 68.75	46.5 61 69.5	47 60 68.5	F=0.09 d.f.=1,73 P=0.763
GENDER	94% (15/16)	73% (43/59)	77% (58/75)	X ² =3.13 d.f.=1 P=0.077
APACHE II	24.75 28 39.5	25 30 35	25 30 37	F=0 d.f.=1,73 P=0.96
% SURGICAL	38% (6/16)	41% (24/59)	40% (30/75)	X ² =0.05 d.f.=1 P=0.818

TABLE 3.29

Baseline characteristics of a vasopressin untreated matched control group of Caucasian ICU septic shock subjects by genotype of arginine vasopressin (AVP) rs 857242. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

CONTROL	AA (N=1)	AC (N=13)	CC (N=67)	Combined (N=81)	Test Statistic
AGE	72 72 72	39 48 65	43.5 55 70	44 56 71.5	F=0.98 d.f.=2,78 P=0.38
GENDER	0% (0/1)	69% (9/13)	69% (46/67)	68% (55/81)	X ² =2.14 d.f.=2 P=0.342
APACHE II	19 19 19	23 30 34	25.5 29 34	24 29 34	F=1.03 d.f.=2,78 P=0.361
% SURGICAL	0% (0/1)	38% (5/13)	34% (23/67)	35% (28/81)	X ² =0.62 d.f.=2 P=0.734

Tables 3.30, 3.31 and 3.32 contain 28-day survival and organ dysfunction data for septic-shock subjects genotyped for AVP rs857242. Vasopressin –treated subjects with the AVP rs857242 AC genotype had a dramatically decreased survival (38 %) compared to controls (54 %) as

- 5 demonstrated by the negative values in the AVP rs857242 AC DELTA column in Table 3.32. Furthermore, vasopressin-treated subjects with the AVP rs857242 AC genotype were observed to have more organ dysfunction as demonstrated by more DAF of organ dysfunction. In contrast, vasopressin-treated subjects with the AVP rs857242 CC genotype were observed to have increased survival (41%) compared with controls (30%). As well, vasopressin-treated subjects with AVP
- 10 rs857242 CC genotype were observed to have increased 28-day survival (47%) compared with that of control subjects (37%) as demonstrated by the positive values in the AVP rs857242 CC DELTA column in Table 3.32. Furthermore, vasopressin-treated subjects with the AVP rs857242 CC genotype were observed to have less organ dysfunction as demonstrated by more DAF of organ dysfunction

15

TABLE 3.30

A response association of arginine vasopressin (AVP) rs857242 in a group of Caucasian ICU septic shock subjects who were treated with vasopressin. For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects. Note: AA genotype frequency = 0.

20

VASOPRESSIN	AC (N=16)	CC (N=59)	Combined (N=75)	Test Statistic
SURVIVAL	38% (6/16)	41% (24/59)	40% (30/75)	Chisquare=0.05 d.f.=1 P=0.818
DAYS ALIVE	2.75 7.5 28	5 19 28	3 15 28	F=0.96 d.f.=1,73 P=0.332
ALI.DAF	1 6.5 17.25	2 6 18.5	1 6 17.5	F=0.4 d.f.=1,73 P=0.528
PRESS.DAF	0 0 18.75	0 7 19	0 3 19	F=1.65 d.f.=1,73 P=0.204
PRESS2.DAF	0 0 18.75	0 7 20.5	0 3 20.5	F=1.22 d.f.=1,73 P=0.273
PRESS5.DAF	0 0 19.5	0 10 21.5	0 3 21	F=1.55 d.f.=1,73 P=0.217
PRESS15.DAF	0 1.5 21	0 14 24	0 7 23.5	F=1.81 d.f.=1,73 P=0.182
INO.DAF	1 6 24.5	2 13 27.5	2 12 26.5	F=0.96 d.f.=1,73 P=0.331
SIRS2.DAF	0 0.5 3	0 0 2	0 0 2.5	F=0.06 d.f.=1,73 P=0.802
SIRS3.DAF	0 2.5 9.75	1 4 12	1 4 11.5	F=0.19 d.f.=1,73 P=0.66
SIRS4.DAF	2 6.5 23.25	2.5 14 22.5	2 10 23	F=0.23 d.f.=1,73 P=0.635
STER.DAF	0 3.5 17.25	1 5 19.5	1 4 19.5	F=0.08 d.f.=1,73 P=0.776
CVS.DAF	0 0 8	0 3 14.5	0 1 14	F=1.21 d.f.=1,73 P=0.276
RESP.DAF	0 0.5 11	0 0 7	0 0 8	F=0.04 d.f.=1,73 P=0.835
PF300.DAF	0 0 0.25	0 0 1	0 0 1	F=0.19 d.f.=1,73 P=0.667
VENT.DAF	0 0 9.25	0 0 7	0 0 8	F=0.23 d.f.=1,73 P=0.632

CNS.DAF	2 6.5 24	3 13 25	2 11 25	F=0.89 d.f.=1,73 P=0.349
COAG.DAF	0.75 3.5 20.75	1.5 9 26.5	1 8 26	F=0.7 d.f.=1,73 P=0.407
INR.DAF	1.75 5.5 24.25	2 13 27	2 10 27	F=0.61 d.f.=1,73 P=0.438
ACRF.DAF	0 3.5 16.25	0.5 6 22	0 5 22	F=0.4 d.f.=1,73 P=0.529
ANYREN.DAF	0 3.5 12.25	0.5 6 9	0 5 19	F=0.72 d.f.=1,73 P=0.399
RENSUP.DAF	1 2 12.25	2 6 28	1 6 27	F=2.25 d.f.=1,73 P=0.138
ACHEP.DAF	1.75 3.5 18.25	2 10 27.5	2 9 26	F=0.57 d.f.=1,73 P=0.453
ANYHEP.DAF	1.75 3.5 18.25	2 10 27.5	2 9 26	F=0.48 d.f.=1,73 P=0.493

TABLE 3.31

A response association of arginine vasopressin (AVP) rs857242 in Caucasian septic-shock control subjects. For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects. Note: AA genotype frequency = 0.

CONTROL	AC (N=13)	CC (N=67)	Combined (N=80)	Test Statistic
SURVIVAL	54% (7/13)	30% (20/67)	34% (27/80)	Chisquare=2.8 d.f.=1 P=0.094
DAYS ALIVE	4 28 28	2.5 7 28	3 8 28	F=1.67 d.f.=1,78 P=0.199
ALL.DAF	1 4 22	1 5 12.5	1 5 15.75	F=0.35 d.f.=1,78 P=0.554
PRESS.DAF	1 17 25	0 3 18.5	0 4 23	F=1.9 d.f.=1,78 P=0.172
PRESS2.DAF	2 17 26	0 3 18.5	0 4 23	F=2.1 d.f.=1,78 P=0.152
PRESS5.DAF	4 20 26	0 4 20.5	0 4 23.5	F=2.21 d.f.=1,78 P=0.141
PRESS15.DAF	4 24 28	0.5 5 25	0.75 5.5 26	F=1.67 d.f.=1,78 P=0.201
INO.DAF	4 20 28	1 5 28	1.75 6 28	F=1.15 d.f.=1,78 P=0.287
SIRS2.DAF	0 2 13	0 0 1	0 0 1	F=4.68 d.f.=1,78 P=0.0335
SIRS3.DAF	2 4 22	0 1 5	0 2 6.25	F=4.99 d.f.=1,78 P=0.0284
SIRS4.DAF	4 22 27	2 5 16	2 6.5 22	F=3.23 d.f.=1,78 P=0.0761
STER.DAF	1 6 26	1 5 17	1 5 21.75	F=0.09 d.f.=1,78 P=0.769
CVS.DAF	0 11 23	0 2 18	0 2.5 19	F=1.58 d.f.=1,78 P=0.212
RESP.DAF	0 4 19	0 1 9	0 1 9.25	F=0.13 d.f.=1,78 P=0.722
PF300.DAF	0 0 0	0 0 1.5	0 0 1	F=0.79 d.f.=1,78 P=0.376
VENT.DAF	0 4 19	0 0 9	0 0 9.25	F=0.75 d.f.=1,78 P=0.39
CNS.DAF	4 22 28	1 5 24	1 7 25	F=3.3 d.f.=1,78 P=0.0732
COAG.DAF	3 12 28	1 6 24	1 6 25.5	F=1.7 d.f.=1,78 P=0.197
INR.DAF	4 14 26	0 4 18	0.75 4.5 23.5	F=1.91 d.f.=1,78 P=0.171
ACRF.DAF	1 7 28	0 4 17.5	0 4 20.75	F=3.05 d.f.=1,78 P=0.0844
ANYREN.DAF	1 7 27	0 3 17.5	0 3.5 20	F=1.2 d.f.=1,78 P=0.278
RENSUP.DAF	1 9 28	1 4 14.5	1 4 16.5	F=0.49 d.f.=1,78 P=0.488
ACHEP.DAF	4 22 28	1 6 21.5	1 6 28	F=2.9 d.f.=1,78 P=0.0926
ANYHEP.DAF	4 22 28	1 5 21.5	1 6 28	F=3.27 d.f.=1,78 P=0.0745

TABLE 3.32

Difference in response association of arginine vasopressin (AVP) rs857242 between cases (vasopressin-treated group) (Treat) and controls (vasopressin untreated matched control) (Cont) of Caucasian ICU subjects diagnosed with septic shock. For all variables besides 28-day survival, data is presented as medians. For 28-day survival, data is presented as % (N survived / N total). N, number of subjects. Note: AA genotype frequency = 0.

	rs857242 AC			rs857242 CC		
	(N=16)	(N=13)		(N=59)	(N=67)	
	Treat	Cont	DELTA	Treat	Cont	DELTA
SURVIVAL	38% (6/16)	54% (7/13)	-16%	41% (24/59)	30% (20/67)	11%
DAYS ALIVE	7.5	28	-20.5	19	7	12
ALL.DAF	6.5	4	2.5	6	5	1

PRESS.DAF	0	17	-17	7	3	4
PRESS2.DAF	0	17	-17	7	3	4
PRESS5.DAF	0	20	-20	10	4	6
PRESS15.DAF	1.5	24	-22.5	14	5	9
INO.DAF	6	20	-14	13	5	8
SIRS2.DAF	0.5	2	-1.5	0	0	0
SIRS3.DAF	2.5	4	-1.5	4	1	3
SIRS4.DAF	6.5	22	-15.5	14	5	9
STER.DAF	3.5	6	-2.5	5	5	0
CVS.DAF	0	11	-11	3	2	1
RESP.DAF	0.5	4	-3.5	0	1	-1
PF300.DAF	0	0	0	0	0	0
VENT.DAF	0	4	-4	0	0	0
CNS.DAF	6.5	22	-15.5	13	5	8
COAG.DAF	3.5	12	-8.5	9	6	3
INR.DAF	5.5	14	-8.5	13	4	9
ACRF.DAF	3.5	7	-3.5	6	4	2
ANYREN.DAF	3.5	7	-3.5	6	3	3
RENSUP.DAF	2	9	-7	6	4	2
ACHEP.DAF	3.5	22	-18.5	10	6	4
ANYHEP.DAF	3.5	22	-18.5	10	5	5

1.3 Arginine Vasopressin Receptor 1a (AVPR1A)

1.3.1 Adverse Response to Vasopressin Treatment of subjects who have the TT Genotype of AVPR1A rs1495027 and Improved Response to Vasopressin Treatment of subjects who have the CC Genotype of AVPR1A rs1495027

It was unknown whether SNPs within the AVPR1A gene and those regions immediately upstream and downstream are associated with the response to vasopressin. It was found that AVPR1A rs1495027 can be used to predict response to vasopressin in subjects with septic shock using 28-day survival and measures of organ dysfunction as respective primary and secondary outcome variables. Of 103 vasopressin-treated and 103 matched-control subjects with septic shock, 72 and 79 were respectively genotyped for AVPR1A rs1495027. Baseline characteristics for subjects with genotypes are shown in Table 3.33 and Table 3.34.

TABLE 3.33

Baseline characteristics of a group of vasopressin-treated Caucasian ICU septic shock subjects by genotype of arginine vasopressin receptor 1a (AVPR1A) rs1495027. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

VASOPRESSIN	CC (N=14)	CT (N=45)	TT (N=13)	Combined (N=72)	Test Statistic
AGE	57 67 72	42 55 66	39 65 71	47 60 68	F=2.6 d.f.=2,69 P=0.0816
GENDER	79% (11/14)	80% (36/66)	62% (8/13)	76% (55/72)	X ² =1.95 d.f.=2 P=0.377
APACHE II	23.75 30 33.75	25 31 37	25 30 40	25 30 37	F=0.12 d.f.=2,69 P=0.889
% SURGICAL	50% (7/14)	40% (18/66)	31% (4/13)	40% (29/72)	X ² =1.04 d.f.=2 P=0.594

TABLE 3.34

Baseline characteristics of a vasopressin untreated matched control group of Caucasian ICU septic shock subjects by genotype of arginine vasopressin receptor 1a (AVPR1A) rs1495027. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N / N total). N, number of subjects.

CONTROL	CC (N=29)	CT (N=37)	TT (N=13)	Combined (N=79)	Test Statistic
AGE	44 57 68	43 52 67	49 64 72	44 56 71.5	F=0.68 d.f.=2,76 P=0.51
GENDER	52% (15/29)	76% (28/37)	77% (10/13)	67% (53/79)	X ² =4.91 d.f.=2 P=0.086
APACHE II	27 31 33	25 29 34	29 34 37	24 29 34	F=1.06 d.f.=2,76 P=0.351
% SURGICAL	24% (7/29)	32% (12/37)	54% (7/13)	33% (26/79)	X ² =3.6 d.f.=2 P=0.166

Tables 3.35, 3.36 and 3.37 contain 28-day survival and organ dysfunction data for septic-shock subjects genotyped for AVPR1A rs1495027. Vasopressin-treated subjects with the AVPR1A rs1495027 TT had a dramatically decreased survival (23 %) compared to controls (46 %) as demonstrated by the negative values in the AVPR1A rs1495027 TT DELTA column in Table 3.37. Furthermore, vasopressin-treated subjects with the AVPR1A rs1495027 TT genotype were observed to have more organ dysfunction as demonstrated by fewer DAF of organ dysfunction. In contrast, vasopressin-treated subjects with the AVPR1A rs1495027 CC genotype were shown to have increased survival (50%) over AVPR1A rs1495027 CC controls (24%) as demonstrated by the positive values in the AVPR1A rs1495027 TT DELTA column in Table 3.37. In addition, vasopressin subjects with the AVPR1A rs1495027 CC genotype had less organ dysfunction as evidenced by more DAF of organ dysfunction.

TABLE 3.35

A response association of AVPR1A rs1495027 in vasopressin-treated Caucasian septic-shock subjects. For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

VASOPRESSIN	CC (N=14)	CT (N=45)	TT (N=13)	Combined (N=72)	Test Statistic
SURVIVAL	50% (7/14)	38% (17/45)	23% (3/13)	38% (27/72)	Chisquare=2.09 d.f.=2 P=0.352
DAYS ALIVE	3.75 18.5 28	2 10 28	12 20 23	3 12 28	F=0.75 d.f.=2,69 P=0.477
ALL.DAF	2.25 5.5 20.75	1 3 17	2 6 17	1 5.5 17	F=0.17 d.f.=2,69 P=0.842
PRESS.DAF	0 8.5 21.75	0 0 19	0 7 14	0 1 18.25	F=0.2 d.f.=2,69 P=0.821
PRESS2.DAF	0 8.5 21.75	0 1 20	0 7 17	0 1 18.5	F=0.16 d.f.=2,69 P=0.855
PRESS5.DAF	0 9 23	0 1 20	0 11 18	0 1.5 20.25	F=0.22 d.f.=2,69 P=0.801
PRESS15.DAF	0 13 26	0 3 22	4 14 20	0 5 23	F=0.84 d.f.=2,69 P=0.435
INO.DAF	2 13.5 26	2 8 28	10 19 22	2 12 26.25	F=0.17 d.f.=2,69 P=0.845
SIRS2.DAF	0 0 4	0 0 3	0 1 2	0 0 3	F=0.83 d.f.=2,69 P=0.442
SIRS3.DAF	1.25 3.5 17	0 2 9	4 7 10	0 3 11.25	F=2.34 d.f.=2,69 P=0.104
SIRS4.DAF	2.5 12 25	1 8 22	8 16 20	2 9 22.25	F=1.33 d.f.=2,69 P=0.272
STER.DAF	0 5 25.0	1 3 19	1 7 15	0.75 3.5 19.25	F=0.01 d.f.=2,69 P=0.989
CVS.DAF	0 4 15.75	0 0 13	0 3 13	0 0 14	F=0.21 d.f.=2,69 P=0.814
RESP.DAF	0 0 10.75	0 0 8	0 1 5	0 0 8	F=0.04 d.f.=2,69 P=0.956
PF300.DAF	0 0 0.75	0 0 1	0 0 2	0 0 1	F=0.04 d.f.=2,69 P=0.962

VENT.DAF	0 0 10.5	0 0 8	0 0 2	0 0 8	F=0.32 d.f.=2,69 P=0.73
CNS.DAF	2.75 12 26.25	2 7 24	9 13 20	2 10.5 24.25	F=0.59 d.f.=2,69 P=0.556
COAG.DAF	2 7 27.75	1 7 26	4 12 20	1 7.5 26	F=0.25 d.f.=2,69 P=0.781
INR.DAF	1 16.5 28	1 7 26	6 13 21	1.75 8 26.25	F=0.42 d.f.=2,69 P=0.658
ACRF.DAF	0 2 25	0 3 24	5 9 14	0 5 20.25	F=0.45 d.f.=2,69 P=0.642
ANYREN.DAF	0 2 17.75	0 3 24	5 9 14	0 5 18.25	F=0.6 d.f.=2,69 P=0.549
RENSUP.DAF	1 2.5 26	1 3 28	2 10 17	1 4.5 27.25	F=0.14 d.f.=2,69 P=0.868
ACHEP.DAF	2.25 8.5 28	1 3 20	10 14 22	2 7.5 24	F=1.62 d.f.=2,69 P=0.204
ANYHEP.DAF	2.25 8 28	1 3 20	10 14 22	2 7 24	F=1.73 d.f.=2,69 P=0.186

TABLE 3.36

A response association of arginine vasopressin receptor 1a AVPR1A rs1495027 in Caucasian septic-shock control subjects. . For all variables besides 28-day survival, data is given as 25th percentile | median | 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

CONTROL	CC (N=29)	CT (N=37)	TT (N=13)	Combined (N=79)	Test Statistic
SURVIVAL	24% (7/29)	35% (13/37)	46% (6/13)	33% (26/79)	Chisquare=2.13 d.f.=2 P=0.345
DAYS ALIVE	2 6 21	3 8 28	4 15 28	3 8 28	F=0.77 d.f.=2,76 P=0.467
ALI.DAF	1 3 11	1 5 14	2 7 20	1 5 14.5	F=0.42 d.f.=2,76 P=0.661
PRESS.DAF	0 3 14	0 4 24	1 9 19	0 4 22	F=0.46 d.f.=2,76 P=0.633
PRESS2.DAF	0 3 14	0 4 24	2 9 19	0 4 22	F=0.48 d.f.=2,76 P=0.62
PRESS5.DAF	0 3 14	0 4 25	2 9 21	0 4 23	F=0.7 d.f.=2,76 P=0.501
PRESS15.DAF	0 3 18	1 6 26	2 15 26	0.5 5 26	F=1.04 d.f.=2,76 P=0.359
INO.DAF	1 3 20	3 7 28	2 15 28	2 6 28	F=1.15 d.f.=2,76 P=0.322
SIRS2.DAF	0 0 0	0 0 2	0 0 2	0 0 1	F=1.05 d.f.=2,76 P=0.355
SIRS3.DAF	1 1 5	0 2 8	2 4 9	0 2 6.5	F=0.94 d.f.=2,76 P=0.394
SIRS4.DAF	1 6 11	2 5 25	4 10 22	2 6 21.5	F=0.76 d.f.=2,76 P=0.471
STER.DAF	0 2 10	1 5 24	2 5 15	1 5 20	F=0.71 d.f.=2,76 P=0.495
CVS.DAF	0 0 13	0 3 18	0 4 19	0 2 18.5	F=0.45 d.f.=2,76 P=0.637
RESP.DAF	0 1 9	0 2 17	0 1 7	0 1 9.5	F=0.37 d.f.=2,76 P=0.694
PF300.DAF	0 0 0	0 0 2	0 0 0	0 0 1.5	F=1.42 d.f.=2,76 P=0.248
VENT.DAF	0 0 9	0 0 12	0 0 7	0 0 9.5	F=0.07 d.f.=2,76 P=0.93
CNS.DAF	1 5 18	1 7 26	4 14 25	1 7 25	F=0.34 d.f.=2,76 P=0.712
COAG.DAF	1 5 15	1 6 28	2 15 28	1 6 24.5	F=0.54 d.f.=2,76 P=0.583
INR.DAF	0 3 21	0 5 21	1 10 27	0 4 21.5	F=0.36 d.f.=2,76 P=0.701
ACRF.DAF	0 3 9	0 6 23	0 10 20	0 4 20	F=0.42 d.f.=2,76 P=0.658
ANYREN.DAF	0 2 9	0 5 23	0 10 20	0 4 19	F=0.28 d.f.=2,76 P=0.757
RENSUP.DAF	1 2 4	1 7 28	2 5 16	1 4 17	F=2.45 d.f.=2,76 P=0.0928
ACHEP.DAF	1 5 19	2 7 28	4 15 28	1 6 26	F=1.21 d.f.=2,76 P=0.303
ANYHEP.DAF	1 5 19	1 6 28	4 15 28	1 6 26	F=0.94 d.f.=2,76 P=0.397

TABLE 3.37

Difference in response association of arginine vasopressin receptor 1a (AVPR1A) rs1495027 between cases (vasopressin-treated group) (Treat) and controls (vasopressin untreated matched control) (Cont) of Caucasian ICU subjects diagnosed with septic shock. For all variables besides 28-day survival, data is presented as medians. For 28-day survival, data is presented as % (N survived / N total). N, number of subjects.

	rs1495027 TT (N=13)			rs1495027 CT (N=45)			rs1495027 CC (N=14)		
	Treat	Cont	DELTA	Treat	Cont	DELTA	Treat	Cont	DELTA
SURVIVAL	23% (3)	46% (6)	-23%	38% (17)	35% (13)	3%	50% (7)	24% (7)	26%
DAYS ALIVE	20	15	5	10	8	2	18.5	6	12.5

ALI.DAF	6	7	-1	3	5	-2	5.5	3	2.5
PRESS.DAF	7	9	-2	0	4	-4	8.5	3	5.5
PRESS2.DAF	7	9	-2	1	4	-3	8.5	3	5.5
PRESS5.DAF	11	9	2	1	4	-3	9	3	6
PRESS15.DAF	14	15	-1	3	6	-3	13	3	10
INO.DAF	19	15	4	8	7	1	13.5	3	10.5
SIRS2.DAF	1	0	1	0	0	0	0	0	0
SIRS3.DAF	7	4	3	2	2	0	3.5	1	2.5
SIRS4.DAF	16	10	6	8	5	3	12	6	6
STER.DAF	7	5	2	3	5	-2	5	2	3
CVS.DAF	3	4	-1	0	3	-3	4	0	4
RESP.DAF	1	1	0	0	2	-2	0	1	-1
PF300.DAF	0	0	0	0	0	0	0	0	0
VENT.DAF	0	0	0	0	0	0	0	0	0
CNS.DAF	13	14	-1	7	7	0	12	5	7
COAG.DAF	12	15	-3	7	6	1	7	5	2
INR.DAF	13	10	3	7	5	2	16.5	3	13.5
ACRF.DAF	9	10	-1	3	6	-3	2	3	-1
ANYREN.DAF	9	10	-1	3	5	-2	2	2	0
RENSUP.DAF	10	5	5	3	7	-4	2.5	2	0.5
ACHEP.DAF	14	15	-1	3	7	-4	8.5	5	3.5
ANYHEP.DAF	14	15	-1	3	6	-3	8	5	3

A logistic regression approach was used to test for a statistically significant interaction between genotype and vasopressin use as predicted by 28-day survival **TABLE 3.38** shows that there was a statistically significant interaction between AVPR1A rs1495027 genotype, vasopressin treatment and survival, confirming vasopressin treatment decreases 28-day survival in AVPR1A rs1495027 TT genotype subjects while vasopressin treatment increases 28-day survival in AVPR1A rs1495027 CC subjects compared to controls (P = 0.04662). Following adjustment for age, admission APACHE II score, gender, medical, surgical diagnosis and days alive and free of 3 of 4 systematic inflammatory response syndrome (SIRS) criteria, there was still a statistically significant interaction of the AVPR1A rs1495027 genotype and treatment with vasopressin (P = 0.0339).

TABLE 3.38

Interaction between genotype and vasopressin use vs. no vasopressin (Controls) and CC or CT genotype vs. TT genotype of arginine vasopressin receptor 1a (AVPR1A) rs1495027 on 28-day survival.

	Estimate	Std. Error	z value	Pr(> z)
Vasopressin vs. controls + genotype interaction	2.195	1.1031	1.99	0.04662
Vasopressin vs. controls + genotype interaction - Adjusted	2.6035	1.2271	2.122	0.03387

Example 1 Summary

Genotyping of SNPs LNPEP rs18059, LNPEP rs27711, LNPEP rs10051637, AVP rs1410713,

AVP rs857240, AVP rs857242, and AVPR1A rs1495027 in subjects with septic shock can predict

response to administration of vasopressin as measured by 28-day survival and/or DAF of organ dysfunction. Subjects with genotypes including LNPEP rs18059 CC, LNPEP rs27711 AA, LNPEP rs10051637 GG, AVP rs1410713 CC, AVP rs857240 CT, AVP rs857242 AC and AVPR1A rs1495027 TT should not be administered a vasopressin receptor agonist as this could potentially decrease survival and increase risk of organ dysfunction. In contrast, subjects with LNPEP rs18059 TT, LNPEP rs27711 GG, LNPEP rs10051637 AA, AVP rs1410713 AA and rs1410713 AC, AVP rs857240 CC, AVP rs857242 CC and AVPR1A rs1495027 CC genotypes should be administered a vasopressin receptor agonist as such treatment has the potential to increase survival and decrease risk of organ dysfunction.

EXAMPLE 2: RISK OF DEATH AND ORGAN DYSFUNCTION

Methods

Cohort Selection

To investigate whether genotype predicts risk of death and organ dysfunction, selected subsets of the ICU cohort were used for this study. All patients who were treated with vasopressin for septic shock were excluded. The four study groups were: ICU Caucasians with SIRS upon admission (n=874), ICU Caucasians with sepsis upon admission (n=690), ICU Caucasians with septic shock upon admission (n=440) and ICU Asians with SIRS upon admission (n=108).

Data Analysis

All data analysis was carried out using statistical packages available in R (R Core Development Group, 2005 - R Development Core Team (www.R-project.org). R: A language and environment for statistical computing. Vienna, Austria. 2005). Chi-square and Kruskal-Wallis (KW) test statistics were used in conjunction with Cox proportional hazards (CPH) regression to identify significant SNP-phenotype associations, as well as to identify baseline characteristics (age, gender, admitting APACHE II score, and medical vs. surgical admitting diagnosis) requiring post-hoc, multivariate adjustment. Genetically heterogeneous populations were subsetted prior to analysis to avoid confounding from potential population stratification.

Results

2.1 Leucyl/Cystinyl Aminopeptidase (LNPEP)

2.1.1 LNPEP rs18059

2.1.1.1 Systematic Inflammatory Response Syndrome – Caucasians

TABLE 4.1 gives the baseline characteristics of 710 Caucasian SIRS subjects who were successfully genotyped (CC vs. CT/TT) at LNPEP rs18059. No significant differences were detected between the two genotype groups on admission to the ICU.

TABLE 4.1

Baseline characteristics of a cohort of Caucasian Subjects with systematic inflammatory response syndrome by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs18059 (CC vs. CT/TT). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	CC (N=155)	CT / TT (N=555)	Combined (N=710)	Test Statistic
AGE	44.5 / 58 / 70	45 / 59 / 71	46 / 59 / 71	F=0.96 d.f.=1,708 P=0.327
GENDER	63% (97/155)	61% (336/555)	61% (433/710)	X ² =0.21 d.f.=1 P=0.645
APACHEII	15 / 20 / 26	16 / 22 / 27	16 / 21.5 / 27	F=2.52 d.f.=1,708 P=0.113
SURGICAL	20% (31/155)	23% (130/555)	23% (161/710)	X ² =0.81 d.f.=1 P=0.368
SEP.ADMIT	81% (125/155)	78% (435/555)	79% (560/710)	X ² =0.37 d.f.=1 P=0.541
SEP.ANY	83% (129/155)	80% (442/555)	80% (571/710)	X ² =0.99 d.f.=1 P=0.32
SS.ADMIT	52% (81/155)	51% (285/555)	52% (366/710)	X ² =0.04 d.f.=1 P=0.842
SS.ANY	55% (85/155)	55% (306/555)	55% (391/710)	X ² =0 d.f.=1 P=0.948

Figure 1 and **TABLE 4.2** summarize important SNP-phenotype associations. Subjects with LNPEP rs18059 CC genotype showed a significantly greater survival ($P = 0.0331$) and had significantly more days alive ($P = 0.0144$) and days alive and free of vasopressors ($P = 0.0088$), days alive and free of vasopressors at doses of more than 2 ug/min ($P=0.0101$), 5 ug/min ($P=0.0037$) and 15 ug/min ($P=0.0157$), inotropes ($P = 0.0252$), coagulation dysfunction ($P = 0.0030$), any renal dysfunction ($P = 0.0088$), renal support ($P = 0.0145$), acute hepatic dysfunction ($P = 0.0335$) and any hepatic dysfunction ($P = 0.0456$). Subjects who carried the LNPEP rs18059 CC genotype also showed a strong trend for more days alive and free of neurological dysfunction ($P = 0.071$). These findings indicate that these patients who have who carry the LNPEP rs18059 CC genotype at LNPEP rs18059 CC have less need of inotrope and vasopressor therapy and have a lower risk of organ dysfunction (coagulation, renal, hepatic and neurological).

TABLE 4.2

Days alive and free of organ dysfunction (DAF) by allele of leucyl/cystinyl aminopeptidase (LNPEP) rs18059 (CC vs. CT/TT) in a cohort of Caucasian subjects with systematic inflammatory response syndrome. For all variables besides 28-day survival, data is given as 25th percentile / median / 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

	CC	CT / TT	Combined	Test
	(N=155)	(N=555)	(N=710)	Statistic

SURVIVAL	75% (117/155)	66% (369/555)	68% (486/710)	$\chi^2=4.54$ d.f.=1 P=0.0331
DA	28 / 28 / 28	10 / 28 / 28	12 / 28 / 28	F=6.02 d.f.=1,708 P=0.0144
PRESS.DAF	17.5 / 27 / 28	7 / 25 / 28	9 / 26 / 28	F=6.9 d.f.=1,708 P=0.0088
PRESS2.DAF	17.5 / 27 / 28	7.5 / 26 / 28	10 / 26 / 28	F=6.64 d.f.=1,708 P=0.0101
PRESS5.DAF	18.5 / 27 / 28	8 / 26 / 28	10 / 26 / 28	F=8.49 d.f.=1,708 P=0.00369
PRESS15.DAF	23.5 / 28 / 28	9 / 28 / 28	12 / 28 / 28	F=5.86 d.f.=1,708 P=0.0157
INO.DAF	24 / 28 / 28	9 / 28 / 28	11.3 / 28 / 28	F=5.03 d.f.=1,708 P=0.0252
CNS.DAF	14 / 27 / 28	7 / 26 / 28	7.25 / 27 / 28	F=3.27 d.f.=1,708 P=0.071
COAG.DAF	20 / 28 / 28	7 / 28 / 28	8.25 / 28 / 28	F=8.87 d.f.=1,708 P=0.00299
INR.DAF	14 / 28 / 28	5 / 27 / 28	7 / 27 / 28	F=3.51 d.f.=1,708 P=0.0615
ANYREN.DAF	9 / 28 / 28	2 / 22 / 28	3 / 25 / 28	F=6.9 d.f.=1,708 P=0.00882
RENSUP.DAF	14 / 28 / 28	4 / 28 / 28	5 / 28 / 28	F=6 d.f.=1,708 P=0.0145
ACHEP.DAF	17 / 28 / 28	7 / 28 / 28	8 / 28 / 28	F=4.54 d.f.=1,708 P=0.0335
ANYHEP.DAF	15.5 / 28 / 28	6 / 28 / 28	7 / 28 / 28	F=4.01 d.f.=1,708 P=0.0456

2.1.1.2 Sepsis – Caucasians

TABLE 4.3 gives the baseline characteristics (age, gender, APACHE II score, medical vs. surgical diagnosis, septic shock upon admission and septic shock anytime) of 561 Caucasian sepsis subjects who were successfully genotyped (CC vs. CT/TT) at LNPEP rs18059. No significant differences were detected between the two genotype groups on admission to the ICU.

TABLE 4.3

Baseline characteristics of a cohort of Caucasian Subjects with sepsis by allele of leucyl/cystinyl aminopeptidase (LNPEP) rs18059 (CC vs. CT/TT). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	CC (N=126)	CT / TT (N=435)	Combined (N=561)	Test Statistic
AGE	46 / 58 / 70.8	45 / 59 / 71.5	47 / 59 / 72	F=0.45 d.f.=1,559 P=0.501
GENDER	65% (82/126)	62% (270/435)	63% (352/561)	$\chi^2=0.38$ d.f.=1 P=0.538
APACHEII	16 / 22 / 27	17 / 23 / 28	17 / 22 / 28	F=1.95 d.f.=1,559 P=0.163
SURGICAL	21% (26/126)	23% (100/435)	22% (126/561)	$\chi^2=0.31$ d.f.=1 P=0.577
SS.ADMIT	64% (81/126)	66% (285/435)	65% (366/561)	$\chi^2=0.07$ d.f.=1 P=0.798
SS.ANY	66% (83/126)	70% (303/435)	69% (386/561)	$\chi^2=0.65$ d.f.=1 P=0.42

TABLE 4.4 summarizes important SNP-phenotype associations. Subjects with the LNPEP

rs18059 CC genotype showed significantly more days alive and free of vasopressors ($P = 0.0377$), days alive and free of vasopressors at doses of more than 2 $\mu\text{g}/\text{min}$ ($P = 0.0424$) and 5 $\mu\text{g}/\text{min}$ ($P = 0.0194$) and coagulation dysfunction ($P = 0.0359$). Subjects who carried the LNPEP rs18059 CC genotype also showed a strong trend for more days alive and free of renal support ($P = 0.07$).

These findings indicate that Caucasian sepsis subjects who carry the LNPEP rs18059 CC genotype have less need of vasopressor therapy and have a lower risk of organ dysfunction (coagulation and renal).

TABLE 4.4

Days alive and free of organ dysfunction (DAF) by allele of leucyl/cystinyl aminopeptidase (LNPEP) rs18059 (CC vs. CT/TT) in a cohort of Caucasian subjects with sepsis. Data is given as 25th percentile / median / 75th percentile. N, number of subjects.

	CC (N=126)	CT / TT (N=435)	Combined (N=561)	Test Statistic
PRESS.DAF	15 / 26 / 28	8 / 25 / 28	10 / 25 / 28	F=4.34 d.f.=1,559 P=0.0377
PRESS2.DAF	15 / 26 / 28	8.5 / 25 / 28	10 / 25 / 28	F=4.14 d.f.=1,559 P=0.0424
PRESS5.DAF	17.3 / 27 / 28	9 / 25 / 28	11 / 26 / 28	F=5.5 d.f.=1,559 P=0.0194
COAG.DAF	20 / 28 / 28	9 / 28 / 28	10 / 28 / 28	F=6.06 d.f.=1,559 P=0.0142
RENSUP.DAF	11.3 / 28 / 28	5 / 28 / 2	6 / 28 / 28	F=3.29 d.f.=1,559 P=0.07

5

2.1.1.3 Septic Shock – Caucasians

TABLE 4.5 gives the baseline characteristics (age, gender, APACHE II score and medical vs. surgical diagnosis) of 366 Caucasian septic shock subjects who were successfully genotyped (CC vs. CT/TT) at LNPEP rs18059. No significant differences were detected between the two genotype groups on admission to the ICU.

10

TABLE 4.5

Baseline characteristics of a cohort of Caucasian Subjects with septic shock by allele of leucyl/cystinyl aminopeptidase (LNPEP) rs18059 (CC vs. CT/TT). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

15

	CC (N=81)	CT / TT (N=285)	Combined (N=366)	Test Statistic
AGE	47 / 59 / 71	48 / 63 / 73	48 / 62 / 73	F=1.91 d.f.=1,364 P=0.168
GENDER	64% (52/81)	60% (172/285)	61% (224/366)	X ² =0.39 d.f.=1 P=0.531
APACHEII	17 / 24 / 29	20 / 25 / 30	19 / 24 / 30	F=1.81 d.f.=1,364 P=0.180
SURGICAL	21% (17/81)	26% (74/285)	25% (91/366)	X ² =0.84 d.f.=1 P=0.360

TABLE 4.6 summarizes important SNP-phenotype associations. Subjects with the LNPEP rs18059 CC genotype showed a strong trend for greater survival (P = 0.0862) and significantly more days alive (P = 0.0353) and days alive and free of vasopressors (P = 0.0404), days alive and free of vasopressors at doses of more than 2 ug/min (P = 0.0372), 5 ug/min (P = 0.0132) and 15 ug/min (P = 0.0373), coagulation dysfunction (P = 0.0079), any renal dysfunction (P = 0.0394) and renal support (P = 0.0364). LNPEP rs18059 CC individuals also showed a strong trend for more days alive and free of inotropes (P = 0.0646) and acute renal dysfunction (P = 0.0593). These findings indicate that Caucasian septic shock subjects who carry the CC genotype at LNPEP rs18059 have less need of inotrope and vasopressor therapy and are have a lower risk of organ dysfunction (coagulation and renal).

20

25

TABLE 4.6

Days alive and free of organ dysfunction (DAF) by allele of leucyl/cystinyl aminopeptidase (LNPEP) rs18059 (CC vs. CT/TT) in a cohort of Caucasian subjects with septic shock. For all variables besides 28-day survival, data is given as 25th percentile / median / 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

	CC (N=81)	CT / TT (N=285)	Combined (N=366)	Test Statistic
SURVIVAL	69% (56/81)	59% (167/285)	61% (223/366)	X ² =2.94 d.f.=1 P=0.0862
DA	22 / 28 / 28	8 / 28 / 28	9 / 28 / 28	F=4.46 d.f.=1,364 P=0.0353
PRESS.DAF	11 / 24 / 27	4 / 21 / 26	5.75 / 23 / 26	F=4.23 d.f.=1,364 P=0.0404
PRESS2.DAF	11 / 24 / 27	4 / 22 / 26	5.75 / 23 / 26	F=4.37 d.f.=1,364 P=0.0372
PRESS5.DAF	13 / 25 / 27	5 / 23 / 27	6 / 24 / 27	F=6.2 d.f.=1,364 P=0.0132
PRESS15.DAF	17 / 27 / 28	6 / 26 / 28	8 / 26 / 28	F=4.37 d.f.=1,364 P=0.0373
INO.DAF	18 / 28 / 28	6 / 26 / 28	7 / 28 / 28	F=3.44 d.f.=1,364 P=0.0646
COAG.DAF	17 / 28 / 28	5 / 24 / 28	6 / 25 / 28	F=7.14 d.f.=1,364 P=0.0079
INR.DAF	12 / 25 / 28	4 / 22 / 28	5 / 24 / 28	F=2.81 d.f.=1,364 P=0.0944
ACRF.DAF	10 / 27 / 28	3 / 20 / 28	3 / 22 / 28	F=3.58 d.f.=1,364 P=0.0593
ANYREN.DAF	9 / 26 / 28	2 / 18 / 28	2.75 / 19.50 / 28	F=4.27 d.f.=1,364 P=0.0394
RENSUP.DAF	10 / 28 / 28	3 / 23 / 28	4 / 25 / 28	F=4.41 d.f.=1,364 P=0.0364

5

2.1.2 LNPEP rs27711

2.1.2.2 Systematic Inflammatory Response Syndrome – Caucasians

TABLE 4.7 summarizes the baseline characteristics (age, gender, APACHE II score, medical vs. surgical diagnosis, sepsis upon admission, sepsis anytime, septic shock upon admission and septic shock anytime) of 717 Caucasian systematic inflammatory response syndrome subjects who were successfully genotyped (AA vs. GG/AG) at LNPEP rs27711. No significant differences were detected between the two genotype groups on admission to the ICU.

15 TABLE 4.7

Baseline characteristics of a cohort of Caucasian Subjects with systematic inflammatory response syndrome by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs27711 (GG/AG vs. AA). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	AA (N=98)	GG / AG (N=619)	Combine d (N=717)	Test Statistic
AGE	43.5 / 57 / 71	45 / 59 / 70.5	46 / 59 / 71	F=1.1 d.f.=1,715 P=0.294
GENDER	60% (59/98)	62% (382/619)	62% (441/717)	X ² =0.08 d.f.=1 P=0.776
APACHEII	15 / 20 / 27	16 / 22 / 27	16 / 21.5 / 27	F=1.42 d.f.=1,715 P=0.234
SURGICAL	19% (19/98)	23% (141/619)	22% (160/717)	X ² =0.56 d.f.=1 P=0.454
SEP.ADMIT	79% (77/98)	79% (487/619)	79% (564/717)	X ² =0 d.f.=1 P=0.981
SEP.ANY	81% (81/98)	80% (497/619)	80% (578/717)	X ² =0.01 d.f.=1 P=0.94

	79/98)		(576/717)	
SS.ADMIT	52% (51/98)	51% (317/619)	51% (368/717)	$X^2=0.02$ d.f.=1 $P=0.879$
SS.ANY	52% (51/98)	55% (342/619)	55% (393/717)	$X^2=0.35$ d.f.=1 $P=0.553$

TABLE 4.8 summarizes important SNP-phenotype associations. Subjects with the LNPEP rs27711 AA genotype showed significantly more days alive and free of vasopressors ($P = 0.0330$), days alive and free of vasopressors at doses of more than 2 ug/min ($P=0.0362$), 5 ug/min ($P=0.0222$) and 15 ug/min ($P=0.0961$). Subjects with the LNPEP rs27711 AA genotype also had a strong trend for more days alive and free of steroids ($P = 0.0871$). These findings indicate that Caucasian subjects who have SIRS and have the AA genotype at LNPEP rs27711 have less need for vasopressor therapy and steroid therapy.

10 **TABLE 4.8**

Days alive and free of organ dysfunction (DAF) by allele of leucyl/cystinyl aminopeptidase (LNPEP) rs27711 (GG/AG vs. AA) in a cohort of Caucasian subjects with systematic inflammatory response syndrome. Data is given as 25th percentile / median / 75th percentile. N, number of subjects.

	AA (N=98)	GG / AG (N=619)	Combined (N=717)	Test Statistic
PRESS.DAF	15 / 27 / 28	9 / 26 / 28	9 / 26 / 28	$F=4.56$ d.f.=1,715 $P=0.0330$
PRESS2.DAF	15 / 27 / 28	9 / 26 / 28	10 / 26 / 28	$F=4.41$ d.f.=1,715 $P=0.0362$
PRESS5.DAF	17 / 28 / 28	10 / 26 / 28	10 / 26 / 28	$F=5.25$ d.f.=1,715 $P=0.0222$
PRESS15.DAF	20.5 / 28 / 28	11 / 28 / 28	12 / 28 / 28	$F=2.78$ d.f.=1,715 $P=0.0961$
STER.DAF	6 / 26.5 / 28	2 / 22 / 28	2 / 23 / 28	$F=2.93$ d.f.=1,715 $P=0.0871$

15

2.1.3 LNPEP rs10051637

2.1.3.1 Systematic Inflammatory Response Syndrome – Caucasians

TABLE 4.9 summarizes the baseline characteristics (age, gender, APACHE II score, medical vs. surgical diagnosis, sepsis upon admission, sepsis anytime, septic shock upon admission and septic shock anytime) of 710 Caucasian SIRS subjects who were successfully genotyped (AA vs. AG/GG) at LNPEP rs10051637. No significant baseline differences were detected between the two genotype groups on admission to the ICU although the AG/GG group is more likely to be diagnosed with sepsis throughout an ICU stay.

25

TABLE 4.9

Baseline characteristics of a cohort of Caucasian Subjects with systematic inflammatory response syndrome by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs10051637 (AA vs. AG/GG). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	AA (N=236)	AG / GG (N=474)	Combine d (N=710)	Test Statistic
AGE	44 / 61 / 72	45.3 / 58 / 70	46 / 59 / 71	F=1.06 d.f.=1,708 P=0.304
GENDER	60% (142/236)	63% (297/474)	62% (439/710)	X ² =0.41 d.f.=1 P=0.52
APACHEII	17 / 22 / 27	15 / 22 / 27	16 / 21.5 / 27	F=0.2 d.f.=1,708 P=0.657
SURGICAL	21% (49/236)	24% (113/474)	23% (162/710)	X ² =0.85 d.f.=1 P=0.357
SEP.ADMIT	75% (177/236)	80% (378/474)	78% (555/710)	X ² =2.08 d.f.=1 P=0.149
SEP.ANY	76% (179/236)	82% (389/474)	80% (568/710)	X ² =3.81 d.f.=1 P=0.051
SS.ADMIT	48% (114/236)	52% (247/474)	51% (361/710)	X ² =0.91 d.f.=1 P=0.339
SS.ANY	51% (121/236)	56% (266/474)	55% (387/710)	X ² =1.49 d.f.=1 P=0.222

TABLE 4.10 summarizes important SNP-phenotype associations. Subjects with the LNPEP rs10051637 AG or GG genotype showed significantly more days alive and free of inotropes ($P = 0.0357$) and 2 of 4 SIRS criteria ($P = 0.0226$). These findings indicate that Caucasian subjects who have SIRS who carry either the AG or GG genotype at LNPEP rs10051637 have less need of inotrope therapy and less SIRS.

TABLE 4.10

Days alive and free of organ dysfunction (DAF) by allele of leucyl/cystinyl aminopeptidase (LNPEP) rs10051637 (AA vs. AG/GG) in a cohort of Caucasian subjects with systematic inflammatory response syndrome. Data is given as 25th percentile / median / 75th percentile. N, number of subjects.

	AA (N=236)	AG / GG (N=474)	Combined (N=710)	Test Statistic
INO.DAF	7 / 28 / 28	15 / 28 / 28	11.3 / 28 / 28	F=4.43 d.f.=1,708 P=0.0357
MSIRS2.DAF	0 / 2 / 20	0 / 6 / 21	0 / 5 / 21	F=5.22 d.f.=1,708 P=0.0226
CSIRS2.DAF	0 / 3 / 20	0 / 5 / 20	0 / 5 / 20	F=3.23 d.f.=1,708 P=0.0726

2.1.4 LNPEP rs38041

2.1.4.1 Systematic Inflammatory Response Syndrome – Caucasians

TABLE 4.11 summarizes the baseline characteristics (age, gender, APACHE II score, medical vs. surgical diagnosis, sepsis upon admission, sepsis anytime, septic shock upon admission and septic shock anytime) of 717 Caucasian SIRS subjects who were successfully genotyped (AA vs. GG/AG) at LNPEP rs38041. No significant differences were detected between the two genotype groups on admission to the ICU.

TABLE 4.11

Baseline characteristics of a cohort of Caucasian Subjects with systematic inflammatory response syndrome by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs38041 (AA vs. GG/AG). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	AA (N=143)	GG / AG (N=574)	Combined (N=717)	Test Statistic
AGE	45.5 / 56 / 70.5	45 / 59 / 71	46 / 59 / 71	F=1.15 d.f.=1.715 P=0.283
GENDER	59% (85/143)	62% (356/574)	62% (441/717)	X ² =0.32 d.f.=1 P=0.57
APACHE II	15 / 21 / 27	16 / 22 / 27	16 / 21.5 / 27	F=0.84 d.f.=1.715 P=0.361
SURGICAL	24% (35/143)	22% (128/574)	23% (163/717)	X ² =0.31 d.f.=1 P=0.579
SEP.ADMIT	82% (117/143)	78% (445/574)	78% (562/717)	X ² =1.24 d.f.=1 P=0.265
SEP.ANY	83% (119/143)	79% (456/574)	80% (575/717)	X ² =1.03 d.f.=1 P=0.311
SS.ADMIT	52% (75/143)	50% (289/574)	51% (364/717)	X ² =0.2 d.f.=1 P=0.653
SS.ANY	55% (78/143)	54% (312/574)	54% (390/717)	X ² =0 d.f.=1 P=0.967

TABLE 4.12 summarizes important SNP-phenotype associations for LNPEP rs38041. Subjects with the LNPEP rs38041 AA genotype showed significantly more days alive and free of vasopressors at doses of more than 5 ug/min (0.0278) and 15 ug/min (0.0384) and any renal dysfunction (P = 0.0475). Subjects with the LNPEP rs38041 AA genotype also showed a strong trend for more days alive and free of vasopressors (P = 0.067) and days alive and free of vasopressors at a dose of more than 2 ug/min (0.0751). These findings indicate that Caucasian subjects who have SIRS and have the AA genotype at LNPEP rs38041 have less need of vasopressor therapy and are a lower risk of organ dysfunction (renal).

TABLE 4.12

Days alive and free of organ dysfunction (DAF) by allele of leucyl/cystinyl aminopeptidase (LNPEP) rs38041 (GG/AG vs. AA) in a cohort of Caucasian subjects with systematic

inflammatory response syndrome. Data is given as 25th percentile / median / 75th percentile. N, number of subjects.

	AA (N=143)	GG / AG (N=574)	Combined (N=717)	Test Statistic
PRESS.DAF	15 / 26 / 28	8 / 26 / 28	9 / 26 / 28	F=3.37 d.f.=1,715 P=0.067
PRESS2.DAF	15 / 26 / 28	8.25 / 26 / 28	10 / 26 / 28	F=3.18 d.f.=1,715 P=0.0751
PRESS5.DAF	17 / 27 / 28	9 / 26 / 28	10 / 26 / 28	F=4.86 d.f.=1,715 P=0.0278
PRESS15.DAF	21 / 28 / 28	10.3 / 28 / 28	12 / 28 / 28	F=4.3 d.f.=1,715 P=0.0384
ANYREN.DAF	9 / 28 / 28	2 / 24 / 28	3 / 25 / 28	F=3.94 d.f.=1,715 P=0.0475

Arginine Vasopressin (AVP)

2.2.1 AVP rs1410713

2.2.1.1 Systematic Inflammatory Response Syndrome – Caucasians

TABLE 4.13 summarizes the baseline characteristics (age, gender, APACHE II score, medical vs. surgical diagnosis, sepsis upon admission, sepsis anytime, septic shock upon admission and septic shock anytime) of 717 Caucasian SIRS subjects who were successfully genotyped at AVP rs1410713. No significant differences were detected between the genotype groups on admission to the ICU.

TABLE 4.13

Baseline characteristics of a cohort of Caucasian Subjects with systematic inflammatory response syndrome by genotype of Arginine Vasopressin (AVP) rs1410713 (AA vs. CC/AC). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	AA (N=49)	CC / AC (N=668)	Combined (N=717)	Test Statistic
AGE	48 / 59 / 74	45 / 59 / 70	46 / 59 / 71	F=1.01 d.f.=1,715 P=0.315
GENDER	51% (25/49)	62% (416/668)	62% (441/717)	X ² =2.44 d.f.=1 P=0.118
APACHEII	16 / 23 / 28	16 / 22 / 27	16 / 21.5 / 27	F=0.25 d.f.=1,715 P=0.617
SURGICAL	18% (9/49)	23% (155/668)	23% (164/717)	X ² =0.61 d.f.=1 P=0.437
SEP.ADMI T	82% (40/49)	78% (523/668)	79% (563/717)	X ² =0.3 d.f.=1 P=0.583
SEP.ANY	82% (40/49)	80% (536/668)	80% (576/717)	X ² =0.06 d.f.=1 P=0.813
SS.ADMIT	47% (23/49)	51% (343/668)	51% (366/717)	X ² =0.36 d.f.=1 P=0.551
SS.ANY	49% (24/49)	55% (367/668)	55% (391/717)	X ² =0.65 d.f.=1 P=0.419

Figure 2 and **TABLE 4.14** summarize important SNP-phenotype associations for AVP rs1410713. Subjects in the AVP rs1410713 CC/AC genotype group had significantly increased survival (P = 0.0140), significantly more days alive (P = 0.0149) and significantly more days alive

and free of neurological dysfunction ($P = 0.0482$), coagulation dysfunction ($P = 0.0167$), INR >1.5 ($P=0.0108$), acute renal dysfunction ($P = 0.0414$), acute hepatic dysfunction ($P = 0.0218$) and any hepatic dysfunction ($P = 0.0175$). The AVP rs1410713 AA group also showed a strong trend for fewer days alive and free of inotropes ($P=0.0709$). These findings indicate that Caucasian subjects with SIRS and either the AVP rs1410713 CC or AC genotype have a lower risk of organ dysfunction (neurological, coagulation, renal and hepatic).

TABLE 4.14

Days alive and free of organ dysfunction (DAF) by genotype of Arginine Vasopressin (AVP) rs1410713 (AA vs. CC/AC) in a cohort of Caucasian subjects with systematic inflammatory response syndrome. For all variables besides 28-day survival, data is given as 25th percentile / median / 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

	AA (N=49)	CC / AC (N=668)	Combined (N=717)	Test Statistic
SURVIVAL	53% (26/49)	70% (467/668)	69% (493/717)	$X^2=6.03$ d.f.=1 $P=0.0140$
DA	6 / 28 / 28	15 / 28 / 28	12 / 28 / 28	$F=5.96$ d.f.=1,715 $P=0.0149$
INO.DAF	6 / 28 / 28	13.8 / 28 / 28	11.3 / 28 / 28	$F=3.27$ d.f.=1,715 $P=0.0709$
CNS.DAF	2 / 22 / 28	8.75 / 27 / 28	7.25 / 27 / 28	$F=3.91$ d.f.=1,715 $P=0.0482$
COAG.DAF	3 / 20 / 28	10 / 28 / 28	8.25 / 28 / 28	$F=5.75$ d.f.=1,715 $P=0.0167$
INR.DAF	2 / 15 / 28	7 / 27 / 28	7 / 27 / 28	$F=6.53$ d.f.=1,715 $P=0.0108$
ACRE.DAF	2 / 16 / 28	5.75 / 27 / 28	5 / 27 / 28	$F=4.18$ d.f.=1,715 $P=0.0414$
ACHEP.DAF	6 / 22 / 28	8.75 / 28 / 28	8 / 28 / 28	$F=5.28$ d.f.=1,715 $P=0.0218$
ANYHEP.DAF	4 / 20 / 28	7 / 28 / 28	7 / 28 / 28	$F=5.67$ d.f.=1,715 $P=0.0175$

2.2.1.2. Sepsis – Caucasians

TABLE 4.15 summarizes the baseline characteristics (age, gender, APACHE II score, medical vs. surgical diagnosis and shock upon admission and septic shock anytime) of 564 Caucasian sepsis subjects who were successfully genotyped at AVP rs1410713. No significant differences, other than a small gender difference, were detected between the genotype groups on admission to the ICU.

TABLE 4.15

Baseline characteristics of a cohort of Caucasian Subjects with sepsis by genotype of Arginine Vasopressin (AVP) rs1410713 (AA vs. CC/AC). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	AA (N=40)	CC / AC (N=524)	Combined (N=564)	Test Statistic
AGE	48 / 60.5 / 73.3	46 / 59 / 71	47 / 59 / 72	$F=1.26$ d.f.=1,562 $P=0.262$
GENDER	48% (19/40)	65% (338/524)	63% (357/564)	$X^2=4.63$ d.f.=1 $P=0.0315$
APACHEII	16 / 23.5 / 28.3	17 / 23 / 28	17 / 22 / 28	$F=0.13$ d.f.=1,562 $P=0.715$
SURGICAL	18% (7/40)	23% (120/524)	23% (127/564)	$X^2=0.62$ d.f.=1 $P=0.431$
SS.ADMIT	57% (23/40)	65% (343/524)	65% (366/564)	$X^2=1.03$ d.f.=1 $P=0.309$

SS.ANY	60% (24/40)	69% (362/524)	68% (386/564)	$X^2=1.42$ d.f.=1 P=0.233
--------	--------------	---------------	---------------	---------------------------

Figure 3 and **TABLE 4.16** summarize important SNP-phenotype associations for AVP rs1410713. Subjects with either the AVP rs1410713 CC or AC genotype had significantly increased survival ($P = 0.0325$), significantly more days alive ($P = 0.0314$) and significantly more days alive and free of acute renal dysfunction ($P = 0.0388$). Subjects with either the AVP rs1410713 CC or AC genotype also had a strong trend for more days alive and free of coagulation dysfunction ($P = 0.0706$), acute hepatic dysfunction ($P = 0.0783$) and any hepatic dysfunction ($P = 0.0627$). These findings indicate that Caucasian sepsis subjects who have either the CC or AC genotype at AVP rs1410713 have a lower risk of organ dysfunction (coagulation, renal and hepatic).

TABLE 4.16

Days alive and free of organ dysfunction (DAF) by genotype of Arginine Vasopressin (AVP) rs1410713 (AA vs. CC/AC) in a cohort of Caucasian subjects with sepsis. For all variables besides 28-day survival, data is given as 25th percentile / median / 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

	AA (N=40)	CC / AC (N=524)	Combined (N=564)	Test Statistic
SURVIVAL	52% (21/40)	69% (361/524)	68% (382/564)	$X^2=4.57$ d.f.=1 P=0.0325
DA	6.75 / 28 / 28	15.75 / 28 / 28	15 / 28 / 28	F=4.65 d.f.=1.562 P=0.0314
COAG.DAF	4 / 22 / 28	11 / 28 / 28	10 / 28 / 28	F=3.28 d.f.=1.562 P=0.0706
INR.DAF	1.75 / 13.50 / 28	8.75 / 27 / 28	8 / 27 / 28	F=7.7 d.f.=1.562 P=0.00571
ACRF.DAF	2 / 15.5 / 28	6 / 26 / 28	6 / 26 / 28	F=4.29 d.f.=1.562 P=0.0388
ANYREN.DAF	1.5 / 15.5 / 28	4 / 24 / 28	3 / 24.5 / 28	F=2.7 d.f.=1.562 P=0.101
ACHEP.DAF	6.75 / 23 / 28	9 / 28 / 28	9 / 28 / 28	F=3.11 d.f.=1.562 P=0.0783
ANYHEP.DAF	6 / 21 / 28	8 / 28 / 28	8 / 28 / 28	F=3.48 d.f.=1.562 P=0.0627

2.2.1.3 Septic Shock – Caucasians

TABLE 4.17 summarizes the baseline characteristics (age, gender, APACHE II score and medical vs. surgical diagnosis) of 366 Caucasian septic shock subjects who were successfully genotyped at AVP rs1410713. No significant differences were detected between the genotype groups on admission to the ICU.

TABLE 4.17

Baseline characteristics of a cohort of Caucasian Subjects with septic shock by genotype of Arginine Vasopressin (AVP) rs1410713 (AA vs. CC/AC). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	AA (N=23)	CC / AC (N=343)	Combined (N=366)	Test Statistic
AGE	50 / 67 / 75.5	48 / 62 / 72	48 / 62 / 73	F=1.16 d.f.=1,364 P=0.283
GENDER	43% (10/23)	62% (214/343)	61% (224/366)	X ² =3.25 d.f.=1 P=0.0716
APACHEII	23.5 / 26 / 31	19.5 / 24 / 30	19 / 24 / 30	F=0.97 d.f.=1,364 P=0.324
SURGICAL	13% (3/23)	25% (87/343)	25% (90/366)	X ² =1.76 d.f.=1 P=0.184

Figure 4 and **TABLE 4.18** summarize important SNP-phenotype associations for AVP

rs1410713. Subjects with either the AVP rs1410713 CC or AC genotype had significantly increased survival ($P = 0.0269$), significantly more days alive ($P = 0.0402$) and significantly more days alive and free of 4 of 4 SIRS criteria ($P = 0.0445$), acute renal dysfunction ($P = 0.0373$) and INR>1.5 ($P=0.00816$). Subjects with either the AVP rs1410713 CC or AC genotype also had a strong trend for more days alive and free of vasopressors at doses of more than 2 ug/min($P = 0.0982$) and 5 ug/min ($P = 0.0982$), inotropes ($P = 0.0962$), coagulation dysfunction ($P = 0.0931$), any renal dysfunction ($P = 0.0744$) and any hepatic dysfunction ($P = 0.0619$). These findings indicate that Caucasian septic shock subjects, who have either the CC or AC genotype at AVP rs1410713 have less need of vasopressor, and inotrope therapy, have less severe SIRS and have a lower risk of organ dysfunction (coagulation, renal and hepatic).

TABLE 4.18

Days alive and free of organ dysfunction (DAF) by genotype of Arginine Vasopressin (AVP) rs1410713 (AA vs. CC/AC) in a cohort of Caucasian subjects with septic shock. For all variables besides 28-day survival, data is given as 25th percentile / median / 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

	AA (N=23)	CC / AC (N=343)	Combined (N=366)	Test Statistic
SURVIVAL	39% (9/23)	62% (214/343)	61% (223/366)	X ² =4.9 d.f.=1 P=0.0269
DA	6 / 15 / 28	9.5 / 28 / 28	9 / 28 / 28	F=4.24 d.f.=1,364 P=0.0402
PRESS.DAF	2 / 9 / 25	7 / 23 / 26	5.75 / 23 / 26	F=2.96 d.f.=1,364 P=0.086
PRESS2.DAF	2 / 9 / 25	7 / 23 / 26	5.75 / 23 / 26	F=2.75 d.f.=1,364 P=0.0982
PRESS5.DAF	2 / 10 / 25	7.5 / 24 / 27	6 / 24 / 27	F=2.75 d.f.=1,364 P=0.0982
INO.DAF	6 / 15 / 28	8 / 28 / 28	7 / 28 / 28	F=2.78 d.f.=1,364 P=0.0962
MSIRS4.DAF	3.5 / 11 / 26.5	7 / 24 / 27	7 / 23.5 / 27	F=4.06 d.f.=1,364 P=0.0445
CSIRS4.DAF	4.5 / 11 / 26.5	8 / 25 / 27	7 / 24 / 27	F=3.93 d.f.=1,364 P=0.0481
COAG.DAF	4 / 15 / 28	8 / 26 / 28	6 / 25 / 28	F=2.83 d.f.=1,364 P=0.0931
INR.DAF	0 / 7 / 26	6 / 23 / 28	5 / 24 / 28	F=7.08 d.f.=1,364 P=0.00816
ACRF.DAF	0 / 10 / 27	4 / 22 / 28	3 / 22 / 28	F=4.37 d.f.=1,364 P=0.0373
ANYREN.DAF	0 / 10 / 27	3 / 19 / 28	2.75 / 19.5 / 28	F=3.2 d.f.=1,364 P=0.0744
ANYHEP.DAF	5 / 12 / 26	6 / 28 / 28	5.75 / 26.5 / 28	F=3.51 d.f.=1,364 P=0.0619

2.2.2 AVP rs857240

2.2.2.1 Sepsis – Caucasians

TABLE 4.19 gives the baseline characteristics (age, gender, APACHE II score, medical vs. surgical diagnosis, shock upon admission and septic shock anytime) of 573 Caucasian Subjects with sepsis who were successfully genotyped at AVP rs857240. No significant differences were detected between the genotype groups on admission to the ICU.

TABLE 4.19

Baseline characteristics of a cohort of Caucasian Subjects with sepsis by genotype of Arginine Vasopressin (AVP) rs857240 (CC vs. CT/TT). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	CC (N=471)	CT / TT (N=102)	Combined (N=573)	Test Statistic
AGE	46 / 59 / 71	43.3 / 55.5 / 71	47 / 59 / 72	F=0.57 d.f.=1,571 P=0.449
GENDER	63% (299/471)	65% (66/102)	64% (365/573)	X ² =0.05 d.f.=1 P=0.816
APACHEII	17 / 23 / 28	15.3 / 21 / 27	17 / 22 / 28	F=2.84 d.f.=1,571 P=0.0926
SURGICAL	22% (103/471)	25% (26/102)	23% (129/573)	X ² =0.63 d.f.=1 P=0.427
SS.ADMIT	64% (303/471)	69% (70/102)	65% (373/573)	X ² =0.68 d.f.=1 P=0.409
SS.ANY	68% (321/471)	72% (73/102)	69% (394/573)	X ² =0.46 d.f.=1 P=0.5

TABLE 4.20 summarizes important SNP-phenotype associations for AVP rs857240. Subjects with either the AVP rs857240 TT or CT genotype had a trend for increased survival (P = 0.0697), significantly more days alive (P = 0.0398), significantly more days alive and free of inotropes (P = 0.0457), coagulation dysfunction (P = 0.0382), INR>1.5 (P=0.036), acute renal dysfunction (P = 0.0238), any renal dysfunction (P = 0.0087), renal support (P = 0.0126), acute hepatic dysfunction (P = 0.0292) and any hepatic dysfunction (P = 0.0251). Subjects with either the AVP rs857240 TT or CT genotype also had a strong trend for more days alive and free of 4 of 4 SIRS criteria (P = 0.0555). These findings indicate that Caucasian subjects who have sepsis who carry either the AVP rs857240 TT or CT genotype at AVP rs857240 have less need of inotrope therapy, have less severe SIRS, and have a lower risk of organ dysfunction (coagulation, renal and hepatic).

TABLE 4.20

Days alive and free of organ dysfunction (DAF) by genotype of Arginine Vasopressin (AVP) rs857240 (CC vs. CT/TT) in a cohort of Caucasian subjects with sepsis. For all variables besides 28-day survival, data is given as 25th percentile / median / 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

	CC (N=471)	CT / TT (N=102)	Combined (N=573)	Test Statistic
SURVIVAL	66% (312/471)	75% (77/102)	68% (389/573)	X ² =3.29 d.f.=1 P=0.0697
DA	11 / 28 / 28	28 / 28 / 28	15 / 28 / 28	F=4.24 d.f.=1,571 P=0.0398
INO.DAF	11 / 28 / 28	25 / 28 / 28	12.3 / 28 / 28	F=4.01 d.f.=1,571 P=0.0457
MSIRS4.DAF	8 / 25 / 28	20.3 / 26 / 28	11 / 25 / 28	F=3.68 d.f.=1,571

				P=0.0555
CSIRS4.DAF	9 / 26 / 28	21 / 26 / 28	11 / 26 / 28	F=3.15 d.f.=1.571 P=0.0764
COAG.DAF	9.5 / 28 / 28	21 / 28 / 28	10 / 28 / 28	F=4.32 d.f.=1.571 P=0.0382
INR.DAF	7 / 27 / 28	17.3 / 27 / 28	8 / 27 / 28	F=0.84 d.f.=1.571 P=0.036
ACRF.DAF	4.5 / 25 / 28	10.3 / 28 / 28	6 / 26 / 28	F=5.14 d.f.=1.571 P=0.0238
ANYREN.DAF	3 / 22 / 28	10 / 28 / 28	3 / 24.5 / 28	F=6.94 d.f.=1.571 P=0.00868
RENSUP.DAF	5 / 28 / 28	15 / 28 / 28	6 / 28 / 28	F=6.26 d.f.=1.571 P=0.0126
ACHEP.DAF	7.5 / 28 / 28	19.3 / 28 / 28	9 / 28 / 28	F=4.78 d.f.=1.571 P=0.0292
ANYHEP.DAF	6 / 28 / 28	18.3 / 28 / 28	8 / 28 / 28	F=5.04 d.f.=1.571 P=0.0251

2.2.2.2 Septic Shock – Caucasians

TABLE 4.21 summarizes the baseline characteristics (age, gender, APACHE II score and medical vs. surgical diagnosis) of 373 Caucasian septic shock subjects who were successfully genotyped at AVP rs857240. No significant differences were detected between the genotype groups on admission to the ICU.

TABLE 4.21

Baseline characteristics of a cohort of Caucasian Subjects with septic shock by genotype of Arginine Vasopressin (AVP) rs857240 (CC vs. CT/TT). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	CC (N=303)	CT / TT (N=70)	Combined (N=373)	Test Statistic
AGE	48 / 61 / 72	46.3 / 59 / 73.8	48 / 62 / 73	F=0 d.f.=1.371 P=0.96
GENDER	62% (187/303)	61% (43/70)	62% (230/373)	X ² =0 d.f.=1 P=0.964
APACHEII	20.5 / 25 / 30	17.5 / 24 / 28	19 / 24 / 30	F=2.3 d.f.=1.371 P=0.130
SURGICAL	23% (70/303)	31% (22/70)	25% (92/373)	X ² =2.12 d.f.=1 P=0.145

TABLE 4.22 summarizes important SNP-phenotype associations for AVP rs857240. Subjects with either the AVP rs857240 TT or CT genotype had a trend for increased survival ($P = 0.091$), significantly more days alive ($P = 0.0467$), significantly more days alive and free of inotropes ($P = 0.0416$), acute renal dysfunction ($P = 0.0114$), any renal dysfunction ($P = 0.0052$), renal support ($P = 0.0266$), acute hepatic dysfunction ($P = 0.0190$) and any hepatic dysfunction ($P = 0.0115$). Subjects with either the AVP rs857240 TT or CT genotype also had a strong trend for fewer days alive and free of vasopressors at doses of more than 5 ug/min ($P = 0.0895$) and 15 ug/min ($P = 0.0747$) and days alive and free of 4 of 4 SIRS criteria ($P = 0.0771$). These findings indicate that

Caucasian subjects with septic shock who had either the TT or CT genotype at AVP rs857240 have less need of vasopressor and inotrope therapy, have less SIRS, and have a lower risk of organ dysfunction (renal and hepatic).

5 TABLE 4.22

Days alive and free of organ dysfunction (DAF) by genotype of Arginine Vasopressin (AVP) rs857240 (CC vs. CT/TT) in a cohort of Caucasian subjects with septic shock. For all variables besides 28-day survival, data is given as 25th percentile / median / 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

	CC (N=303)	CT / TT (N=70)	Combined (N=373)	Test Statistic
SURVIVAL	59% (179/303)	70% (49/70)	61% (228/373)	$\chi^2=2.86$ d.f.=1 P=0.091
DA	8 / 28 / 28	22.5 / 28 / 28	9 / 28 / 28	F=3.98 d.f.=1,371 P=0.0467
PRESS5.DAF	5 / 23 / 27	16.5 / 25 / 27	6 / 24 / 27	F=2.9 d.f.=1,371 P=0.0895
PRESS15.DAF	6 / 26 / 28	19.8 / 27 / 28	8 / 26 / 28	F=3.2 d.f.=1,371 P=0.0747
INO.DAF	6 / 27 / 28	20.3 / 28 / 28	7 / 28 / 28	F=4.18 d.f.=1,371 P=0.0416
MSIRS4.DAF	6 / 23 / 27	15.3 / 25 / 27	7 / 23.5 / 27	F=3.14 d.f.=1,371 P=0.0771
ACRF.DAF	3 / 20 / 28	10 / 27.5 / 28	3 / 22 / 28	F=6.47 d.f.=1,371 P=0.0114
ANYREN.DAF	1.50 / 18 / 28	9.25 / 27 / 28	2.75 / 19.50 / 28	F=7.91 d.f.=1,371 P=0.00517
RENSUP.DAF	3 / 24 / 28	12.5 / 28 / 28	4 / 25 / 28	F=4.95 d.f.=1,371 P=0.0266
ACHEP.DAF	5.5 / 27 / 28	17.3 / 28 / 28	6 / 28 / 28	F=5.55 d.f.=1,371 P=0.0190
ANYHEP.DAF	5 / 24 / 28	16.25 / 28 / 28	5.75 / 26.5 / 28	F=6.45 d.f.=1,371 P=0.0115

10

2.2.3 AVP rs857242

2.2.3.1 Systematic Inflammatory Response Syndrome – Caucasians

TABLE 4.23 summarizes the baseline characteristics (age, gender, APACHE II score, medical vs. surgical diagnosis, sepsis upon admission, sepsis anytime, septic shock upon admission and septic shock anytime) of 722 Caucasian systematic inflammatory response syndrome subjects who were successfully genotyped at AVP rs857242. Significant differences were detected between the genotype groups on admission to the ICU (APACHE II).

15

TABLE 4.23

Baseline characteristics of a cohort of Caucasian Subjects with systematic inflammatory response syndrome by genotype of Arginine Vasopressin (AVP) rs857242 (AC/AA vs. CC). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

20

	AC / AA (N=154)	CC (N=568)	Combined (N=722)	Test Statistic
AGE	43.3 / 56 / 69.8	45 / 59.5 / 71	46 / 59 / 71	F=1.93 d.f.=1,720 P=0.165
GENDER	64% (98/154)	61% (349/568)	62% (447/722)	$\chi^2=0.25$ d.f.=1 P=0.619
APACHEII	15 / 20 / 26	16 / 22 / 28	16 / 21.5 / 27	F=4.63 d.f.=1,720 P=0.0317
SURGICAL	25% (39/154)	22% (124/568)	23% (163/722)	$\chi^2=0.85$ d.f.=1 P=0.358
SEP.ADMI T	73% (112/154)	80% (454/568)	78% (566/722)	$\chi^2=3.71$ d.f.=1 P=0.0541

SEP.ANY	74% (114/154)	82% (465/568)	80% (579/722)	$X^2=4.69$ d.f.=1 $P=0.0304$
SS.ADMIT	49% (76/154)	51% (292/568)	51% (368/722)	$X^2=0.21$ d.f.=1 $P=0.65$
SS.ANY	53% (82/154)	55% (312/568)	55% (394/722)	$X^2=0.14$ d.f.=1 $P=0.71$

Figure 5 and **TABLE 4.24** summarize important SNP-phenotype associations for AVP rs857242.

Subjects with either the AVP rs857242 AC or AA genotype had significantly increased survival ($P = 0.0108$), significantly more days alive ($P = 0.0032$) and significantly more days alive and free of

vasopressors at doses of more than 5 ug/min ($P = 0.0361$) and 15 ug/min ($P = 0.0026$), days alive

and free of inotropes ($P = 0.0394$), 3 of 4 SIRS criteria ($P=0.0170$), 4 of 4 SIRS criteria ($P =$

0.0043), neurological dysfunction ($P = 0.033$), coagulation dysfunction ($P < 0.001$), acute renal

dysfunction ($P = 0.0341$), any renal dysfunction ($P = 0.0127$), renal support ($P = 0.0017$), acute

hepatic dysfunction ($P = 0.0013$) and any hepatic dysfunction ($P = 0.0021$). The AVP rs857242

AC or AA individuals also showed a strong trend for days alive and free of vasopressors

($P=0.0752$), days alive and free of vasopressors at a dose of more than 2 ug/min ($P=0.0524$), 2 of 4

SIRS criteria ($P=0.059$), INR>1.5 ($P=0.0679$). These findings indicate that Caucasian subjects

with SIRS who had either the AC or AA genotype at AVP rs857242 have less need of vasopressor

and inotrope therapy, have less severe SIRS and have a lower risk of organ dysfunction

(neurological, coagulation, renal and hepatic).

TABLE 4.24

Days alive and free of organ dysfunction (DAF) by genotype of Arginine Vasopressin (AVP) rs857242 (AC/AA vs. CC) in a cohort of Caucasian subjects with systematic inflammatory response syndrome. For all variables besides 28-day survival, data is given as 25th percentile / median / 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

	AC / AA (N=154)	CC (N=568)	Combined (N=722)	Test Statistic
SURVIVAL	77% (119/154)	67% (378/568)	69% (497/722)	$X^2=6.49$ d.f.=1 $P=0.0108$
DA	28 / 28 / 28	9.75 / 28 / 28	12 / 28 / 2	$F=8.74$ d.f.=1,720 $P=0.00321$
PRESS.DAF	18.3 / 26 / 28	7 / 26 / 28	9 / 26 / 28	$F=3.18$ d.f.=1,720 $P=0.0752$
PRESS2.DAF	18.3 / 26 / 28	7 / 26 / 28	10 / 26 / 28	$F=3.78$ d.f.=1,720 $P=0.0524$
PRESS5.DAF	20.25 / 27 / 28	7.75 / 26 / 28	10 / 26 / 28	$F=4.41$ d.f.=1,720 $P=0.0361$
PRESS15.DAF	25 / 28 / 28	9 / 28 / 28	12 / 28 / 28	$F=9.16$ d.f.=1,720 $P=0.00256$
INO.DAF	25 / 28 / 28	8 / 28 / 28	11.3 / 28 / 28	$F=4.26$ d.f.=1,720 $P=0.0394$
MSIRS2.DAF	1 / 6 / 22	0 / 4 / 20.3	0 / 5 / 21	$F=3.58$ d.f.=1,720 $P=0.059$
MSIRS3.DAF	7.25 / 22 / 26	2 / 19 / 26	3 / 19 / 26	$F=5.72$ d.f.=1,720 $P=0.0170$
MSIRS4.DAF	19.50 / 27 / 28	7 / 26 / 28	9.25 / 26 / 28	$F=8.19$ d.f.=1,720 $P=0.00434$
CSIRS2.DAF	1 / 5.5 / 22	0 / 4 / 20	0 / 5 / 20	$F=3.23$ d.f.=1,720 $P=0.0726$
CSIRS3.DAF	8 / 22 / 26	3 / 19 / 26	4 / 20 / 26	$F=5.84$ d.f.=1,720 $P=0.0159$
CSIRS4.DAF	21 / 27 / 28	8 / 26 / 28	10 / 26 / 28	$F=8.22$ d.f.=1,720 $P=0.00427$
CNS.DAF	18.25 / 27 / 28	5.75 / 27 / 28	7.25 / 27 / 28	$F=4.56$ d.f.=1,720 $P=0.033$
COAG.DAF	21.25 / 28 / 28	7 / 28 / 28	8.25 / 28 / 28	$F=11.6$ d.f.=1,720 $P<0.001$
INR.DAF	15 / 28 / 28	5 / 27 / 28	7 / 27 / 28	$F=3.34$ d.f.=1,720 $P=0.0679$
ACRF.DAF	10 / 28 / 28	4 / 26 / 28	5 / 27 / 28	$F=4.51$ d.f.=1,720 $P=0.0341$

ANYREN.DAF	9 / 28 / 28	2 / 23 / 28	3 / 25 / 28	F=6.25 d.f.=1,720 P=0.0127
RENSUP.DAF	15 / 28 / 28	4 / 28 / 28	5 / 28 / 28	F=9.92 d.f.=1,720 P=0.00171
ACHEP.DAF	21 / 28 / 28	6.75 / 28 / 28	8 / 28 / 28	F=10.4 d.f.=1,720 P=0.00132
ANYHEP.DAF	18.8 / 28 / 28	6 / 28 / 28	7 / 28 / 28	F=9.52 d.f.=1,720 P=0.00211

2.2.3.2 Sepsis – Caucasians

TABLE 4.25 gives the baseline characteristics (age, gender, APACHE II score, medical vs.

- 5 surgical diagnosis, shock upon admission and septic shock anytime) of 567 Caucasian sepsis subjects who were successfully genotyped at AVP rs857242. No significant differences were detected between the genotype groups on admission to the ICU.

TABLE 4.25

- 10 Baseline characteristics of a cohort of Caucasian Subjects with sepsis by genotype of Arginine Vasopressin (AVP) rs857242 (AC/AA vs. CC). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	AC / AA (N=112)	CC (N=455)	Combined (N=567)	Test Statistic
AGE	44 / 56 / 69.3	46 / 60 / 71	47 / 59 / 72	F=1.05 d.f.=1,565 P=0.306
GENDER	63% (71/112)	64% (289/455)	63% (360/567)	X ² =0 d.f.=1 P=0.98
APACHEII	16 / 21 / 27	17.5 / 23 / 28	17 / 22 / 28	F=2.8 d.f.=1,565 P=0.0945
SURGICAL	27% (30/112)	21% (96/455)	22% (126/567)	X ² =1.68 d.f.=1 P=0.195
SS.ADMIT	68% (76/112)	64% (292/455)	65% (368/567)	X ² =0.53 d.f.=1 P=0.465
SS.ANY	72% (81/112)	68% (308/455)	69% (389/567)	X ² =0.89 d.f.=1 P=0.344

- 15 **Figure 6** and **TABLE 4.26** summarize important SNP-phenotype associations for AVP rs857242. Subjects with either the AVP rs857242 AC or AA genotype had significantly increased survival (P = 0.0220), significantly more days alive (P = 0.0059) and significantly days alive and free of vasopressors at a dose of more than 15 ug/min (P = 0.0078), 3 of 4 SIRS criteria (P=0.0219), 4 of 4 SIRS criteria (P = 0.0058), coagulation dysfunction (P = 0.0012), acute renal dysfunction (P = 0.0116), any renal dysfunction (P = 0.0089), renal support (P = 0.0104), acute hepatic dysfunction (P = 0.0013) and any hepatic dysfunction (P = 0.0014). Subjects with either the AVP rs857242 AC or AA genotype also had a strong trend for more days alive and free of inotropes (P = 0.0646) INR>1.5 (P=0.0636) and neurological dysfunction (P = 0.0803). These findings indicate that Caucasian subjects with sepsis who had either the AVP rs857242 AC or AA genotype at AVP
- 20 rs857242 have less need of vasopressor and inotrope therapy, have less severe SIRS and are have a lower risk of organ dysfunction (neurological, coagulation, renal and hepatic).

TABLE 4.26

Days alive and free of organ dysfunction (DAF) by genotype of Arginine Vasopressin (AVP) rs857242 (AC/AA vs. CC) in a cohort of Caucasian subjects with sepsis. For all variables besides 28-day survival, data is given as 25th percentile / median / 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

	AC / AA (N=112)	CC (N=455)	Combined (N=567)	Test Statistic
SURVIVAL	77% (86/112)	65% (298/455)	68% (384/567)	$\chi^2=5.24$ d.f.=1 P=0.0220
DA	28 / 28 / 28	10 / 28 / 28	15 / 28 / 28	F=7.62 d.f.=1.565 P=0.00595
PRESS15.DAF	24.8 / 28 / 28	9.5 / 27 / 28	13 / 27.5 / 28	F=7.13 d.f.=1.565 P=0.00779
INO.DAF	24.8 / 28 / 28	9 / 28 / 28	12.3 / 28 / 28	F=3.43 d.f.=1.565 P=0.0646
MSIRS3.DAF	8 / 19 / 26	2 / 16 / 25	3 / 17 / 25	F=5.29 d.f.=1.565 P=0.0219
MSIRS4.DAF	19 / 27 / 28	8 / 25 / 28	11 / 25 / 28	F=7.66 d.f.=1.565 P=0.00582
CSIRS3.DAF	8 / 21 / 26	3 / 17 / 25	4 / 19 / 25	F=5.32 d.f.=1.565 P=0.0214
CSIRS4.DAF	21 / 27 / 28	8 / 25 / 28	11 / 26 / 28	F=6.87 d.f.=1.565 P=0.00902
CNS.DAF	18 / 26 / 28	7 / 26 / 28	8 / 26 / 28	F=3.07 d.f.=1.565 P=0.0803
COAG.DAF	22 / 28 / 28	8.5 / 28 / 28	10 / 28 / 28	F=10.6 d.f.=1.565 P=0.00123
INR.DAF	15.8 / 27.5 / 28	6 / 26 / 28	8 / 27 / 28	F=3.46 d.f.=1.565 P=0.0636
ACRF.DAF	11 / 28 / 28	4 / 25 / 28	6 / 26 / 28	F=6.42 d.f.=1.565 P=0.0116
ANYREN.DAF	10 / 28 / 28	3 / 22 / 28	3 / 24.5 / 28	F=6.9 d.f.=1.565 P=0.00887
RENSUP.DAF	15 / 28 / 28	5 / 28 / 28	6 / 28 / 28	F=6.61 d.f.=1.565 P=0.0104
ACHEP.DAF	21.8 / 28 / 28	7 / 28 / 28	9 / 28 / 28	F=10.4 d.f.=1.565 P=0.00131
ANYHEP.DAF	21 / 28 / 28	6 / 28 / 28	8 / 28 / 28	F=10.2 d.f.=1.565 P=0.00145

2.2.3.3 Septic Shock – Caucasians

TABLE 4.27 summarizes the baseline characteristics (age, gender, APACHE II score and medical vs. surgical diagnosis) of 368 Caucasian septic shock subjects who were successfully genotyped at AVP rs857242. No significant differences were detected between the genotype groups on admission to the ICU.

TABLE 4.27

Baseline characteristics of a cohort of Caucasian Subjects with septic shock by genotype of Arginine Vasopressin (AVP) rs857242 (AC/AA vs. CC). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	AC / AA (N=76)	CC (N=292)	Combined (N=368)	Test Statistic
AGE	44.8 / 57 / 71	48 / 63 / 72	48 / 62 / 73	F=1.28 d.f.=1.366 P=0.258
GENDER	59% (45/76)	62% (181/292)	61% (226/368)	$\chi^2=0.2$ d.f.=1 P=0.658
APACHEII	17 / 24 / 28.3	20.8 / 25 / 3	19 / 24 / 30	F=2.52 d.f.=1.366 P=0.113
SURGICAL	32% (24/76)	22% (65/292)	24% (89/368)	$\chi^2=2.86$ d.f.=1 P=0.091

Figure 7 and **TABLE 4.28** summarize important SNP-phenotype associations for AVP rs857242.

Subjects with either the AVP rs857242 AC or AA genotype had significantly increased survival (P = 0.0466), significantly more days alive (P = 0.0129) and significantly more days alive and free of vasopressors at a dose of more than 15 ug/min (P = 0.0032), 4 of 4 SIRS criteria (P = 0.0146), neurological dysfunction (P = 0.0365) coagulation dysfunction (P = 0.0027), acute renal

dysfunction ($P = 0.0103$), any renal dysfunction ($P = 0.0063$), renal support ($P = 0.0165$), acute hepatic dysfunction ($P = 0.0013$) and any hepatic dysfunction ($P < 0.001$). Subjects with either the AVP rs857242 AC or AA genotype also had a strong trend for days alive and free of vasopressors at doses of more than 2 $\mu\text{g}/\text{min}$ ($P = 0.0839$) and 5 $\mu\text{g}/\text{min}$ ($P = 0.054$), $\text{INR} > 1.5$ ($P = 0.0549$) and inotropes ($P = 0.0592$). These findings indicate that Caucasian subjects with septic shock who had either the AC or AA genotype at AVP rs857242 had less need of vasopressor, and inotrope therapy, had more severe SIRS and had a lower risk of organ dysfunction (neurological, coagulation, renal and hepatic).

TABLE 4.28

Days alive and free of organ dysfunction (DAF) by genotype of Arginine Vasopressin (AVP) rs857242 (AC/AA vs. CC) in a cohort of Caucasian subjects with septic shock. For all variables besides 28-day survival, data is given as 25th percentile / median / 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

	AC / AA (N=76)	CC (N=292)	Combined (N=368)	Test Statistic
SURVIVAL	71% (54/76)	59% (171/292)	61% (225/368)	$\chi^2=3.96$ d.f.=1 $P=0.0466$
DA	23.3 / 28 / 28	7 / 28 / 28	9 / 28 / 28	$F=6.25$ d.f.=1.366 $P=0.0129$
PRESS.DAF	13.75 / 24 / 26	4 / 22 / 26	5.75 / 23 / 26	$F=2.91$ d.f.=1.366 $P=0.089$
PRESS2.DAF	13.75 / 24 / 26	4 / 22 / 26	5.75 / 23 / 26	$F=3$ d.f.=1.366 $P=0.0839$
PRESS5.DAF	15.8 / 25 / 27	5 / 23 / 27	6 / 24 / 27	$F=3.74$ d.f.=1.366 $P=0.054$
PRESS15.DAF	21 / 27 / 28	6 / 26 / 28	8 / 26 / 28	$F=8.81$ d.f.=1.366 $P=0.0032$
INO.DAF	19.8 / 28 / 28	6 / 28 / 28	7 / 28 / 28	$F=3.58$ d.f.=1.366 $P=0.0592$
MSIRS2.DAF	0.75 / 2.50 / 17.75	0 / 2 / 15	0 / 2 / 16	$F=3.08$ d.f.=1.366 $P=0.0803$
MSIRS3.DAF	6.75 / 15.50 / 25	1 / 12 / 23	2 / 13 / 23	$F=4.42$ d.f.=1.366 $P=0.0362$
MSIRS4.DAF	14.25 / 25 / 28	5.75 / 23 / 27	7 / 23.50 / 27	$F=6.02$ d.f.=1.366 $P=0.0146$
CSIRS3.DAF	6 / 16 / 25	2 / 13.5 / 23.3	3 / 14 / 24	$F=3.79$ d.f.=1.366 $P=0.0525$
CSIRS4.DAF	15.8 / 25 / 28	6 / 24 / 27	7 / 24 / 27.3	$F=5.22$ d.f.=1.366 $P=0.0229$
CNS.DAF	14.8 / 25.5 / 28	5 / 24 / 28	6 / 25 / 28	$F=4.41$ d.f.=1.366 $P=0.0365$
COAG.DAF	15 / 28 / 28	6 / 24 / 28	6 / 25 / 28	$F=9.15$ d.f.=1.366 $P=0.00266$
INR.DAF	14.8 / 25.5 / 28	3 / 22 / 28	5 / 24 / 28	$F=3.71$ d.f.=1.366 $P=0.0549$
ACRF.DAF	10 / 27.5 / 28	3 / 20 / 28	3 / 22 / 28	$F=6.65$ d.f.=1.366 $P=0.0103$
ANYREN.DAF	9.75 / 27 / 28	2 / 18 / 28	2.75 / 19.5 / 28	$F=7.55$ d.f.=1.366 $P=0.00628$
RENSUP.DAF	13.5 / 28 / 28	3 / 24 / 28	4 / 25 / 28	$F=5.81$ d.f.=1.366 $P=0.0165$
ACHEP.DAF	17.5 / 28 / 28	5 / 25.5 / 28	6 / 28 / 28	$F=10.4$ d.f.=1.366 $P=0.00134$
ANYHEP.DAF	16 / 28 / 28	5 / 23.50 / 28	5.75 / 26.5 / 28	$F=11.7$ d.f.=1.366 $P<0.001$

Arginine Vasopressin Receptor 1a (AVPR1A)

2.3.1 AVPR1A rs1495027

2.3.1.1 Septic Shock – Caucasians

TABLE 4.29 gives the baseline characteristics (age, gender, APACHE II score, and medical vs.

surgical diagnosis) of the 361 Caucasian septic shock subjects who were successfully genotyped at AVPR1A rs1495027 (CC vs. CT/TT). No significant differences were detected between the two genotype groups on admission to the ICU.

TABLE 4.29

Baseline characteristics of a cohort of Caucasian Subjects with septic shock by genotype of arginine vasopressin receptor 1a (AVPR1A) rs1495027 (CC vs. CT/TT). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	CC (N=129)	CT / TT (N=232)	Combined (N=361)	Test Statistic
AGE	47 / 61 / 72	48.8 / 61.5 / 72.3	48 / 62 / 73	F=0.42 d.f.=1,359 P=0.516
GENDER	59% (76/129)	64% (148/232)	62% (224/361)	X ² =0.84 d.f.=1 P=0.36
APACHEII	19 / 25 / 31	20 / 25 / 29	19 / 24 / 30	F=0.01 d.f.=1,359 P=0.918
SURGICAL	22% (28/129)	25% (59/232)	24% (87/361)	X ² =0.63 d.f.=1 P=0.428

TABLE 4.30 summarizes important SNP-phenotype associations for AVPR1A rs1495027.

Subjects with either the AVPR1A rs1495027 CT or TT genotype had significantly more days alive and free of renal support (P = 0.0325). Subjects with either the AVPR1A rs1495027 CT or TT genotype also had a strong trend for more days alive and free of vasopressors at a dose of 5 ug/min (P = 0.0832) and 2 of 4 SIRS criteria (P = 0.0958). These findings indicate that Caucasian subjects with septic shock with the CT or TT genotype at AVPR1A rs1495027 have less need of vasopressors and have decreased risk of SIRS and organ dysfunction (renal).

TABLE 4.30

Days alive and free of organ dysfunction (DAF) by genotype of arginine vasopressin receptor 1a (AVPR1A) rs1495027 (CC vs. CT/TT) in a cohort of Caucasian subjects with septic shock. Data is given as 25th percentile / median / 75th percentile. N, number of subjects.

	CC (N=129)	CT / TT (N=232)	Combined (N=361)	Test Statistic
PRESS5.DAF	5 / 23 / 26	8 / 24 / 27	6 / 24 / 27	F=3.02 d.f.=1,359 P=0.0832
MSIRS2.DAF	0 / 1 / 13	0 / 2 / 16	0 / 2 / 16	F=2.99 d.f.=1,359 P=0.0845
RENSUP.DAF	3 / 18 / 28	6 / 28 / 28	4 / 25 / 28	F=4.61 d.f.=1,359 P=0.0325

2.3.2 AVPR1A rs3803107

2.3.2.1 Systematic inflammatory response syndrome - Caucasians

TABLE 4.31 gives the baseline characteristics (age, gender, APACHE II score, medical vs. surgical diagnosis, sepsis upon admission, sepsis anytime, septic shock upon admission and septic shock anytime) of the 729 Caucasian SIRS subjects who were successfully genotyped (CT/TT vs. CC) at AVPR1A rs3803107. No significant differences were detected between the two genotype groups on admission to the ICU.

TABLE 4.31

Baseline characteristics of a cohort of Caucasian Subjects with systematic inflammatory response syndrome by genotype of arginine vasopressin receptor 1a (AVPR1A) rs3803107 (CC/CT vs. TT). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	CC / CT (N=706)	TT (N=23)	Combined (N=729)	Test Statistic
AGE	44 / 58 / 71	47.5 / 61 / 69	46 / 59 / 71	F=0.01 d.f.=1,727 P=0.934
GENDER	62% (435/706)	65% (15/23)	62% (450/729)	X ² =0.12 d.f.=1 P=0.726
APACHEII	16 / 22 / 27	19 / 25 / 27.5	16 / 21.5 / 27	F=2 d.f.=1,727 P=0.157
SURGICAL	23% (159/706)	22% (5/23)	22% (164/729)	X ² =0.01 d.f.=1 P=0.93
SEP.ADMIT	78% (549/706)	87% (20/23)	78% (569/729)	X ² =1.1 d.f.=1 P=0.294
SEP.ANY	80% (562/706)	87% (20/23)	80% (582/729)	X ² =0.75 d.f.=1 P=0.387
SS.ADMIT	50% (354/706)	70% (16/23)	51% (370/729)	X ² =3.36 d.f.=1 P=0.0667
SS.ANY	54% (380/706)	70% (16/23)	54% (396/729)	X ² =2.22 d.f.=1 P=0.136

Figure 8 and **TABLE 4.32** summarize important SNP-phenotype association results for AVPR1A rs3803107. Subjects with either the AVPR1A rs3803107 CC or CT genotype had a strong trend for increased 28-day survival (P = 0.0709) and significantly more days alive (P = 0.0468) and significantly more days alive and free of vasopressors (P = 0.0270), more days alive and free of vasopressors at doses of 2 ug/min (P = 0.0286) and 5 ug/min (P = 0.0163), cardiovascular dysfunction (P = 0.0304) and respiratory dysfunction (P = 0.0476). Subjects with either the AVPR1A rs3803107 CC or CT genotype also had a strong trend for more days alive and free of inotropes (P = 0.0966), 4 of 4 SIRS criteria (P = 0.0621), mechanical ventilation (P = 0.0763) and acute hepatic dysfunction (P = 0.0871). These findings indicate that. Caucasian subjects with SIRS who had either the CC or CT genotype at AVPR1A rs3803107 have less need of vasopressors therapy and have decreased risk of SIRS and organ dysfunction (cardiovascular, respiratory, and hepatic).

TABLE 4.32

Days alive and free of organ dysfunction (DAF) by genotype of arginine vasopressin receptor 1a (AVPR1A) rs3803107 (CC/CT vs. TT) in a cohort of Caucasian subjects with systematic inflammatory response syndrome. For all variables besides 28-day survival, data is given as 25th percentile / median / 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

	CC / CT (N=706)	TT (N=23)	Combined (N=729)	Test Statistic
SURVIVAL	70% (493/706)	52% (12/706)	69% (505/706)	X ² =3.26 d.f.=1 P=0.0709
DA	15 / 28 / 28	4.5 / 28 / 28	12 / 28 / 28	F=3.97 d.f.=1,727 P=0.0468
ALL.DAF	5 / 24.5 / 28	2 / 9 / 27.5	4 / 24 / 28	F=3.41 d.f.=1,727 P=0.0651
PRESS.DAF	10.3 / 26 / 28	3 / 22 / 26	9 / 26 / 28	F=4.91 d.f.=1,727 P=0.0270
PRESS2.DAF	11 / 26 / 28	3 / 22 / 26	10 / 26 / 28	F=4.81 d.f.=1,727 P=0.0286

PRESS5.DAF	11.3 / 26 / 28	3 / 25 / 26	10 / 26 / 28	F=5.8 d.f.=1,727 P=0.0163
INO.DAF	14 / 28 / 28	4 / 23 / 28	11.3 / 28 / 28	F=2.77 d.f.=1,727 P=0.0966
MSIRS4.DAF	11 / 26 / 28	3.50 / 16 / 27.50	9.25 / 26 / 28	F=3.49 d.f.=1,727 P=0.0621
CSIRS4.DAF	11 / 26 / 28	3.5 / 16 / 28	10 / 26 / 28	F=3.46 d.f.=1,727 P=0.0632
CVS.DAF	6 / 23 / 27	2.5 / 8 / 24.5	5 / 23 / 27	F=4.7 d.f.=1,727 P=0.0304
RESP.DAF	1 / 21 / 27	1 / 6 / 20.5	1 / 20 / 26	F=3.94 d.f.=1,727 P=0.0476
PF300.DAF	0 / 1 / 11	0 / 0 / 2	0 / 1 / 10	F=3.11 d.f.=1,727 P=0.0783
VENT.DAF	0 / 19 / 26	0 / 6 / 20.5	0 / 19 / 26	F=3.15 d.f.=1,727 P=0.0763
ACHEP.DAF	8.25 / 28 / 2	4.50 / 10 / 28	8 / 28 / 28	F=2.94 d.f.=1,727 P=0.0871

2.3.2.2 Systematic inflammatory response syndrome – Asians

TABLE 4.33 summarizes the baseline characteristics (age, gender, APACHE II score, medical vs. surgical diagnosis, sepsis upon admission, sepsis anytime, septic shock upon admission and septic shock anytime) of the 108 Asian SIRS subjects who were successfully genotyped (C vs. T) at AVPR1A rs3803107. No significant differences were detected between the two allelic groups on admission to the ICU.

TABLE 4.33

Baseline characteristics of a cohort of Asian Subjects with systematic inflammatory response syndrome by allele of arginine vasopressin receptor 1a (AVPR1A) rs3803107 (C vs. T). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	C (N=186)	T (N=30)	Combined (N=216)	Test Statistic
AGE	51 / 68 / 76	58 / 71.5 / 76.8	54.5 / 69 / 76	F=0.57 d.f.=1,214 P=0.451
GENDER	61% (114/186)	47% (14/30)	59% (128/216)	X ² =2.29 d.f.=1 P=0.130
APACHEII	17 / 22.5 / 29	19 / 25.5 / 33.5	17 / 23 / 30	F=3.12 d.f.=1,214 P=0.0787
SURGICAL	24% (44/186)	13% (4/30)	22% (48/216)	X ² =1.59 d.f.=1 P=0.207
SEP.ADMIT	77% (143/186)	77% (23/30)	77% (166/216)	X ² =0 d.f.=1 P=0.98
SEP.ANY	80% (148/186)	80% (24/30)	80% (172/216)	X ² =0 d.f.=1 P=0.957
SS.ADMIT	55% (102/186)	53% (16/30)	55% (118/216)	X ² =0.02 d.f.=1 P=0.878
SS.ANY	63% (118/186)	60% (18/30)	63% (136/216)	X ² =0.13 d.f.=1 P=0.717

Figure 9 and **TABLE 4.34** summarize important SNP-phenotype association results for AVPR1A rs3803107. Subjects with the C allele had a significantly increased 28-day survival (P = 0.0377) and significantly more days alive (P = 0.0206) and significantly more days alive and free of vasopressors (P = 0.0386), more days alive and free of vasopressors at doses of 2 ug/min (P = 0.02=286), 5 (P = 0.0296) and 15 ug/min (P = 0.0132), inotropes (P = 0.0379), 4 of 4 SIRS criteria (P = 0.0494), cardiovascular dysfunction (P = 0.0365), respiratory dysfunction (P = 0.0214) mechanical ventilation (P = 0.0411), neurological dysfunction (P = 0.0488) and INR>1.5 (P=0.0296). Subjects with the AVPR1A rs3803107 C allele also had a strong trend for more days

alive and free of any hepatic dysfunction ($P = 0.0894$). These findings indicate that, Asian subjects with SIRS who had the C allele at AVPR1A rs3803107 have less need of vasopressors and are at decreased risk of SIRS and organ dysfunction (cardiovascular, respiratory, neurological and hepatic).

5

TABLE 4.34

Days alive and free of organ dysfunction (DAF) by allele of arginine vasopressin receptor 1a (AVPR1A) rs3803107 (C vs. T) in a cohort of Asian subjects with systematic inflammatory response syndrome. For all variables besides 28-day survival, data is given as 25th percentile / median / 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

10

	C (N=186)	T (N=30)	Combined (N=216)	Test Statistic
SURVIVAL	60% (112/186)	40% (12/30)	57% (124/216)	$\chi^2=4.32$ d.f.=1 $P=0.0377$
DA	7 / 28 / 28	3.25 / 10.5 / 28	6 / 28 / 28	$F=5.44$ d.f.=1,214 $P=0.0206$
PRESS.DAF	4 / 24 / 28	1 / 8 / 26	2 / 21.5 / 28	$F=4.33$ d.f.=1,214 $P=0.0386$
PRESS2.DAF	4 / 24.50 / 28	1 / 8 / 26	2.75 / 21.50 / 28	$F=4.33$ d.f.=1,214 $P=0.0386$
PRESS5.DAF	5 / 25 / 28	1 / 8 / 26.75	3.75 / 23.50 / 28	$F=4.8$ d.f.=1,214 $P=0.0296$
PRESS15.DAF	6 / 27 / 28	1 / 8 / 27	4.75 / 26 / 28	$F=6.25$ d.f.=1,214 $P=0.0132$
INO.DAF	6 / 28 / 28	2.25 / 9 / 28	4.75 / 27.50 / 28	$F=4.36$ d.f.=1,214 $P=0.0379$
MSIRS2.DAF	0 / 3.5 / 21	0 / 0 / 3	0 / 3 / 20	$F=9.25$ d.f.=1,214 $P=0.00265$
MSIRS3.DAF	1 / 17 / 27	0 / 1.5 / 21.5	1 / 14.5 / 26	$F=7.43$ d.f.=1,214 $P=0.00693$
MSIRS4.DAF	5 / 25 / 28	2 / 7 / 27.8	4 / 25 / 28	$F=3.66$ d.f.=1,214 $P=0.057$
CSIRS2.DAF	0 / 4 / 23	0 / 0 / 6	0 / 3 / 21.3	$F=9.13$ d.f.=1,214 $P=0.00282$
CSIRS3.DAF	2 / 17 / 27	0 / 2 / 19.3	1 / 16 / 26	$F=8.5$ d.f.=1,214 $P=0.00394$
CSIRS4.DAF	5 / 25 / 28	2.25 / 7.50 / 27.75	4.75 / 25 / 28	$F=3.91$ d.f.=1,214 $P=0.0494$
CVS.DAF	1 / 13.5 / 27	0 / 4 / 17	1 / 11 / 26	$F=4.43$ d.f.=1,214 $P=0.0365$
RESP.DAF	0 / 15 / 27	0 / 1.5 / 23.5	0 / 10 / 27	$F=5.37$ d.f.=1,214 $P=0.0214$
VENT.DAF	0 / 10 / 26	0 / 0.5 / 19	0 / 8.5 / 26	$F=4.22$ d.f.=1,214 $P=0.0411$
CNS.DAF	5 / 27 / 28	1 / 7 / 28	3 / 24 / 28	$F=3.93$ d.f.=1,214 $P=0.0488$
INR.DAF	5 / 27 / 28	1 / 7.5 / 28	4 / 25 / 28	$F=4.79$ d.f.=1,214 $P=0.0296$
ANYHEP.DAF	4.25 / 27 / 28	1 / 8.5 / 28	2 / 20 / 28	$F=2.91$ d.f.=1,214 $P=0.0894$

2.3.3 AVPR1A rs10877970

2.3.3.1 Systematic inflammatory response syndrome - Caucasians

15

TABLE 4.35 gives the baseline characteristics (age, gender, APACHE II score, medical vs. surgical diagnosis, sepsis upon admission, sepsis anytime, septic shock upon admission and septic shock anytime) of 725 Caucasian SIRS subjects who were successfully genotyped (CC vs.

TT/CT) at AVPR1A rs10877970. No significant differences were detected between the two genotype groups on admission to the ICU.

TABLE 4.35

- 5 Baseline characteristics of a cohort of Caucasian Subjects with systematic inflammatory response syndrome by genotype of arginine vasopressin receptor 1a (AVPR1A) rs10877970 (CC vs. TT/CT). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	CC (N=20)	TT / CT (N=705)	Combined (N=725)	Test Statistic
AGE	49.5 / 56 / 68.5	44 / 58 / 71	46 / 59 / 71	F=0.1 d.f.=1,723 P=0.75
GENDER	70% (14/20)	61% (432/705)	62% (446/725)	X ² =0.63 d.f.=1 P=0.429
APACHEII	22 / 25.5 / 27.3	16 / 22 / 27	16 / 21.5 / 27	F=3.25 d.f.=1,723 P=0.0716
SURGICAL	15% (3/20)	22% (158/705)	22% (161/725)	X ² =0.62 d.f.=1 P=0.432
SEP.ADMIT	80% (16/20)	78% (552/705)	78% (568/725)	X ² =0.03 d.f.=1 P=0.855
SEP.ANY	80% (16/20)	80% (565/705)	80% (581/725)	X ² =0 d.f.=1 P=0.987
SS.ADMIT	60% (12/20)	51% (357/705)	51% (369/725)	X ² =0.68 d.f.=1 P=0.409
SS.ANY	60% (12/20)	54% (383/705)	54% (395/725)	X ² =0.25 d.f.=1 P=0.615

- 10 **TABLE 4.36** summarizes important SNP-phenotype associations for AVPR1A rs10877970.

Subjects with either the TT or CT genotype had significantly more days alive and free of acute lung injury (P = 0.0331), respiratory dysfunction (P = 0.0134) and mechanical ventilation (P = 0.0276). Subjects with either the AVPR1A rs10877970 TT or CT genotype also had a strong

- 15 trend for more days alive and free of vasopressors (P = 0.0183), and more days alive and free of vasopressors at doses of 2 ug/min (P = 0.0638) and 5 ug/min (0.0575). These findings indicate that Caucasian subjects with SIRS with the TT or CT genotype at AVPR1A rs10877970 have less need of vasopressors, are at decreased risk of acute lung injury and organ dysfunction (respiratory).

- 20 **TABLE 4.36**

Days alive and free of organ dysfunction (DAF) by genotype of arginine vasopressin receptor 1a (AVPR1A) rs10877970 (CC vs. TT/CT) in a cohort of Caucasian subjects with systematic inflammatory response syndrome. Data is given as 25th percentile / median / 75th percentile. N, number of subjects.

	CC (N=20)	TT / CT (N=705)	Combined (N=725)	Test Statistic
ALL.DAF	2 / 9 / 24	5 / 24 / 28	4 / 24 / 28	F=4.56 d.f.=1,723 P=0.0331
PRESS.DAF	6 / 21 / 25.3	10 / 26 / 28	9 / 26 / 28	F=3.45 d.f.=1,723 P=0.0638
PRESS2.DAF	6 / 21 / 26	10 / 26 / 28	10 / 26 / 28	F=3.31 d.f.=1,723 P=0.0692
PRESS5.DAF	6.5 / 23 / 26	11 / 26 / 28	10 / 26 / 28	F=3.62 d.f.=1,723 P=0.0575
CVS.DAF	3.25 / 14 / 24.25	5 / 23 / 27	5 / 23 / 27	F=2.68 d.f.=1,723 P=0.102

RESP.DAF	0 / 5.5 / 20	1 / 21 / 27	1 / 20 / 26	F=6.15 d.f.=1,723 P=0.0134
PF300.DAF	0 / 0 / 2.75	0 / 1 / 11	0 / 1 / 10	F=3.4 d.f.=1,723 P=0.0656
VENT.DAF	0 / 5.5 / 20	0 / 19 / 26	0 / 19 / 26	F=4.87 d.f.=1,723 P=0.0276
AFFD.DAF	0 / 0 / 0	0 / 0 / 4	0 / 0 / 3	F=3.12 d.f.=1,723 P=0.0779

2.3.3.2 Systematic inflammatory response syndrome - Asians

TABLE 4.37 gives the baseline characteristics (age, gender, APACHE II score, medical vs.

surgical diagnosis, sepsis upon admission, sepsis anytime, septic shock upon admission and septic shock anytime) of the 108 Asian systematic inflammatory response syndrome subjects who were successfully genotyped (C vs. T) at AVPR1A rs10877970. No significant differences, other than a small difference in APACHE II score, were detected between the two allelic groups on admission to the ICU.

TABLE 4.37

Baseline characteristics of a cohort of Asian Subjects with systematic inflammatory response syndrome by allele of arginine vasopressin receptor 1a (AVPR1A) rs10877970 (C vs. T). For age and APACHE II score, data is given as 25th percentile / median / 75th percentile. For all other variables, data is given as % (N survived / N total). N, number of subjects.

	C (N=33)	T (N=183)	Combined (N=216)	Test Statistic
AGE	57 / 73 / 77.0	51 / 68 / 77	54.5 / 69 / 76	F=0.52 d.f.=1,214 P=0.471
GENDER	48% (16/33)	60% (110/183)	58% (126/216)	X ² =1.55 d.f.=1 P=0.212
APACHEII	19 / 26 / 34	17 / 23 / 29	17 / 23 / 30	F=4 d.f.=1,214 P=0.0467
SURGICAL	18% (6/33)	24% (44/183)	23% (50/216)	X ² =0.54 d.f.=1 P=0.462
SEP.ADMIT	76% (25/33)	76% (139/183)	76% (164/216)	X ² =0 d.f.=1 P=0.98
SEP.ANY	79% (26/33)	79% (144/183)	79% (170/216)	X ² =0 d.f.=1 P=0.99
SS.ADMIT	52% (17/33)	54% (99/183)	54% (116/216)	X ² =0.08 d.f.=1 P=0.784
SS.ANY	58% (19/33)	63% (115/183)	62% (134/216)	X ² =0.33 d.f.=1 P=0.566

Figure 10 and **TABLE 4.38** summarizes important SNP-phenotype association results for AVPR1A rs10877970. Subjects with the AVPR1A rs10877970 T allele had a strong trend for increased 28-day survival (P = 0.0586) and significantly more days alive (P = 0.0349) and significantly more days alive and free of vasopressors at doses of 5 ug/min (P = 0.0417) and 15 ug/min (P = 0.0175), inotropes (P = 0.0423) and respiratory dysfunction (P = 0.0427). Subjects with the AVPR1A rs10877970 T allele also showed a strong trend for more days alive and free of 4 of 4 SIRS criteria (P = 0.0655) cardiovascular dysfunction (P = 0.079), ventilation (P = 0.057), neurological dysfunction (P = 0.064) and any hepatic dysfunction (P = 0.0827). These findings indicate that Asian subjects with SIRS who had the T allele at AVPR1A rs10877970 have less

need of vasopressors and are at a decreased risk of severe SIRS and organ dysfunction (cardiovascular, respiratory, neurological and hepatic).

TABLE 4.38

- 5 Days alive and free of organ dysfunction (DAF) by allele of arginine vasopressin receptor 1a (AVPR1A) rs10877970 (C vs. T) in a cohort of Asian subjects with systematic inflammatory response syndrome. For all variables besides 28-day survival, data is given as 25th percentile / median / 75th percentile. For 28-day survival, data is given as % (N survived / N total). N, number of subjects.

	C (N=33)	T (N=183)	Combined (N=216)	Test Statistic
SURVIVAL	42% (14/33)	60% (110/183)	57% (124/216)	X ² =3.58 d.f.=1 P=0.0586
DA	4 / 12 / 28	7 / 28 / 28	6 / 28 / 28	F=4.51 d.f.=1,214 P=0.0349
PRESS.DAF	1 / 9 / 26	4 / 23 / 28	2 / 21.5 / 28	F=3.72 d.f.=1,214 P=0.0551
PRESS2.DAF	1 / 9 / 26	4 / 24 / 28	2.75 / 21.5 / 28	F=3.72 d.f.=1,214 P=0.0551
PRESS5.DAF	1 / 9 / 27	5 / 25 / 28	3.75 / 23.5 / 28	F=4.2 d.f.=1,214 P=0.0417
PRESS15.DAF	1 / 9 / 27	6 / 27 / 28	4.75 / 26 / 28	F=5.73 d.f.=1,214 P=0.0175
INO.DAF	3 / 9 / 28	6 / 28 / 28	4.75 / 27.5 / 28	F=4.17 d.f.=1,214 P=0.0423
MSIRS2.DAF	0 / 0 / 7	0 / 3 / 21.5	0 / 3 / 20	F=8.5 d.f.=1,214 P=0.00393
MSIRS3.DAF	0 / 2 / 22	1 / 16 / 27	1 / 14.5 / 26	F=6.29 d.f.=1,214 P=0.0129
MSIRS4.DAF	2 / 7 / 28	5 / 25 / 28	4 / 25 / 28	F=3.19 d.f.=1,214 P=0.0757
CSIRS2.DAF	0 / 0 / 8	0 / 5 / 23	0 / 3 / 21.3	F=7.82 d.f.=1,214 P=0.00565
CSIRS3.DAF	0 / 3 / 20	2 / 18 / 27	1 / 16 / 26	F=7.12 d.f.=1,214 P=0.00819
CSIRS4.DAF	3 / 8 / 28	5 / 25 / 28	4.75 / 25 / 28	F=3.43 d.f.=1,214 P=0.0655
CVS.DAF	0 / 5 / 21	1 / 13 / 27	1 / 11 / 26	F=3.11 d.f.=1,214 P=0.079
RESP.DAF	0 / 5 / 24	0 / 14 / 27	0 / 10 / 27	F=4.16 d.f.=1,214 P=0.0427
VENT.DAF	0 / 1 / 19	0 / 10 / 26	0 / 8.5 / 26	F=3.66 d.f.=1,214 P=0.057
CNS.DAF	1 / 9 / 28	5 / 27 / 28	3 / 24 / 28	F=3.47 d.f.=1,214 P=0.064
INR.DAF	1 / 9 / 28	5 / 27 / 28	4 / 25 / 28	F=3.67 d.f.=1,214 P=0.0568
ANYHEP.DAF	1 / 9 / 28	4.5 / 28 / 28	2 / 20 / 28	F=3.04 d.f.=1,214 P=0.0827

10

EXAMPLE 3: INCREASED USE OF VASOPRESSIN**Methods****Cohort Selection**

To investigate whether genotype predicts increased use of vasopressin, a subset of Caucasian
 15 subjects with septic shock was selected for this analysis (N=543).

Data Analysis

All data analysis was carried out using statistical packages available in R (R Core Development
 Group, 2005 - R Development Core Team (www.R-project.org). R: A language and environment
 20 for statistical computing. Vienna, Austria. 2005). Chi-square tests were used to identify significant

associations between SNP and increased use of vasopressin as well as to identify baseline characteristics (age, gender, admitting APACHE II score, and medical vs. surgical admitting diagnosis) requiring post-hoc, multivariate adjustment.

5 Results

3.1 Leucyl/Cystinyl Aminopeptidase (LNPEP)

3.1.1 Association of CC genotype of LNPEP rs18059 with Use of Vasopressin

It was unknown whether SNPs within the LNPEP gene and those regions immediately upstream and downstream are associated with the use of vasopressin. It was found that LNPEP rs18059 is associated with the use of vasopressin by comparing LNPEP rs18059 genotypes for vasopressin-treated subjects (N=73) with control subjects who did not receive vasopressin at any time during their ICU stay (N=366). Baseline characteristics for septic shock subjects with LNPEP rs18059 genotypes are shown in Table 5.1. No significant differences between the genotype groups were detected on admission to the ICU.

TABLE 5.1

Baseline characteristics of Caucasian ICU septic-shock subjects by leucyl/cystinyl aminopeptidase (LNPEP) rs18059 genotype. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

	CC (N=108)	CT (N=231)	TT (N=100)	Combined (N=439)	Test Statistic
AGE	46 59 71	48 63 72	48.75 62.5 72	48 61 72	F=1.1 d.f.=2,436 P=0.334
GENDER	65% (70/108)	64% (148/231)	62% (62/100)	64% (280/439)	X ² =0.2 d.f.=2 P=0.907
APACHE II	19 25 32	20.5 26 31	21 25 30	20 26 31	F=0.39 d.f.=2, 436 P=0.679
SURGICAL	28% (30/108)	29% (66/231)	25% (25/100)	28% (121/439)	X ² =0.45 d.f.=2 P=0.799

Table 5.2 shows the distribution of vasopressin administration by LNPEP rs18059 genotype.

Subjects with the LNPEP rs18059 CC genotype were observed to have been administered vasopressin more frequently than controls compared with subjects who were LNPEP rs18059 CT or TT (P = 0.0257)

TABLE 5.2

Measure of vasopressin treatment of Caucasian ICU septic shock subjects by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs18059.

	No Vasopressin (N=366)	Vasopressin- treated (N=73)	Combined (N=439)	Test Statistic
CC	22% (81/366)	37% (27/73)	25% (108/439)	X ² =7.32 d.f.=2 P=0.0257

CT	54% (198/366)	45% (33/73)	53% (231/439)	
TT	24% (87/366)	18% (13/73)	23% (100/439)	

3.1.2 Association of AA genotype of LNPEP rs27711 with Use of Vasopressin

It was unknown whether SNPs within the LNPEP gene and those regions immediately upstream and downstream are associated with the use of vasopressin. It was found that LNPEP rs27711 is associated with the use of vasopressin by comparing the frequency of LNPEP rs27711 genotypes for vasopressin-treated subjects (N=70) and control subjects who did not receive vasopressin at any time during their ICU stay (N=368). Baseline characteristics for septic shock subjects with LNPEP rs27711 genotypes are shown in Table 5.3. No significant differences between the genotype groups were detected on admission to the ICU.

TABLE 5.3

Baseline characteristics of Caucasian ICU septic shock subjects by leucyl/cystinyl aminopeptidase (LNPEP) rs27711 genotype. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N /N total). N, number of subjects.

	AA (N=72)	AG (N=223)	GG (N=143)	Combined (N=438)	Test Statistic
AGE	44.5 58.5 71	48 63 72	49 63 72	48 61 72	F=0.78 d.f.=2,435 P=0.46
GENDER	65% (47/72)	64% (142/223)	63% (90/143)	64% (279/438)	X ² =0.11 d.f.=2 P=0.945
APACHE II	19 25.5 33	20.5 26 30	21 26 30	20 26 31	F=0.16 d.f.=2,435 P=0.854
SURGICAL	28% (20/72)	29% (64/223)	22% (32/143)	26% (116/438)	X ² =1.86 d.f.=2 P=0.394

Table 5.4 shows the distribution of vasopressin administration by LNPEP rs27711 genotype.

Subjects with the LNPEP rs27711 AA genotype were more frequently observed to be administered vasopressin compared to subjects with LNPEP rs27711 AG or GG genotypes (P = 0.0033).

TABLE 5.4

Measure of vasopressin treatment of Caucasian ICU septic shock subjects by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs27711.

	No Vasopressin (N=368)	Vasopressin- treated (N=70)	Combined (N=438)	Test Statistic
AA	14% (51/368)	30% (21/70)	16% (72/438)	X ² =11.45 d.f.=2 P=0.0033
AG	53% (195/368)	40% (28/70)	51% (223/438)	
GG	33% (122/368)	30% (21/70)	33% (143/438)	

3.1.3 Association of GG genotype of LNPEP rs10051637 with Use of Vasopressin

It was unknown whether SNPs within the LNPEP gene and those regions immediately upstream and downstream are associated with the use of vasopressin. It was found that LNPEP rs10051637 is associated with the use of vasopressin by comparing the frequency of LNPEP rs10051637 genotypes for vasopressin-treated subjects (N=72) with control subjects (N=361) who did not receive vasopressin at any time during their ICU stay. Baseline characteristics for septic shock subjects with LNPEP rs10051637 genotypes are shown in Table 5.5. No significant differences between the genotype groups were detected on admission to the ICU.

TABLE 5.5

Baseline characteristics of Caucasian ICU septic shock subjects by leucyl/cystinyl aminopeptidase (LNPEP) rs10051637 genotype. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

	AA (N=133)	AG (N=223)	GG (N=77)	Combined (N=433)	Test Statistic
AGE	49 63 72	48 63 72	43 58 71	48 61 72	F=2.05 d.f.=2,430 P=0.130
GENDER	62% (82/133)	66% (147/223)	66% (51/77)	65% (280/433)	X ² =0.76 d.f.=2 P=0.682
APACHE II	21 26 31	21 26 30	19 25 33	20 26 31	F=0.04 d.f.=2,430 P=0.96
SURGICAL	23% (30/133)	29% (64/223)	29% (22/77)	27% (116/433)	X ² =1.75 d.f.=2 P=0.416

Table 5.4 shows the distribution of vasopressin administration by LNPEP rs10051637 genotype. Subjects with the GG genotype of LNPEP rs10051637 were more frequently observed to be administered vasopressin ($P < 0.001$) compared to subjects who carried the AG or AA genotype of LNPEP rs10051637 (TABLE 5.6).

TABLE 5.6

Measure of vasopressin treatment of Caucasian ICU septic shock subjects by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs10051637.

	No Vasopressin (N=361)	Vasopressin- treated (N=72)	Combined (N=433)	Test Statistic
AA	32% (114)	26% (19)	31% (133)	X ² =14.38 d.f.=2 P<0.001
AG	54% (194)	40% (29)	52% (223)	
GG	15% (53)	33% (24)	18% (77)	

3.2 Arginine Vasopressin Receptor 1a (AVPR1A)

3.2.1 Association of CT genotype of AVPR1A rs1495027 with Use of Vasopressin

It was unknown whether SNPs within the AVPR1A gene and those regions immediately upstream and downstream are associated with the use of vasopressin in subjects with septic shock. It was

found that AVPR1A rs1495027 is associated with the use of vasopressin by comparing the frequency of AVPR1A rs1495027 genotypes for vasopressin-treated subjects (N=72) with control subjects (N=361) who did not receive vasopressin at any time during their ICU stay.

- 5 Baseline characteristics for septic shock subjects with AVPR1A rs1495027 genotypes are shown in Table 5.7. No significant differences between the genotype groups were detected on admission to the ICU.

TABLE 5.7

- 10 Baseline characteristics of Caucasian ICU septic shock subjects by genotype of arginine vasopressin receptor 1a (AVPR1A) rs1495027. For age and APACHE II score, data is given as 25th percentile | median | 75th percentile. For all other variables, data is given as % (N/N total). N, number of subjects.

	CC (N=143)	CT (N=218)	TT (N=72)	Combined (N=433)	Test Statistic
AGE	48 61 72	46 60 71.75	51 63.50 73	48 61 72	F=0.84 d.f.=2,430 P=0.433
GENDER	61% (87/143)	69% (150/218)	58% (42/72)	64% (279/433)	X ² =3.8 d.f.=2 P=0.15
APACHE II	19.5 26 31	20 25 31	21.75 26 30.75	20 26 31	F=0.62 d.f.=2,430 P=0.536
SURGICAL	24% (35/143)	28% (62/218)	26% (19/72)	27% (116/433)	X ² =0.7 d.f.=2 P=0.705

- 15 Table 5.4 shows the distribution of vasopressin administration by AVPR1A rs1495027 genotype. Subjects with the AVPR1A rs1495027 CT genotype had significantly increased use of vasopressin (P = 0.0240) compared to subjects who carried either the CC or TT genotype of AVPR1A T AVPR1A rs1495027 (**TABLE 5.8**).

TABLE 5.8

20 Measure of vasopressin treatment of Caucasian ICU septic shock subjects by genotype of vasopressin receptor 1a (AVPR1A) rs1495027.

	No Vasopressin (N=361)	Vasopressin- treated (N=72)	Combined (N=433)	Test Statistic
CC	36% (129)	19% (14)	33% (143)	X ² =7.46 d.f.=2 P=0.0240
CT	48% (173)	62% (45)	50% (218)	
TT	16% (59)	18% (13)	17% (72)	

EXAMPLE 4: BIOLOGICAL PLAUSIBILITY

- 25 Examples 1-3 show that polymorphisms of the AVP, AVPR1A and LNPEP genes are associated with altered outcome in critically ill subjects. To further explore the relationship between inflammation and infection, the present example examines subjects with non-septic causes of systemic inflammatory response syndrome by analyzing SNP-phenotype interactions in subjects having undergone cardiopulmonary bypass surgery. If an AVP, AVPR1A, LNPEP or LRAP gene

polymorphism was associated with altered survival and organ dysfunction, that polymorphism is also likely to be associated with changes in pro-inflammatory proteins such as serum granulocyte colony stimulating factor (GCSF), interleukin 8 (IL-8) and monocyte chemotactic protein 1 (MCP1).

5 METHODS

Cohort Selection

The Biological Plausibility cohort was used for this study.

Measurement of Chemokine and Cytokines

- 10 After induction of anesthesia and placement of systemic and pulmonary artery catheters that were routinely inserted for clinical purposes at SPH, blood was obtained at baseline and at 3 hours post-operatively for serum. GCSF, MCP1 and IL-8 measurements were made using ELISA.

Data Analysis

- 15 The primary outcome variables for the Biological Plausibility cohort were change in GCSF, MCP1 and IL-8 concentrations from baseline to three hours after surgery. All data analysis was carried out using statistical packages available in R (R Core Development Group, 2005 - R Development Core Team (www.R-project.org), Vienna Austria 2005). Chi-squared and Kruskal-Wallis test statistics were used to identify significant SNP-phenotype and associations, as well as to look at
20 baseline characteristics.

Results

4.1 Leucyl/Cystinyl Aminopeptidase (LNPEP)

4.1.1 LNPEP rs18059

- 25 **TABLE 6.1** summarizes the baseline characteristics of 69 non-septic SIRS subjects who were successfully genotyped (LNPEP rs18059 CC (N=20) vs CT (N=36) vs TT (N=13)) at LNPEP rs18059. No significant differences were detected between the three genotype groups on admission to the CSICU.

30

TABLE 6.1

Baseline characteristics of a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs18059 (CC vs. CT vs TT).

	CC (N=20)	CT (N=36)	TT (N=13)	Combined (N=69)	Test Statistic
AGE	59.25 64.50 73.25	61.00 65.00 70.25	60.00 66.00 72.00	58.25 65.50 70.75	F=0.15 d.f.=2.66 P=0.865
GENDER	70% (14)	61% (22)	77% (10)	67% (46)	X ² =1.22 d.f.=2

					P=0.545
SMOKER	25% (5)	19% (7)	38% (5)	25% (17)	X ² =1.86 d.f.=2 P=0.394
DIABETES	15% (3)	22% (8)	23% (3)	20% (14)	X ² =0.49 d.f.=2 P=0.782
H.TENSE	60% (12)	56% (20)	46% (6)	55% (38)	X ² =0.62 d.f.=2 P=0.734
EJEC.FRAC	0.37 0.50 0.60	0.50 0.50 0.60	0.46 0.58 0.60	0.50 0.50 0.60	F=0.56 d.f.=2.64 P=0.575
BYPASS	1.48 1.65 2.02	1.13 1.57 2.00	1.33 1.73 2.45	1.31 1.65 2.05	F=0.56 d.f.=2.66 P=0.575
CLAMP	1.04 1.32 1.57	0.83 1.19 1.69	0.93 1.43 1.78	0.92 1.29 1.70	F=0.2 d.f.=2.66 P=0.822
APROTININ	5% (1)	8% (3)	8% (1)	7% (5)	X ² =0.22 d.f.=2 P=0.897

TABLE 6.2 summarizes important SNP-biomarker associations. Subjects with the CC genotype had significantly smaller increase in serum GCSF levels ($P = 0.0135$) post-cardiopulmonary bypass surgery. These findings suggest that non-septic SIRS Subjects with the CC genotype at LNPEP rs18059 are more likely to experience a less intense chemokine (GCSF) response after cardiopulmonary bypass surgery.

TABLE 6.2

Biological plausibility of leucyl/cystinyl aminopeptidase association using biomarkers in a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs18059. Biomarkers are measured in pg/ml.

	CC (N=20)	CT (N=36)	TT (N=13)	Combined (N=69)	Test Statistic
GCSF.3	123/183/276	219/292/497	236/287/344	179/260/368	F=5.26 d.f.=2.66 P=0.00758
GCSF.DI	108/164/266	199/287/492	210/264/330	161/249/365	F=4.6 d.f.=2.66 P=0.0135
MCPI.0	125.2/186.6/211.3	165.0/195.3/281.2	95.7/138.1/226.7	134.9/182.0/245.2	F=2.54 d.f.=2.66 P=0.0862

4.1.2 LNPEP rs27711

TABLE 6.3 summarizes the baseline characteristics of 69 non-septic SIRS subjects who were successfully genotyped (AA (N=14) vs. AG/GG (N=55)) at LNPEP rs27711. No significant differences between the genotype groups were detected on admission to the CSICU.

TABLE 6.3

Baseline characteristics of a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs27711 (AA vs. GG/AG).

	AA (N=14)	GG/AG (N=55)	Combined (N=69)	Test Statistic
AGE		60.50/65.00/71.50	58.25/65.50/70.75	F=0.52 d.f.=1.67

	60.25/63.00/69.25			P=0.473
GENDER	64% (9)	69% (38)	68% (47)	X ² =0.12 d.f.=1 P=0.73
SMOKER	29% (4)	24% (13)	25% (17)	X ² =0.15 d.f.=1 P=0.702
DIABETES	14% (2)	20% (11)	19% (13)	X ² =0.24 d.f.=1 P=0.625
H.TENSE	64% (9)	55% (30)	57% (39)	X ² =0.43 d.f.=1 P=0.512
EJEC.FRAC	0.35/0.50/0.60	0.50/0.50/0.60	0.50/0.50/0.60	F=0.37 d.f.=1.65 P=0.544
BYPASS	1.51225/1.63350/ 2.06225	1.25850/1.65000/2.0 8300	1.31700/1.65000/2.0 5000	F=0.44 d.f.=1.67 P=0.511
CLAMP	1.07900/1.33300/ 1.61225	0.85850/1.21700/1.6 7500	0.92475/1.29150/1.7 0000	F=0.44 d.f.=1.67 P=0.511
APROTEININ	7% (1)	7% (4)	7% (5)	X ² =0 d.f.=1 P=0.987

TABLE 6.4 summarizes important SNP-biomarker associations observed for LNPEP rs27711.

Subjects with the LNPEP rs27711 AA genotype showed a smaller change in GCSF levels from baseline to 3 hours post-surgery ($P < 0.001$) and had lower preoperative interleukin 8 (IL8) levels ($P = 0.05$) than subjects with LNPEP rs27711 AG or GG genotypes. These findings suggest that non-septic SIRS Subjects with the AA genotype at LNPEP rs27711 are more likely to experience a less intense chemokine (GCSF) response after cardiopulmonary bypass and are more likely to have higher baseline levels of IL-8.

TABLE 6.4

Biological plausibility of leucyl/cystinyl aminopeptidase association using biomarkers in a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of leucyl/cystinyl aminopeptidase rs27711 (AA vs. GG/AG).

	AA (N=14)	GG/AG (N=55)	Combined (N=69)	Test Statistic
GCSF.3	115/145/209	221/287/442	179/260/368	F=15.4 d.f.=1.67 $P < 0.001$
GCSF.DIF	103/138/181	205/274/431	161/249/365	F=14.3 d.f.=1.67 $P < 0.001$
IL8.0	0.0/0.0/12.8	0.0/13.4/21.1	0.0/7.2/20.2	F=3.89 d.f.=1.67 $P = 0.0528$

4.1.3 LNPEP rs10051637

TABLE 6.5 summarizes the baseline characteristics of 70 non-septic SIRS subjects who were successfully genotyped (AA/AG vs. GG) at LNPEP rs10051637. No significant differences between the genotype groups were detected on admission to the CSICU.

TABLE 6.5

Baseline characteristics of a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs10051637 (GG vs. AA/AG)

	AA/AG	GG	Combined	Test
	(N=56)	(N=14)	(N=70)	Statistic

AGE	60.75/66.00/72.00	60.25/63.00/69.25	58.25/65.50/70.75	F=0.65 d.f.=1.68 P=0.423
GENDER	68% (38)	64% (9)	67% (47)	X ² =0.06 d.f.=1 P=0.799
SMOKER	23% (13)	29% (4)	24% (17)	X ² =0.17 d.f.=1 P=0.676
DIABETES	21% (12)	14% (2)	20% (14)	X ² =0.36 d.f.=1 P=0.55
H.TENSE	54% (30)	64% (9)	56% (39)	X ² =0.52 d.f.=1 P=0.47
EJEC.FRAC	0.50/0.50/0.60	0.35/0.50/0.60	0.50/0.50/0.60	F=0.41 d.f.=1.66 P=0.525
BYPASS	1.26275/1.65000/2.05800	1.51225/1.63350/2.06225	1.31700/1.65000/2.05000	F=0.4 d.f.=1.68 P=0.527
CLAMP	0.86275/1.20850/1.67100	1.07900/1.33300/1.61225	0.92475/1.29150/1.70000	F=0.48 d.f.=1.68 P=0.489
APROTININ	7% (4)	7% (1)	7% (5)	X ² =0 d.f.=1 P=1

TABLE 6.6 summarizes important SNP-biomarker associations. Subjects with the LNPEP rs10051637 GG genotype showed a smaller change in serum GCSF levels from baseline to 3 hours post-surgery than subjects with the LNPEP rs10051637 AG or AA genotypes ($P < 0.001$).

- 5 Furthermore, LNPEP rs10051637 AA subjects were observed to have lower baseline interleukin-8 (IL8) levels ($P = 0.0443$) 3 hours post- surgery. These findings suggest that non-septic SIRS subjects with the LNPEP rs10051637 GG genotype have a decreased chemokine (GCSF) and proinflammatory (IL-8) response after cardiopulmonary bypass.

10 **TABLE 6.6**

Biological plausibility of leucyl/cystinyl aminopeptidase association using biomarkers in a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs10051637 (GG vs. AA/AG). Biomarkers are measured in pg/ml.

	AA/AG (N=56)	GG (N=14)	Combined (N=70)	Test Statistic
GCSF.3	221/288/441	115/145/209	179/260/368	F=15.7 d.f.=1.68 P<0.001
GCSF.DI F	207/279/424	103/138/181	161/249/365	F=14.6 d.f.=1.68 P<0.001
IL8.0	0.0/13.6/22.2	0.0/0.0/13.8	0.0/7.2/20.2	F=4.2 d.f.=1.68 P=0.0443

15

4.1.4 LNPEP rs38041

TABLE 6.7 summarizes the baseline characteristics of 70 non-septic SIRS subjects who were successfully genotyped (GG/AG vs. AA) at LNPEP rs38041. No significant differences between the two genotype groups were detected on admission to the CSICU.

20

TABLE 6.7

Baseline characteristics of a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of leucyl/cystinyl aminopeptidase (LNPEP) rs38041 (AA vs. GG/AG)

	AA	AG/GG	Combined	Test
	(N=18)	(N=52)	(N=70)	Statistic
AGE	60.25/63.00/69.25	60.75/66.00/72.25	58.25/65.50/70.75	F=1.46 d.f.=1,68 P=0.231
GENDER	67% (12)	67% (35)	67% (47)	X ² =0 d.f.=1 P=0.96
SMOKER	22% (4)	25% (13)	24% (17)	X ² =0.06 d.f.=1 P=0.813
DIABETES	17% (3)	21% (11)	20% (14)	X ² =0.17 d.f.=1 P=0.682
H.TENSE	61% (11)	54% (28)	56% (39)	X ² =0.29 d.f.=1 P=0.593
EJEC.FRAC	0.50/0.55/0.60	0.48/0.50/0.60	0.50/0.50/0.60	F=0.02 d.f.=1,66 P=0.881
BYPASS	1.42075/1.63350/ 2.00000	1.30450/1.65000/2. 17900	1.31700/1.65000/2. 05000	F=0.12 d.f.=1,68 P=0.73
CLAMP	0.93325/1.33300/ 1.69600	0.87475/1.20850/1. 65425	0.92475/1.29150/1. 70000	F=0.26 d.f.=1,68 P=0.608
APROTININ	6% (1)	8% (4)	7% (5)	X ² =0.09 d.f.=1 P=0.762

- 5 **TABLE 6.8** summarizes important SNP-biomarker associations. Subjects with the AA genotype had a significantly smaller change in serum GCSF levels from baseline to three hours post-cardiopulmonary bypass (P = 0.00226) and significantly lower baseline serum interleukin-8 (IL8) levels (P = 0.0417) compared to subjects with LNPEP rs38041 AG or GG. These findings suggest that non-septic SIRS subjects with LNPEP rs38041 AA have a decreased chemokine (GCSF) response after cardiopulmonary bypass and lower baseline serum IL-8 levels..
- 10

TABLE 6.8

Biological plausibility of leucyl/cystinyl aminopeptidase association using biomarkers in a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of leucyl/cystinyl aminopeptidase rs38041 (AA vs. GG/AG). Biomarkers are measured in pg/ml.

15

	AA (N=18)	GG/AG (N=52)	Combined (N=70)	Test Statistic
GCSF.3	115/164/266	221/288/423	179/260/368	F=10.7 d.f.=1,68 P=0.00168
GCSF.DIF	103/154/244	211/279/415	161/249/365	F=10.1 d.f.=1,68 P=0.00226
IL8.0	0.0/0.0/16.0	0.0/13.6/22.2	0.0/7.2/20.2	F=4.31 d.f.=1,68 P=0.0417

4.2 Arginine Vasopressin (AVP)

4.2.1. AVP rs857242

- 20 **TABLE 6.9** summarizes the baseline characteristics of 57 non-septic SIRS subjects who were genotyped at AVP rs857242. No significant differences between the genotype groups were detected on admission to the CSICU.

TABLE 6.9

Baseline characteristics of a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of Arginine Vasopressin (AVP) rs857242.

	AC (N=11)	CC (N=57)	Combined (N=68)	Test Statistic
AGE	60.50/65.00/71.00	60.00/65.00/72.00	58.25/65.50/70.75	F=0.04 d.f.=1.66 P=0.837
GENDER	64% (7)	67% (38)	66% (45)	Chisquare=0.04 d.f.=1 P=0.846
SMOKER	27% (3)	23% (13)	24% (16)	Chisquare=0.1 d.f.=1 P=0.749
DIABETES	9% (1)	23% (13)	21% (14)	Chisquare=1.06 d.f.=1 P=0.303
H.TENSE	64% (7)	56% (32)	57% (39)	Chisquare=0.21 d.f.=1 P=0.645
EJEC.FRAC	0.45/0.50/0.60	0.50/0.50/0.60	0.50/0.50/0.60	F=0.02 d.f.=1.64 P=0.897
BYPASS	1.0415/1.3330/1.96 65	1.3670/1.6500/2.0830	1.3170/1.6500/2.05 00	F=1.25 d.f.=1.66 P=0.268
CLAMP	0.78350/1.03300/1. 65850	0.93300/1.25000/1.63 300	0.92475/1.29150/1. 70000	F=0.41 d.f.=1.66 P=0.525
APROTININ	9% (1)	7% (4)	7% (5)	Chisquare=0.06 d.f.=1 P=0.81

TABLE 6.10 summarizes important SNP-biomarker associations for AVP rs857242. Subjects with the AVP rs857242 CC genotype showed a strong trend towards a smaller change in GCSF levels at three hours post-cardiopulmonary bypass than subjects with the AVP rs857242 AC genotype (p=0.0978). These findings suggest that non-septic SIRS subjects with the AVP position rs857242 CC genotype have a decreased chemokine (GCSF) response after cardiopulmonary bypass surgery.

TABLE 6.10

Biological plausibility of Factor V association using biomarkers in a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of Arginine Vasopressin (AVP) rs857242 . Biomarkers are measured in pg/ml.

	AC (N=11)	CC (N=57)	Combined (N=68)	Test Statistic
GCSF.3	257 319 540	180 255 368	179 260 368	F=3.38 d.f.=1.66 P=0.0704
GCSF.DIF	257 314 519	169 240 368	161 249 365	F=2.82 d.f.=1.66 P=0.0978

4.3 Arginine Vasopressin Receptor 1a (AVPR1A)

4.3.1 AVPR1A rs1495027

TABLE 6.11 summarizes the baseline characteristics of 69 non-septic SIRS subjects who were successfully genotyped (CT/TT vs. CC) at AVPR1A rs1495027. Subjects with the CC genotype had shorter clamp time (P = 0.03) than subjects with the CT/TT genotypes. There were no other significant differences prior to cardiopulmonary bypass surgery.

TABLE 6.11

Baseline characteristics of a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of arginine vasopressin receptor 1a (AVPR1A) rs1495027 (CC vs. CT/TT).

	CC	CT/TT	Combined	Test
	(N=26)	(N=43)	(N=69)	Statistic
AGE	58.50/64.50/68.50	61.00/66.00/73.00	58.25/65.50/70.75	F=1.41 d.f.=1.67 P=0.239
GENDER	69% (18)	67% (29)	68% (47)	X ² =0.02 d.f.=1 P=0.877
SMOKER	19% (5)	28% (12)	25% (17)	X ² =0.66 d.f.=1 P=0.418
DIABETES	31% (8)	14% (6)	20% (14)	X ² =2.83 d.f.=1 P=0.0924
H.TENSE	46% (12)	63% (27)	57% (39)	X ² =1.82 d.f.=1 P=0.177
EJEC.FRAC	0.45/0.50/0.60	0.50/0.50/0.60	0.50/0.50/0.60	F=0.35 d.f.=1.65 P=0.557
BYPASS	1.0955/1.4415/2.033 0	1.4415/1.7330/2.0580	1.3170/1.6500/2.0500	F=3.29 d.f.=1.67 P=0.0743
CLAMP	0.77100/0.97500/1.5 2075	1.06700/1.30000/1.73 350	0.92475/1.29150/1.70 000	F=4.64 d.f.=1.67 P=0.0348
APROTININ	4% (1)	9% (4)	7% (5)	X ² =0.72 d.f.=1 P=0.397

5 **TABLE 6.12** summarizes important SNP-biomarker associations for AVPR1A rs1495027.

Subjects with the AVPR1A rs1495027 CC genotype were observed to have lower interleukin 8 (IL8) levels at baseline (p=0.046) and at three hours post cardiopulmonary bypass (p=0.0231) and had a strong trend towards smaller change in IL8 levels post-cardiopulmonary bypass surgery when compared to AVPR1A rs1495027 CT or TT subjects (P = 0.0664). These findings suggest

10 that non-septic SIRS Subjects with the AVPR1A rs1495027 CC genotype have a decreased pro-inflammatory cytokine (IL8) response at baseline and after cardiopulmonary bypass surgery. A trend towards lower MCP1 levels at baseline was also observed for subjects with the CC genotype compared with AVPR1A rs1495027 subjects with AVPR1A rs1495027 CT/TT genotypes P = 0.09).

15 **TABLE 6.12**

Biological plausibility of arginine vasopressin receptor 1a association using biomarkers in a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of arginine vasopressin receptor 1a (AVPR1A) rs1495027 (CC vs. CT/TT). Biomarkers are measured in pg/ml.

	CC (N=26)	CT/TT (N=43)	Combined (N=69)	Test Statistic
IL8.0	0.0/0.0/16.0	0.0/15.6/21.1	0.0/7.2/20.2	F=4.13 d.f.=1.67 P=0.0461
IL8.3	26.0/37.6/67.2	33.7/63.6/136.3	27.9/44.9/78.4	F=5.41 d.f.=1.67 P=0.0231
IL8.DIF	21.6/27.2/58.9	24.4/47.7/116.1	22.2/35.7/67.0	F=3.48 d.f.=1.67 P=0.0664
MCP1.0	117/169/203	155/188/262	135/182/245	F=2.83 d.f.=1.67 P=0.0973

20

4.3.2 AVPR1A rs3803107

TABLE 6.13 summarizes the baseline characteristics of the 70 non-septic SIRS subjects who were successfully genotyped (CT/TT vs. CC) at AVPR1A position rs3803107. No significant differences were detected between the two genotype groups prior to cardiopulmonary bypass surgery.

5 **TABLE 6.13**

Baseline characteristics of a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of arginine vasopressin receptor 1a (AVPR1A) rs3803107 (CT/TT vs. CC).

	CC (N=49)	CT/TT (N=21)	Combined (N=70)	Test Statistic
AGE	61.00/65.00/71.00	57.00/66.00/72.00	58.25/65.50/70.75	F=0.07 d.f.=1.68 P=0.79
GENDER	63% (31)	76% (16)	67% (47)	X ² =1.11 d.f.=1 P=0.291
SMOKER	22% (11)	29% (6)	24% (17)	X ² =0.3 d.f.=1 P=0.584
DIABETES	20% (10)	19% (4)	20% (14)	X ² =0.02 d.f.=1 P=0.896
H.TENSE	51% (25)	67% (14)	56% (39)	X ² =1.46 d.f.=1 P=0.227
EJEC.FRAC	0.50/0.50/0.60	0.48/0.50/0.60	0.50/0.50/0.60	F=0.01 d.f.=1.66 P=0.934
BYPASS	1.333/1.667/2.133	1.350/1.600/1.767	1.317/1.650/2.050	F=0.63 d.f.=1.68 P=0.431
CLAMP	0.93300/1.30000/1.75	0.88300/1.13300/1.433	0.92475/1.29150/1.700	F=1.34 d.f.=1.68 P=0.252
APROTININ	8% (4)	5% (1)	7% (5)	X ² =0.26 d.f.=1 P=0.613

10 **TABLE 6.14** summarizes important SNP-biomarker associations for AVPR1A rs3803107.

Subjects with the AVPR1A rs3803107 CC genotype had significantly higher serum MCP1 concentrations at baseline compared to those with AVPR1A rs3803107 CT or TT(P = 0.0288). This finding suggests that the non-septic SIRS subjects with the AVPR1A rs3803107 CC genotype had higher MCP1 levels at baseline.

15

TABLE 6.14

Biological plausibility of arginine vasopressin receptor 1a association using biomarkers in a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of arginine vasopressin receptor 1a (AVPR1A) rs3803107 (CT/TT vs. CC). Biomarkers are measured in pg/ml.

20

	CC (N=49)	CT/TT (N=21)	Combined (N=70)	Test Statistic
MCP1.0	162.2/187.2/261.5	78.7/133.8/223.4	134.9/182.0/245.2	F=4.99 d.f.=1.68 P=0.0288

4.3.3 AVPR1A rs10877970

TABLE 6.15 summarizes the baseline characteristics of the 69 non-septic SIRS subjects who were successfully genotyped (CC/CT vs. TT) at AVPR1A rs10877970. No significant differences were detected between the two genotype groups prior to cardiopulmonary bypass surgery.

25

TABLE 6.15

Baseline characteristics of a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of arginine vasopressin receptor 1a (AVPR1A) rs10877970 (CC/CT vs. TT).

	CT/CC (N=20)	TT (N=49)	Combined (N=69)	Test Statistic
AGE	57.00/66.50/70.50	61.00/65.00/72.00	58.25/65.50/70.75	F=0.29 d.f.=1.67 P=0.591
GENDER	75% (15)	63% (31)	67% (46)	X ² =0.88 d.f.=1 P=0.348
SMOKER	25% (5)	24% (12)	25% (17)	X ² =0 d.f.=1 P=0.964
DIABETES	25% (5)	18% (9)	20% (14)	X ² =0.39 d.f.=1 P=0.534
H.TENSE	65% (13)	51% (25)	55% (38)	X ² =1.12 d.f.=1 P=0.290
EJEC.FRAC	0.405/0.550/0.600	0.500/0.500/0.600	0.500/0.500/0.600	F=0 d.f.=1.65 P=0.967
BYPASS	1.3250/1.6915/2.32 10	1.3330/1.6500/2.033 0	1.3170/1.6500/2.0500	F=0.01 d.f.=1.67 P=0.917
CLAMP	0.87075/1.35850/1. 600	0.93300/1.25000/1.7 17	0.92475/1.29150/1.70 0	F=0.14 d.f.=1.67 P=0.714
APROTININ	5% (1)	8% (4)	7% (5)	X ² =0.21 d.f.=1 P=0.646

TABLE 6.16 summarizes important SNP-biomarker associations for AVPR1A rs10877970.

Subjects with the AVPR1A rs10877970 TT genotype showed a trend towards higher serum MCP levels (P = 0.0865) at baseline compared to subjects with AVPR1A rs10877970 CT or CC. This finding suggests that non-septic SIRS subjects who carry either the AVPR1A rs10877970 CT or CC genotypes had lower MCP1 levels at baseline.

TABLE 6.16

Biological plausibility of arginine vasopressin receptor 1a association using biomarkers in a cohort of non-septic CSICU subjects diagnosed with systematic inflammatory response syndrome by genotype of arginine vasopressin receptor 1a (AVPR1A) rs10877970 (CC/CT vs. TT). Biomarkers are measured in pg/ml.

	CT/CC (N=20)	TT (N=49)	Combined (N=69)	Test Statistic
MCP1.0	76.4/148.8/236.0	162.2/187.2/249.6	134.9/182.0/245.2	F=3.05 d.f.=1.67 P=0.0856

SUMMARY

Numerous discoveries described herein show that single nucleotide polymorphisms of the vasopressin (AVP rs1410713, rs857240, rs857242) gene, the arginine vasopressin A1 receptor (AVPR1A rs1495027) gene, and the leucyl/cystinyl aminopeptidase (LNPEP rs18059, rs27711, and rs10051637) gene are associated with response (measured as survival, organ dysfunction and need of life support) to AVP.

Furthermore, markers in the vasopressinase gene (LNPEP rs18059, rs27711, and rs10051637) and the vasopressin A1 receptor gene (AVPR1A rs1495027) are also markers of increased use of AVP in a cohort of critically ill subjects who have septic shock. Accordingly, clinicians more frequently administer infused AVP to subjects who have LNPEP genotypes rs18059 CC, rs27711 AA and
5 rs10051637 GG and subjects who have the AVPR1A genotype, rs1495027 CT. These genotypes also have a significantly decreased chance of survival when treated with infused AVP compared to comparable subjects who have septic shock but who are not infused with AVP (control).

In a separate study of an independent cohort of subjects with cardiopulmonary bypass surgery, we
10 have also found that LNPEP rs18059 CC, LNPEP rs27711 AA and LNPEP rs10051637 GG are associated with decreased inflammatory response (measured as GCSF and IL-8 response) to non-septic causes of systemic inflammatory response syndrome (subjects having cardiopulmonary bypass surgery).

The clinical utility of these discoveries is that before subjects who have SIRS, sepsis or septic shock and other inflammatory conditions listed below are considered for treatment with a vasopressin receptor agonist, they may be genotyped for single nucleotide polymorphisms of the vasopressin (AVP) gene (rs1410713, rs857240, and rs857242), the vasopressin A1 receptor (AVPR1A) gene (rs1495027), and the vasopressinase (LNPEP) gene (rs18059, rs27711 and
20 rs10051637). Subjects who have AVP rs857240 CT or rs857242 AC genotypes; the AVPR1A rs1495027 TT genotype, or the LNPEP rs18059 CC, rs27711 AA or rs10051637 GG genotypes should not receive vasopressin receptor agonist(s) (e.g. V-1 receptor agonist, e.g. a V1a receptor agonist, e.g. an AVPR1 agonist) because vasopressin receptor agonist(s) dramatically decreases their survival and increases the risk of organ dysfunction.

Similarly, before subjects who have SIRS, sepsis or septic shock and the conditions listed below are considered for treatment with any vasopressin receptor agonist(s), they should be genotyped for single nucleotide polymorphisms of the vasopressin (AVP) gene (rs1410713, rs857240 and rs857242), the vasopressin A1 receptor (AVPR1A) gene (rs1495027), and the vasopressinase (LNPEP) gene (rs18059, rs27711 and rs10051637). Subjects who have the AVP rs1410713 AA or AC, rs857240 CC or rs857242 CC genotypes; the AVPR1A rs1495027 CC genotype, and the
30 LNPEP rs18059 TT or rs27711 GG genotypes should receive vasopressin receptor agonist(s) (e.g. V-1 receptor agonist, e.g. a V1a receptor agonist, e.g. an AVPR1 agonist) because vasopressin receptor agonist(s) dramatically increases their survival and decreases the risk of organ
35 dysfunction.

Furthermore, subjects undergoing or having cardiac surgery (of all types in all ages and hypotensions), cardiac surgery requiring cardiopulmonary bypass, cardiac surgery not requiring cardiopulmonary bypass, cardiac transplantation and hypotension, dialysis-induced hypotension, autonomic neuropathy, trauma and hypotension are also likely to be administered a vasopressin receptor agonist and should also be genotypes for single nucleotide polymorphisms of the vasopressin (AVP) gene (rs1410713, rs857240, and rs857242), the vasopressin A1 receptor (AVPR1A) gene (rs1495027), and the vasopressinase (LNPEP) gene (rs18059, rs27711 and rs10051637).

Similarly, before subjects who have pregnancy-associated diuresis, diabetes insipidus and are considered for treatment with vasopressin, they should be genotyped for single nucleotide polymorphisms of the vasopressin (AVP) gene (rs1410713, rs857240, and rs857242), the vasopressin A1 receptor (AVPR1A) gene (rs1495027), and the vasopressinase (LNPEP) gene (rs18059, rs27711 and rs10051637).

TABLE 7.1 shows that subjects who have the LNPEP rs18059 CC, rs27711 AA or rs10051637 GG genotypes ($P = 0.0398$ interaction statistic of LNPEP rs18059 TT and AVP infusion and survival) who receive AVP infusion have decreased survival compared to subjects who have the LNPEP rs18059 CC, rs27711 AA or rs10051637 GG genotypes who do not receive AVP infusion.

Furthermore, **TABLE 7.1** shows that subjects who carry the LNPEP rs18059 CC genotype have a significantly increased chance of receiving AVP infusion than subjects who do not carry the LNPEP rs18059 CC genotype ($p = 0.0257$). Furthermore, subjects who carry the LNPEP rs27711 AA genotype have a significantly increased chance of receiving AVP infusion than subjects who do not carry the LNPEP rs27711 AA genotype ($p = 0.0033$). Furthermore, subjects who carry the LNPEP rs10051637 GG genotype have a significantly increased chance of receiving AVP infusion than subjects who do not carry the LNPEP rs10051637 GG genotype ($p < 0.001$).

TABLE 7.1

Summary of Key Results of SNPs, Alleles and Genotypes of the Vasopressinase Gene (LNPEP)

LNPEP SNP	INCREASE IN USE OF VASO	GROUP	SURVIVAL (%) BY GENOTYPE			BIOLOGICAL PLAUSIBILITY	P
rs18059	Geno = CC		CC	CT	TT	CC: Smaller increase of GCSF	0.003
	$P = 0.0257$	CONT	67	28	15		
		VASO	44	36	38		
		Sig ($P < 0.05$)			0.0398		

		Interaction					
rs27711	Geno = AA		AA	AG	GG	AA: Smaller increase of GCSF	<0.001
	P = 0.0033	CONT	60	36	19	AA: Smaller increase of IL-8	0.05
		VASO	43	36	33		
rs10051637	Geno = GG		GG	AG	AA	GG: Smaller increase of GCSF	0.001
	P < 0.001	CONT	60	35	20	GG: Smaller increase of IL-8	0.04
		VASO	46	38	26		

In addition, subjects who have the LNPEP rs18059 CC genotype have a less pronounced rise in GCSF after cardiac surgery ($p = 0.003$). In addition, subjects who carry the LNPEP rs27711 AA genotype have a less pronounced rise in GCSF ($p = 0.001$) and IL-8 ($p = 0.05$) after cardiac surgery. In addition, subjects who have the LNPEP rs10051637 GG genotype have a less pronounced rise in GCSF ($p = 0.001$) and IL-8 ($p = 0.04$) after cardiac surgery.

TABLE 7.2 shows that subjects who have the AVP rs1410713 CC, AVP rs857240 CT, and AVP rs857242 AC genotypes who receive AVP infusion have decreased survival compared to subjects who have the AVP rs1410713 CC, AVP rs857240 CT, and AVP rs857242 AC genotypes who do not receive AVP infusion.

TABLE 7.2

Summary of Key Results of SNPs, Alleles and Genotypes of the Vasopressin Gene (AVP).

AVP SNP	GROUP	SURVIVAL (%) BY GENOTYPE			BIOLOGICAL PLAUSIBILITY	P
rs1410713		CC	AC	AA		
	CONT	35	37	0		
	VASO	32	47	38		
rs857240		CT	CC			
	CONT	43	30			
	VASO	29	41			
rs857242		AC	CC			
	CONT	54	30		AC: INCREASED GCSF	0.07
	VASO	38	41			

Subjects who have the AVP rs857242 AC genotype have a greater rise in GCSF ($p = 0.07$) after cardiac surgery than subjects who do have the AVP rs857242 CC genotype.

TABLE 7.3 shows that subjects who have the AVPR1A rs1495027 TT genotype (P = 0.0466 interaction statistic of AVPR1A rs1495027 TT and AVP infusion and survival) who receive AVP infusion have decreased survival compared to subjects who have the AVPR1A rs1495027 TT genotype who do not receive AVP infusion.

5

TABLE 7.3

Summary of Key Results of SNPs, Alleles and Genotypes of the AVPR1 Gene.

AVPR1 SNP	INCREASE IN USE OF VASO	GROUP	SURVIVAL (%) BY GENOTYPE			BIOLOGICAL PLAUSIBILITY	P
rs1495027	Geno = CT		TT	CT	CC		
	P = 0.0240	CONT	46	35	24	CT/TT: Greater increase IL-8	0.06
		VASO	23	38	50		
		Sig (P<0.05) Interaction			0.0466		

Furthermore, **TABLE 7.3** shows that subjects who carry the AVPR1A rs1495027 CT genotype have a significantly increased chance of receiving AVP infusion than subjects who do not carry the AVPR1A rs1495027 CT genotype (p = 0.0240).

10

Subjects who have the AVPR1A rs1495027 CT/TT genotypes have a greater rise in IL-8 (p = 0.06) after cardiac surgery than subjects who do have the AVPR1A rs1495027 CC genotype.

15

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of skill in the art in light of the teachings of this invention that changes and modification may be made thereto without departing from the spirit or scope of the appended claims.

CLAIMS

What is Claimed is:

1. A method for obtaining a prognosis for a subject having, or at risk of developing, an inflammatory condition, the method comprising determining a genotype of said subject which
5 includes one or more polymorphic sites in the subject's vasopressin pathway gene sequences or a combination thereof, wherein said genotype is indicative of an ability of the subject to recover from the inflammatory condition.
2. The method of claim 1, wherein the polymorphic site is selected from one or more of the following: rs18059; rs27711; rs38041; rs10051637; rs1410713; rs857240; rs857242; rs10877970;
10 rs3803107; and rs1495027; or a polymorphic site in linkage disequilibrium thereto.
3. The method of claim 2, wherein the polymorphic site in linkage disequilibrium is selected from one or more of the following: rs2762; rs10051637; rs1477364; rs7731592; rs7736466; rs1363974; rs2351010; rs1423357; rs1544777; rs2161548; rs38032; rs38034; rs38041; rs27436; rs27306; rs27307; rs27397; rs27659; rs27711; rs27290; rs38030; rs27294; rs27747; rs39602;
15 rs248215; rs27302; rs2278018; rs1559355; rs3734015; rs4869315; rs2247650; rs2549781; rs2549782; rs2161657; rs251339; rs187265; rs2548527; rs1056893; rs2548523; rs2255546; rs2255637; rs1019503; rs251344; rs1981846; rs10071975; rs7700332; rs38042; rs18059; rs9127; rs7972829; rs10784339; rs3803107; rs11836346; rs7308008; rs11835545; rs7959001; rs11832877; rs10877977; rs2201895; rs7302323; rs10877986; rs2030106; rs1495027;
20 rs10877962; rs1042615; rs16856; rs18059; rs27296; rs27300; rs27613; rs27711; rs38033; rs38035; rs38036; rs38041; rs38043; rs716848; rs1216565; rs1230358; rs1363907; rs1974871; rs2042385; rs2113050; rs2113189; rs2161658; rs2255633; rs2255634; rs2287988; rs2548524; rs2548529; rs2548530; rs2548532; rs2548533; rs2548536; rs2548538; rs2548539; rs2548540; rs2549783; rs2549784; rs2549790; rs2549791; rs2549794; rs2549795; rs2549796; rs2549797;
25 rs2617447; rs2910686; rs2927609; rs3797796; rs3849749; rs3849750; rs4360063; rs4869314; rs4869316; rs6556942; rs7713127; rs7716222; rs7719705; rs10044354; rs10051637; rs10058476; rs12516666; and rs12716486.
4. The method of any one of claims 1-3, further comprising comparing the genotype so determined with known genotypes which are known to be indicative of a prognosis for recovery
30 from:
 - (i) the subject's type of inflammatory condition; or
 - (ii) another inflammatory condition.
5. The method of any one of claims 1-4, further comprising obtaining vasopressin pathway gene sequence information for the subject.

6. The method of any one of claims 1-5, wherein the genotype is determined using a nucleic acid sample from the subject.

7. The method of claim 6, further comprising obtaining the nucleic acid sample from the subject.

5 8. The method of any one of claims 1-7, wherein said genotype is determined using one or more of the following techniques:

- (a) restriction fragment length analysis;
- (b) sequencing;
- (c) micro-sequencing assay;
- 10 (d) hybridization;
- (e) invader assay;
- (f) gene chip hybridization assays;
- (g) oligonucleotide ligation assay;
- (h) ligation rolling circle amplification;
- 15 (i) 5' nuclease assay;
- (j) polymerase proofreading methods;
- (k) allele specific PCR;
- (l) matrix assisted laser desorption ionization time of flight (MALDI-TOF) mass spectroscopy;
- 20 (m) ligase chain reaction assay;
- (n) enzyme-amplified electronic transduction;
- (o) single base pair extension assay; and
- (p) reading sequence data.

9. The method of any one of claims 1-8, wherein the genotype of the subject is indicative of increased risk of death or organ dysfunction from the inflammatory condition.

10. The method of claim 9, wherein the subject is critically ill and the genotype is indicative of a prognosis of severe cardiovascular or respiratory dysfunction.

11. The method of claim 9 or 10, wherein the genotype comprises at least one of the following risk genotypes: rs18059CT; rs18059TT; rs27711GA; rs27711GG; rs38041GA; rs38041GG; 30 rs10051637GA; rs10051637GG; rs1410713AA; rs857240CC; rs857242CC; rs10877970CC; rs3803107TT; and rs1495027TT; or a polymorphic site in linkage disequilibrium thereto.

12. The method of claim 9 or 10, wherein the genotype comprises at least one of the following risk alleles: rs3803107T; and rs10877970C; or a polymorphic site in linkage disequilibrium thereto.

13. The method of any one of claims 1-8, wherein the genotype of the subject is indicative of decreased risk of death or organ dysfunction from the inflammatory condition.

14. The method of claim 13, wherein the subject is critically ill and the genotype is indicative of a prognosis of mild cardiovascular or respiratory dysfunction.

15. The method of claim 13 or 14, wherein the genotype comprises at least one of the following reduced risk genotypes: rs18059CC; rs27711AA; rs38041AA; rs10051637AA; rs1410713CC; rs1410713AC; rs857240TT; rs857240CT; rs857242AA; rs857242AC; rs10877970TT; rs10877970CT; rs3803107CC; rs3803107CT; rs1495027CC and rs1495027CT; or a polymorphic site in linkage disequilibrium thereto.

16. The method of claim 13 or 14, wherein the genotype comprises at least one of the following reduced risk alleles: rs3803107C; and rs10877970T; or a polymorphic site in linkage disequilibrium thereto.

17. The method of claim 11 or 12, wherein the genotype of the polymorphic site in linkage disequilibrium is selected from one or more of the polymorphic sites and corresponding genotypes set out in TABLES 1B and 1D.

18. The method of claim 15 or 16, wherein the genotype of the polymorphic site in linkage disequilibrium is selected from one or more of the polymorphic sites and corresponding genotypes set out in TABLES 1B and 1D.

19. The method of any one of claims 1-18, wherein the inflammatory condition is selected from the group consisting of: sepsis, septicemia, pneumonia, septic shock, systemic inflammatory response syndrome (SIRS), Acute Respiratory Distress Syndrome (ARDS), acute lung injury, aspiration pneumonitis, infection, pancreatitis, bacteremia, peritonitis, abdominal abscess, inflammation due to trauma, inflammation due to surgery, chronic inflammatory disease, ischemia, ischemia-reperfusion injury of an organ or tissue, tissue damage due to disease, tissue damage due to chemotherapy or radiotherapy, and reactions to ingested, inhaled, infused, injected, or delivered substances, glomerulonephritis, bowel infection, opportunistic infections, and for subjects undergoing major surgery or dialysis, subjects who are immunocompromised, subjects on immunosuppressive agents, subjects with HIV/AIDS, subjects with suspected endocarditis, subjects with fever, subjects with fever of unknown origin, subjects with cystic fibrosis, subjects with diabetes mellitus, subjects with chronic renal failure, subjects with acute renal failure, oliguria, subjects with acute renal dysfunction, glomerulo-nephritis, interstitial-nephritis, acute tubular necrosis (ATN), subjects, subjects with bronchiectasis, subjects with chronic obstructive lung disease, chronic bronchitis, emphysema, or asthma, subjects with febrile neutropenia, subjects with meningitis, subjects with septic arthritis, subjects with urinary tract infection, subjects with

necrotizing fasciitis, subjects with other suspected Group A streptococcus infection, subjects who have had a splenectomy, subjects with recurrent or suspected enterococcus infection, other medical and surgical conditions associated with increased risk of infection, Gram positive sepsis, Gram negative sepsis, culture negative sepsis, fungal sepsis, meningococemia, post-pump syndrome, cardiac stun syndrome, myocardial infarction, stroke, congestive heart failure, hepatitis, epiglottitis, E. coli 0157:H7, malaria, gas gangrene, toxic shock syndrome, pre-eclampsia, eclampsia, HELLP syndrome, mycobacterial tuberculosis, Pneumocystis carinii, pneumonia, Leishmaniasis, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, Dengue hemorrhagic fever, pelvic inflammatory disease, Legionella, Lyme disease, Influenza A, Epstein-Barr virus, encephalitis, inflammatory diseases and autoimmunity including Rheumatoid arthritis, osteoarthritis, progressive systemic sclerosis, systemic lupus erythematosus, inflammatory bowel disease, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, systemic vasculitis, Wegener's granulomatosis, transplants including heart, liver, lung kidney bone marrow, graft-versus-host disease, transplant rejection, sickle cell anemia, nephrotic syndrome, toxicity of agents such as OKT3, cytokine therapy, and cirrhosis.

20. The method of any one of claims 1-19, wherein the inflammatory condition is selected from one or more of the following: SIRS, sepsis and septic shock.

21. A method for selecting a group of subjects for determining the efficacy of a candidate drug known or suspected of being useful for the treatment of an inflammatory condition, the method comprising determining a genotype at one or more polymorphic sites in a vasopressin pathway gene sequence for each subject, wherein said genotype is indicative of the subject's ability to recover from the inflammatory condition and sorting subjects based on their genotype.

22. The method of claim 21 further comprising, administering the candidate drug to the subjects or a subset of subjects and determining each subject's ability to recover from the inflammatory condition.

23. The method of claim 22, further comprising comparing subject response to the candidate drug based on genotype of the subject.

24. A method of treating an inflammatory condition in a subject in need thereof, the method comprising administering to the subject a vasopressin receptor agonist, wherein said subject has an improved response genotype in their vasopressin pathway associated gene sequence.

25. A method of treating an inflammatory condition in a subject in need thereof, the method comprising selectively not administering a vasopressin receptor agonist to the subject, wherein said subject has an adverse response genotype in their vasopressin pathway associated gene sequence.

26. A method of selecting a subject for the treatment of an inflammatory condition with a vasopressin receptor agonist, comprising the step of identifying a subject having an improved response genotype in their vasopressin pathway associated gene sequence, wherein the identification of a subject with the improved response genotype is predictive of increased responsiveness to the treatment of the inflammatory condition with the vasopressin receptor agonist.

27. A method of selecting a subject for the treatment of an inflammatory condition, comprising the step of identifying a subject having an adverse response genotype in their vasopressin pathway associated gene sequence and selectively not treating with a vasopressin receptor agonist, wherein the identification of a subject with the adverse response genotype is predictive of decreased responsiveness to the treatment of the inflammatory condition with the vasopressin receptor agonist.

28. A use of a vasopressin receptor agonist in the manufacture of a medicament for the treatment of an inflammatory condition, wherein the subjects treated have an improved response genotype in their vasopressin pathway associated gene sequence.

29. A use of a vasopressin receptor agonist in the manufacture of a medicament for the treatment of an inflammatory condition, wherein the subjects treated do not have an adverse response genotype in their vasopressin pathway associated gene sequence.

30. A use of a vasopressin receptor agonist for administration to a subject in need thereof, said subject having an improved response genotype in their vasopressin pathway associated gene sequence.

31. The method or use of any one of claims 24 to 30, further comprising determining the number of organ system failures for the subject as an assessment of subject risk.

32. The method of claim 31, wherein 2 or more organ system failures are indicative of increased subject risk.

33. The method or use of any one of claims 24-32, wherein the inflammatory condition is selected from the group consisting of: sepsis, septicemia, pneumonia, septic shock, systemic inflammatory response syndrome (SIRS), Acute Respiratory Distress Syndrome (ARDS), acute lung injury, aspiration pneumonitis, infection, pancreatitis, bacteremia, peritonitis, abdominal abscess, inflammation due to trauma, inflammation due to surgery, chronic inflammatory disease, ischemia, ischemia-reperfusion injury of an organ or tissue, tissue damage due to disease, tissue damage due to chemotherapy or radiotherapy, and reactions to ingested, inhaled, infused, injected, or delivered substances, glomerulonephritis, bowel infection, opportunistic infections, and for subjects undergoing major surgery or dialysis, subjects who are immunocompromised, subjects on

immunosuppressive agents, subjects with HIV/AIDS, subjects with suspected endocarditis, subjects with fever, subjects with fever of unknown origin, subjects with cystic fibrosis, subjects with diabetes mellitus, subjects with chronic renal failure, subjects with acute renal failure, oliguria, subjects with acute renal dysfunction, glomerulo-nephritis, interstitial-nephritis, acute tubular necrosis (ATN), subjects with bronchiectasis, subjects with chronic obstructive lung disease, chronic bronchitis, emphysema, or asthma, subjects with febrile neutropenia, subjects with meningitis, subjects with septic arthritis, subjects with urinary tract infection, subjects with necrotizing fasciitis, subjects with other suspected Group A streptococcus infection, subjects who have had a splenectomy, subjects with recurrent or suspected enterococcus infection, other medical and surgical conditions associated with increased risk of infection, Gram positive sepsis, Gram negative sepsis, culture negative sepsis, fungal sepsis, meningococemia, post-pump syndrome, cardiac stun syndrome, myocardial infarction, stroke, congestive heart failure, hepatitis, epiglottitis, E. coli 0157:H7, malaria, gas gangrene, toxic shock syndrome, pre-eclampsia, eclampsia, HELLP syndrome, mycobacterial tuberculosis, Pneumocystis carinii, pneumonia, Leishmaniasis, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, Dengue hemorrhagic fever, pelvic inflammatory disease, Legionella, Lyme disease, Influenza A, Epstein-Barr virus, encephalitis, inflammatory diseases and autoimmunity including Rheumatoid arthritis, osteoarthritis, progressive systemic sclerosis, systemic lupus erythematosus, inflammatory bowel disease, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, systemic vasculitis, Wegener's granulomatosis, transplants including heart, liver, lung kidney bone marrow, graft-versus-host disease, transplant rejection, sickle cell anemia, nephrotic syndrome, toxicity of agents such as OKT3, cytokine therapy, and cirrhosis.

34. The method or use of any one of claims 24-33, wherein the inflammatory condition is selected from one or more of the following: SIRS, sepsis and septic shock.

35. The method or use of any one of claims 24-34, wherein the improved response genotype is found at one or more of the following polymorphic sites: rs18059; rs27711; rs10051637; rs1410713; rs857240; rs857242; and rs1495027; or a polymorphic site in linkage disequilibrium thereto.

36. The method or use of claim 35, wherein the polymorphic site in linkage disequilibrium is selected from one or more of the following: rs2762; rs10051637; rs1477364; rs7731592; rs7736466; rs1363974; rs2351010; rs1423357; rs1544777; rs2161548; rs38032; rs38034; rs38041; rs27436; rs27306; rs27307; rs27397; rs27659; rs27711; rs27290; rs38030; rs27294; rs27747; rs39602; rs248215; rs27302; rs2278018; rs1559355; rs3734015; rs4869315; rs2247650; rs2549781; rs2549782; rs2161657; rs251339; rs187265; rs2548527; rs1056893; rs2548523;

rs2255546; rs2255637; rs1019503; rs251344; rs1981846; rs10071975; rs7700332; rs38042;
 rs18059; rs9127; rs7972829; rs10784339; rs3803107; rs11836346; rs7308008; rs11835545;
 rs7959001; rs11832877; rs10877977; rs2201895; rs7302323; rs10877986; rs2030106 and rs18059;
 rs27296; rs27300; rs27613; rs27711; rs38033; rs38035; rs38036; rs38041; rs38043; rs716848;
 5 rs1216565; rs1230358; rs1363907; rs1974871; rs2042385; rs2113050; rs2113189; rs2161658;
 rs2255633; rs2255634; rs2287988; rs2548524; rs2548529; rs2548530; rs2548532; rs2548533;
 rs2548536; rs2548538; rs2548539; rs2548540; rs2549783; rs2549784; rs2549790; rs2549791;
 rs2549794; rs2549795; rs2549796; rs2549797; rs2617447; rs2910686; rs2927609 rs3797796;
 rs3849749; rs3849750; rs4360063; rs4869314; rs4869316; rs6556942; rs7713127; rs7716222;
 10 rs7719705; rs10044354; rs10051637; rs10058476; rs12516666; and rs12716486.

37. The method or use of claim 35, wherein the improved response genotype is selected from one or more of the following: rs18059CT; rs18059TT; rs27711GG; rs10051637GA; rs10051637AA; rs1410713AC; rs1410713AA; rs857240CC; rs857242CC; rs1495027CC; and rs1495027CT; or a polymorphic site in linkage disequilibrium thereto.

15 38. The method or use of claim 37, wherein the genotype of the polymorphic site in linkage disequilibrium is selected from one or more of the polymorphic sites and corresponding genotypes set out in TABLES 1B and 1D.

39. The method or use of claim 37 or 38, wherein the subject having one or more improved response genotypes is selectively administered the vasopressin receptor agonist.

20 40. The method or use of claim 37, wherein the subject has an adverse response genotype which is selected from one or more of the following: rs18059CC; rs27711AA; rs10051637GG; rs1410713CC; rs857240CT; rs857242AC; and rs1495027TT; or a polymorphic site in linkage disequilibrium thereto.

41. The method or use of claim 40, wherein the genotype of the polymorphic site in linkage
 25 disequilibrium is selected from one or more of the polymorphic sites and corresponding genotypes set out in TABLES 1B and 1D.

42. The method or use of claim 40 or 41, wherein the subject having one or more adverse response genotypes is selectively not administered the vasopressin receptor agonist.

43. The method or use of any one of claims 24-42, wherein the vasopressin receptor agonist is
 30 vasopressin.

44. Two or more oligonucleotides or peptide nucleic acids of about 10 to about 400 nucleotides that hybridize specifically to a sequence contained in a human target sequence consisting of a subject's vasopressin pathway associated gene sequence, a complementary sequence of the target sequence or RNA equivalent of the target sequence and wherein the

oligonucleotides or peptide nucleic acids are operable in determining the presence or absence of two or more polymorphism(s) or in their vasopressin pathway associated gene sequence selected from of the following polymorphic sites: rs18059; rs27711; rs38041; rs10051637; rs1410713; rs857240; rs857242; rs10877970; rs3803107; and rs1495027; or one or more polymorphic sites in linkage disequilibrium thereto.

45. The oligonucleotides or peptide nucleic acids of claim 44, wherein the one or more polymorphic sites in linkage disequilibrium thereto is selected from one or more of the following polymorphic sites: rs2762; rs10051637; rs1477364; rs7731592; rs7736466; rs1363974; rs2351010; rs1423357; rs1544777; rs2161548; rs38032; rs38034; rs38041; rs27436; rs27306; rs27307; rs27397; rs27659; rs27711; rs27290; rs38030; rs27294; rs27747; rs39602; rs248215; rs27302; rs2278018; rs1559355; rs3734015; rs4869315; rs2247650; rs2549781; rs2549782; rs2161657; rs251339; rs187265; rs2548527; rs1056893; rs2548523; rs2255546; rs2255637; rs1019503; rs251344; rs1981846; rs10071975; rs7700332; rs38042; rs18059; rs9127; rs7972829; rs10784339; rs3803107; rs11836346; rs7308008; rs11835545; rs7959001; rs11832877; rs10877977; rs2201895; rs7302323; rs10877986; rs2030106; rs1495027; rs10877962; rs1042615; rs16856; rs18059; rs27296; rs27300; rs27613; rs27711; rs38033; rs38035; rs38036; rs38041; rs38043; rs716848; rs1216565; rs1230358; rs1363907; rs1974871; rs2042385; rs2113050; rs2113189; rs2161658; rs2255633; rs2255634; rs2287988; rs2548524; rs2548529; rs2548530; rs2548532; rs2548533; rs2548536; rs2548538; rs2548539; rs2548540; rs2549783; rs2549784; rs2549790; rs2549791; rs2549794; rs2549795; rs2549796; rs2549797; rs2617447; rs2910686; rs2927609; rs3797796; rs3849749; rs3849750; rs4360063; rs4869314; rs4869316; rs6556942; rs7713127; rs7716222; rs7719705; rs10044354; rs10051637; rs10058476; rs12516666; and rs12716486.

46. Two or more oligonucleotides or peptide nucleic acids selected from the group consisting of:

- (a) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:1 having a T at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:1 having a C at position 201;
- (b) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:1 having a C at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:1 having a T at position 201;
- (c) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:2 having a G at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:2 having a A at position 201;

- (d) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:2 having an A at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:2 having a G at position 201;
- (e) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:3 having an A at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:3 having a G at position 201;
- (f) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:3 having a G at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:3 having an A at position 201;
- (g) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:4 having a G at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:4 having an A at position 201;
- (h) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:4 having an A at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:4 having a G at position 201;
- (i) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:5 having an A at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:5 having a C at position 201;
- (j) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:5 having a C at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:5 having an A at position 201;
- (k) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:6 having an T at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:6 having a C at position 201;
- (l) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:6 having a C at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:6 having an T at position 201;
- (m) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:7 having an A at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:7 having a C at position 201;
- (n) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:7 having a C at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:7 having an A at position 201;

(o) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:8 having a T at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:8 having a C at position 201;

(p) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:8 having a C at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:8 having a T at position 201;

(q) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:9 having a C at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:9 having a T at position 201;

(r) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:9 having a T at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:9 having a C at position 201;

(s) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:10 having a T at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:10 having a C at position 201;

(t) an oligonucleotide or peptide nucleic acid that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:10 having a C at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:10 having a T at position 201;

(u) an oligonucleotide or peptide nucleic acid capable of hybridizing under high stringency conditions to a nucleic acid molecule comprising a first allele for a given polymorphism selected from the polymorphisms listed in TABLE 1D but not capable of hybridizing under high stringency conditions to a nucleic acid molecule comprising a second allele for the given polymorphism selected from the polymorphisms listed in TABLE 1D; and

(v) an oligonucleotide or peptide nucleic acid capable of hybridizing under high stringency conditions to a nucleic acid molecule comprising the second allele for a given polymorphism selected from the polymorphisms listed in TABLE 1D but not capable of hybridizing under high stringency conditions to a nucleic acid molecule comprising the first allele for the given polymorphism selected from the polymorphisms listed in TABLE 1D.

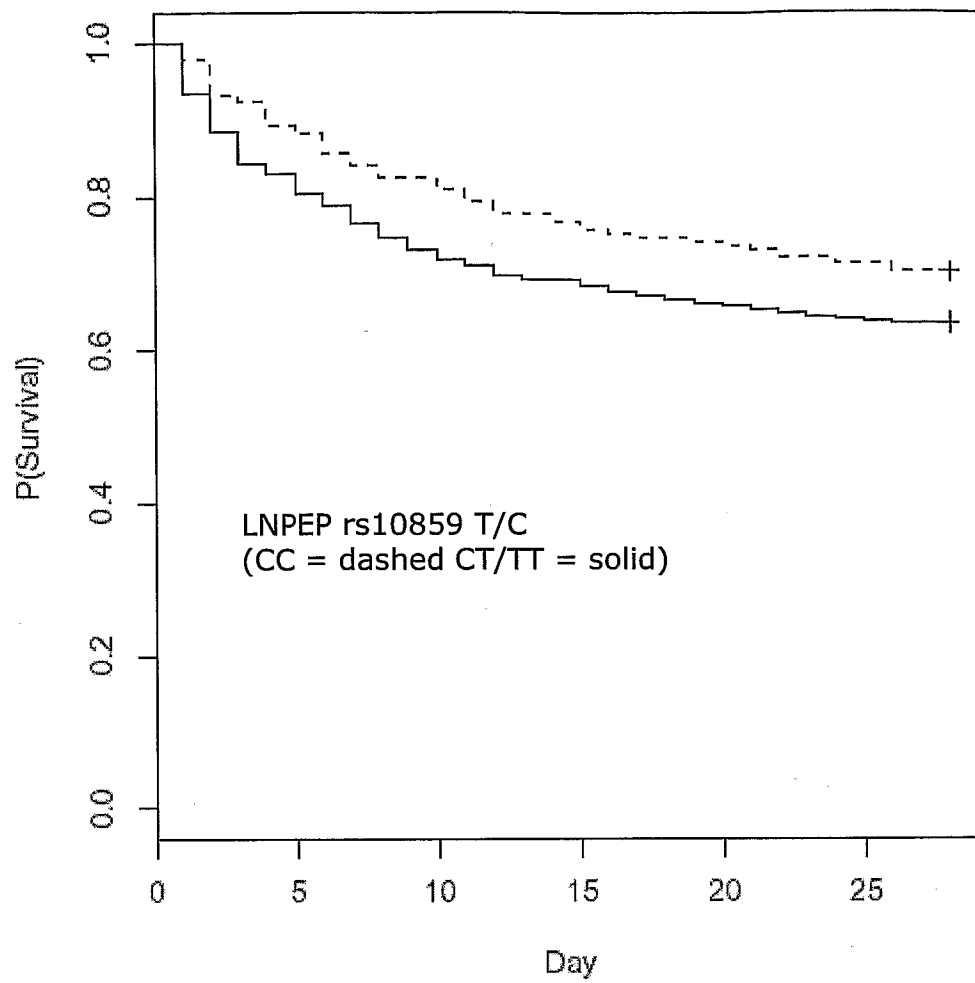
47. An array of oligonucleotides or peptide nucleic acids attached to a solid support, the array comprising two or more of the oligonucleotides or peptide nucleic acids set out in any one of claims 44-46.

48. A composition comprising an addressable collection of two or more oligonucleotides or peptide nucleic acids, the two or more oligonucleotides or peptide nucleic acids consisting essentially of two or more nucleic acid molecules set out in SEQ ID NO:1-264 or compliments,

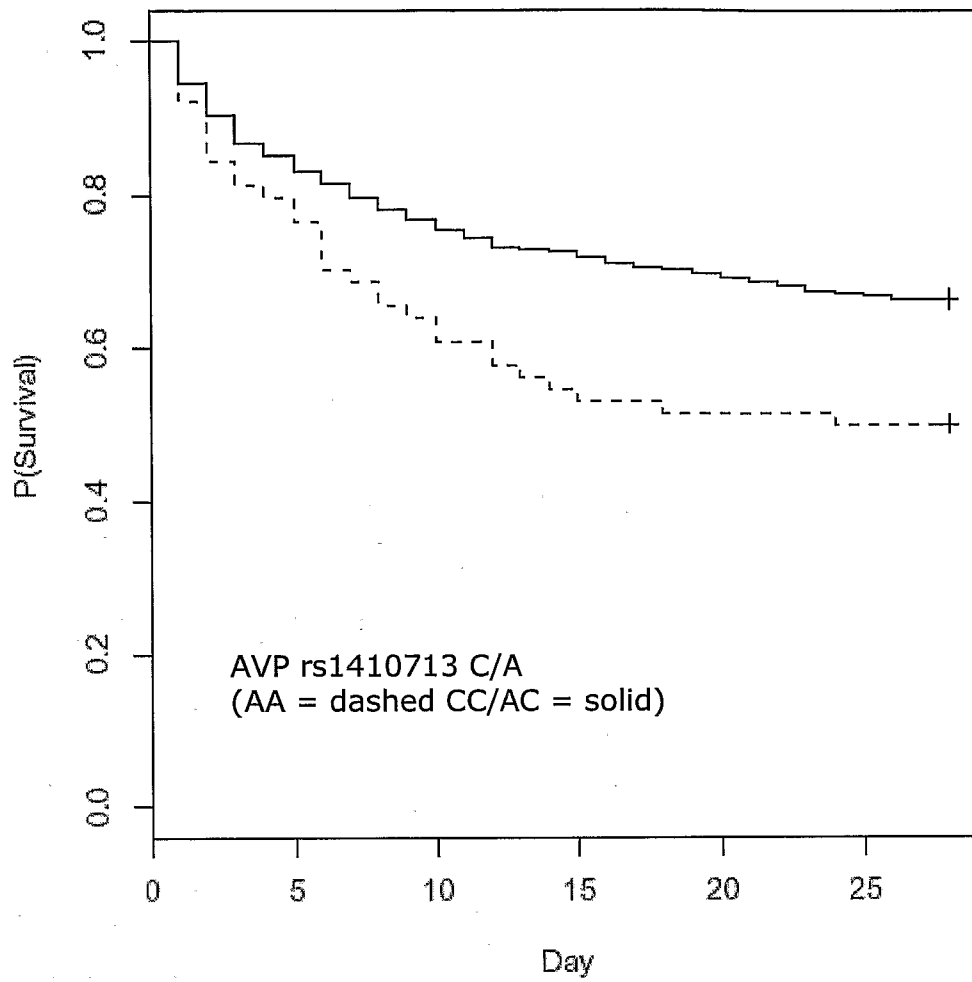
fragments, variants, or analogs thereof.

49. The oligonucleotides or peptide nucleic acids of any one of claims 44 to 48, further comprising one or more of the following: a detectable label; a quencher; a mobility modifier; a contiguous non-target sequence situated 5' or 3' to the target sequence or 5' and 3' to the target sequence.

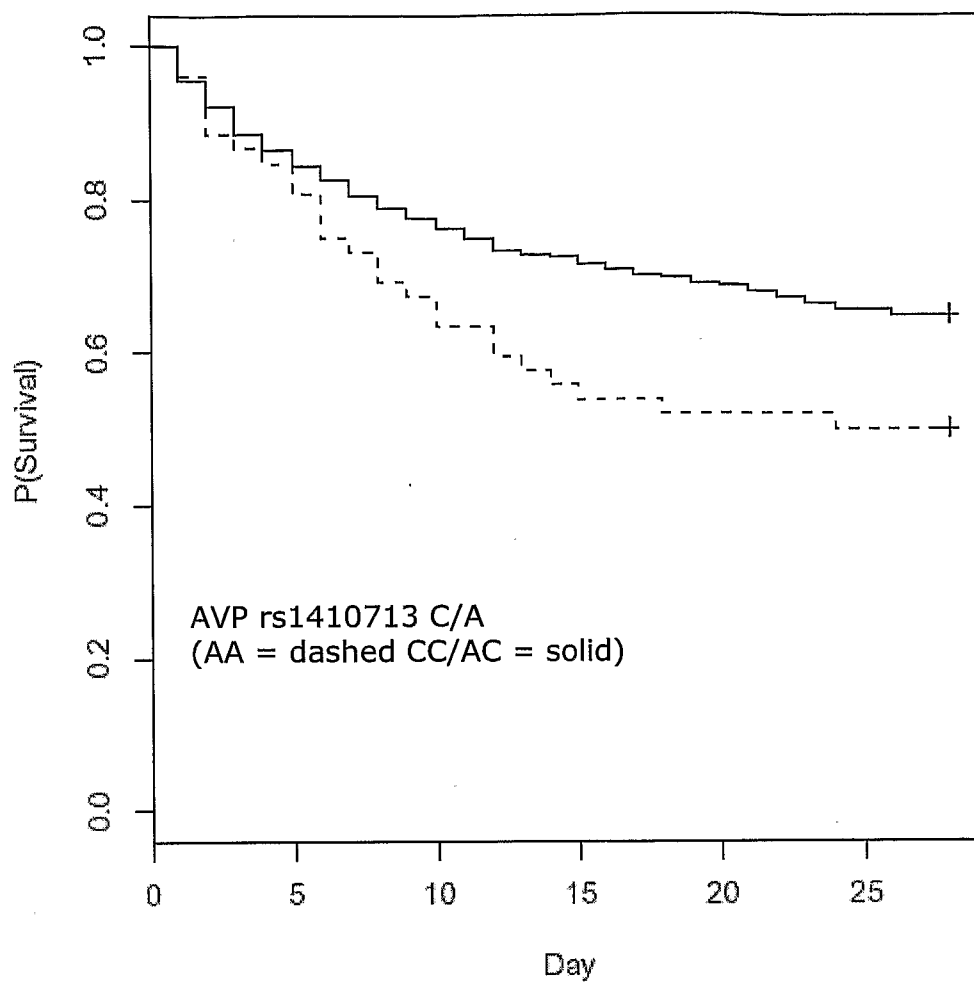
1/10

**FIGURE 1**

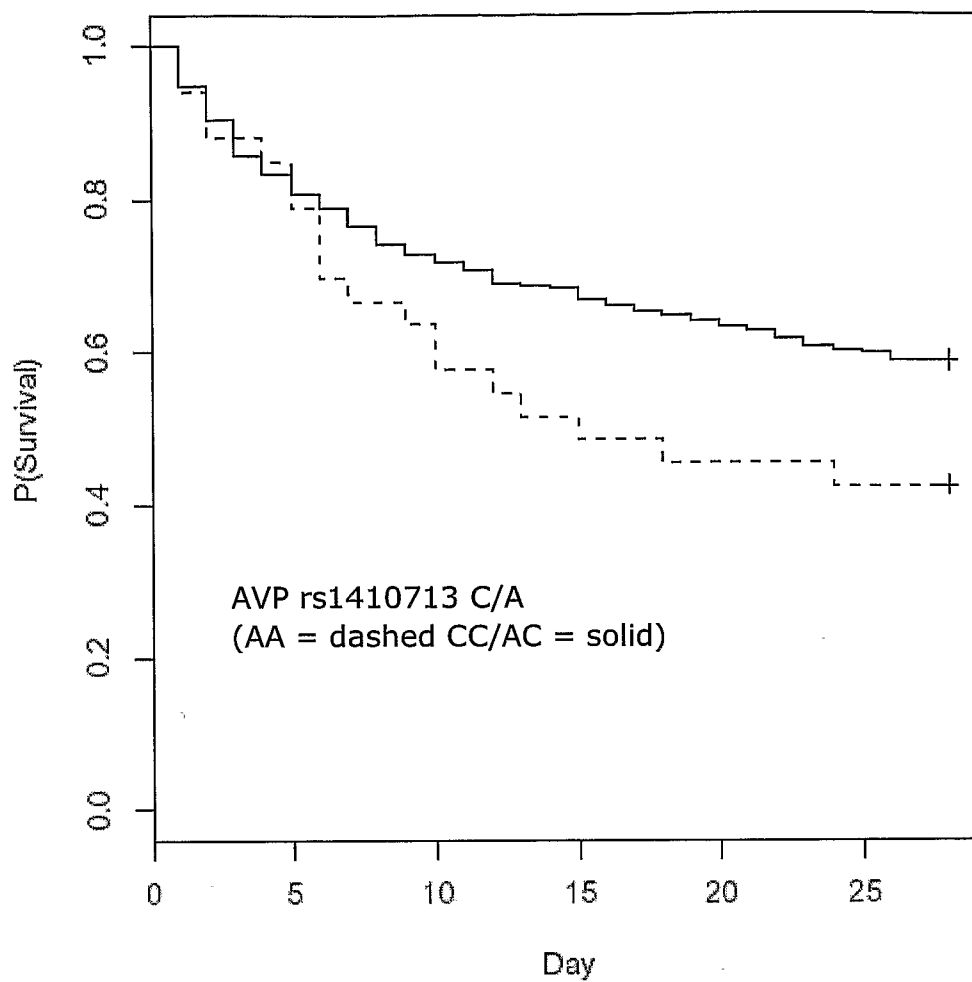
2/10

**FIGURE 2**

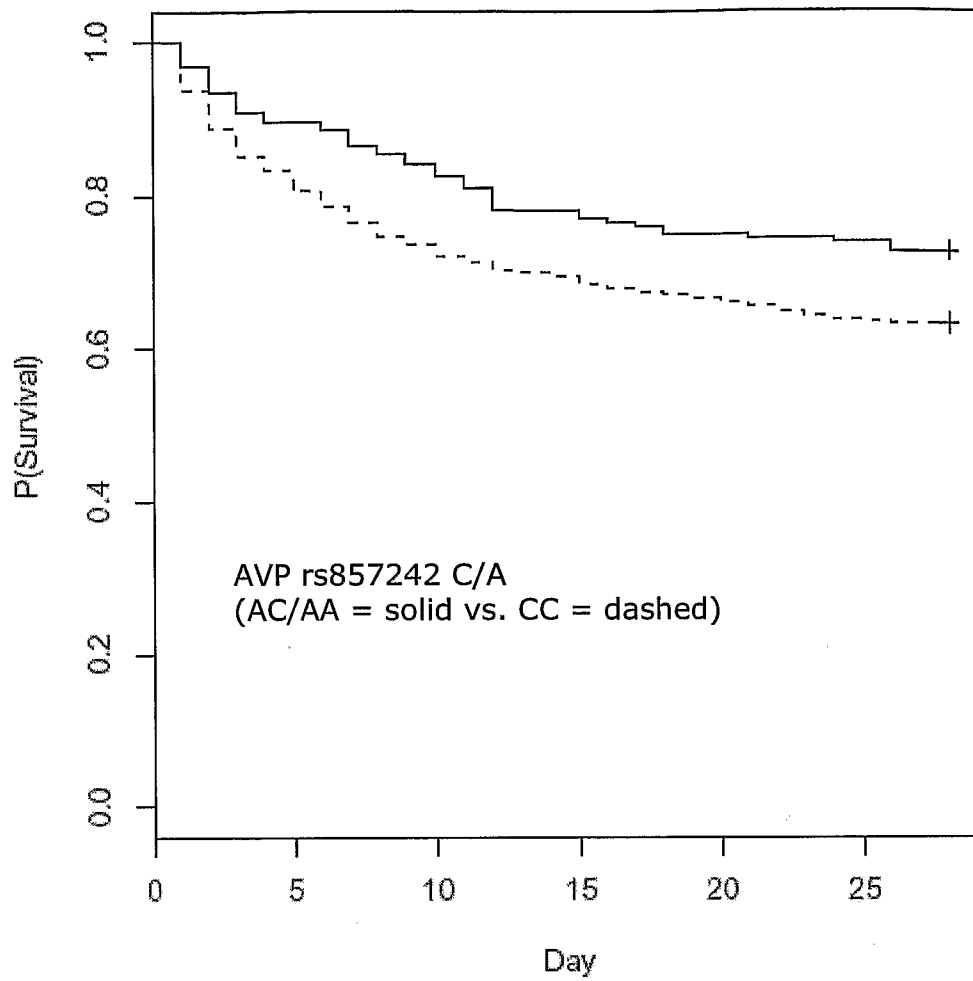
3/10

**FIGURE 3**

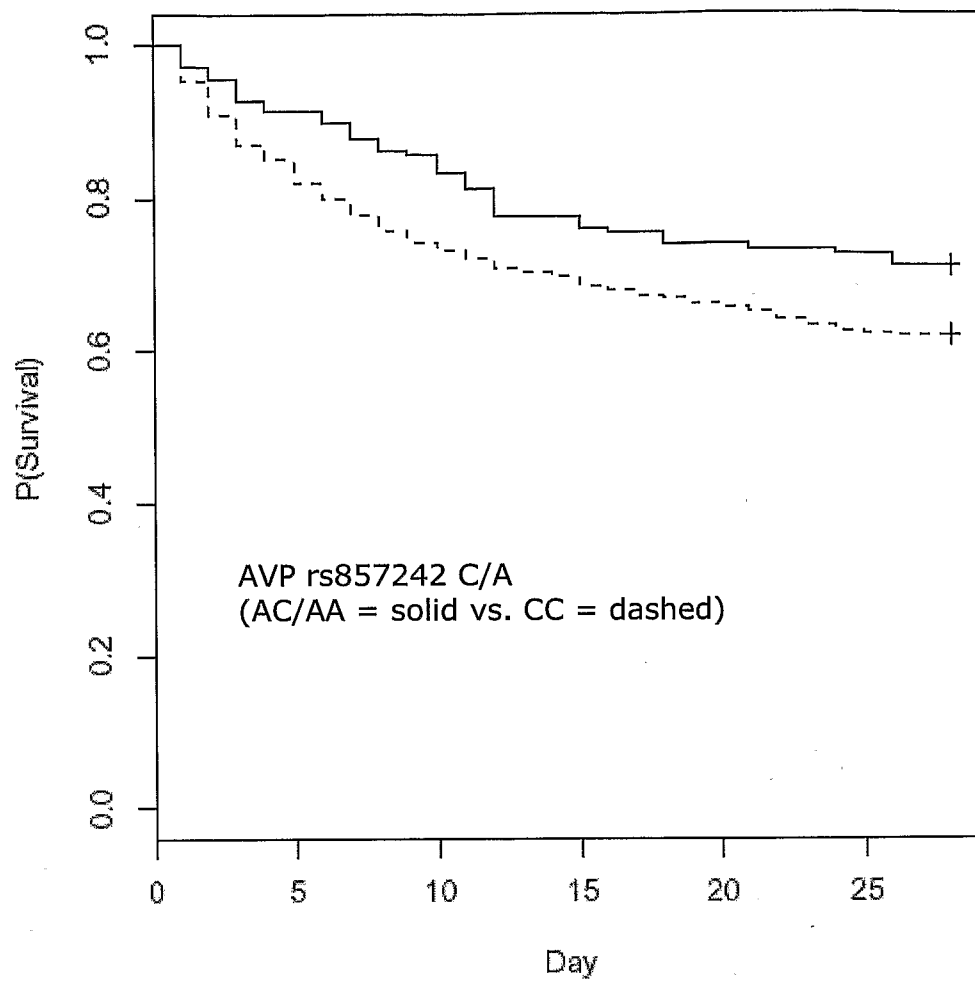
4/10

**FIGURE 4**

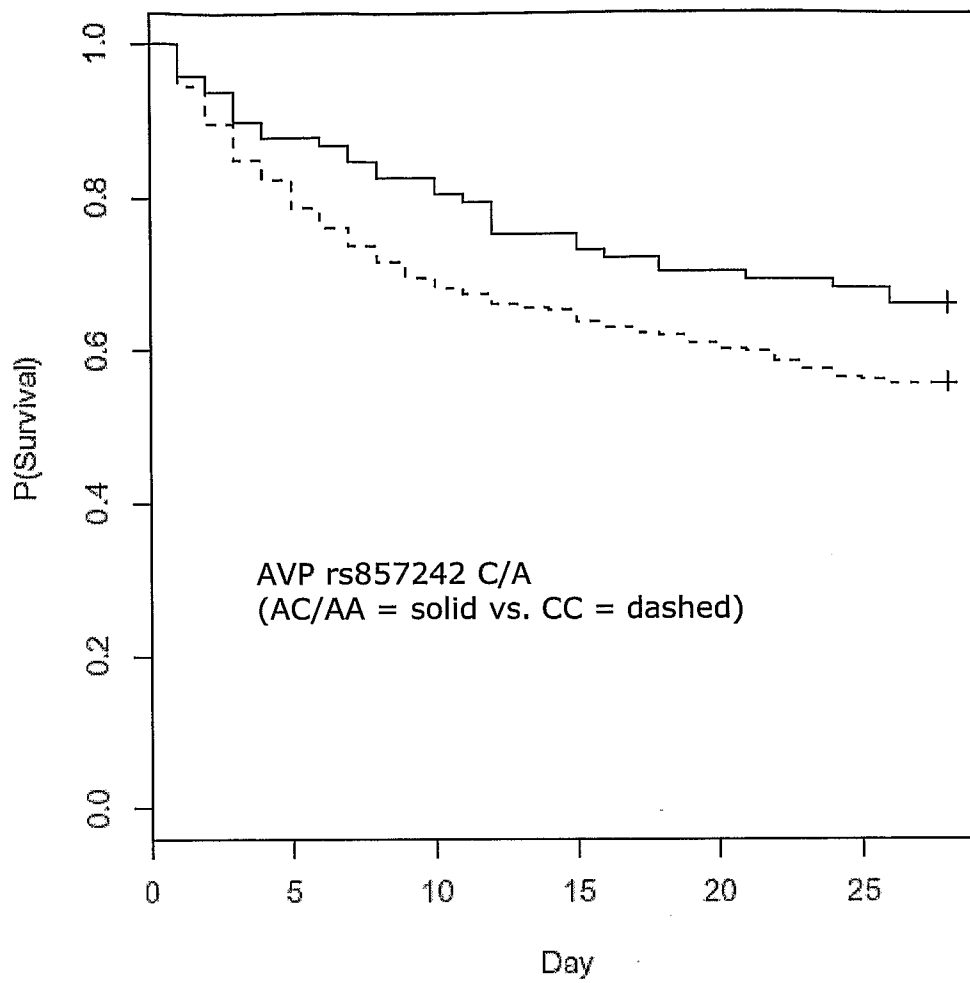
5/10

**FIGURE 5**

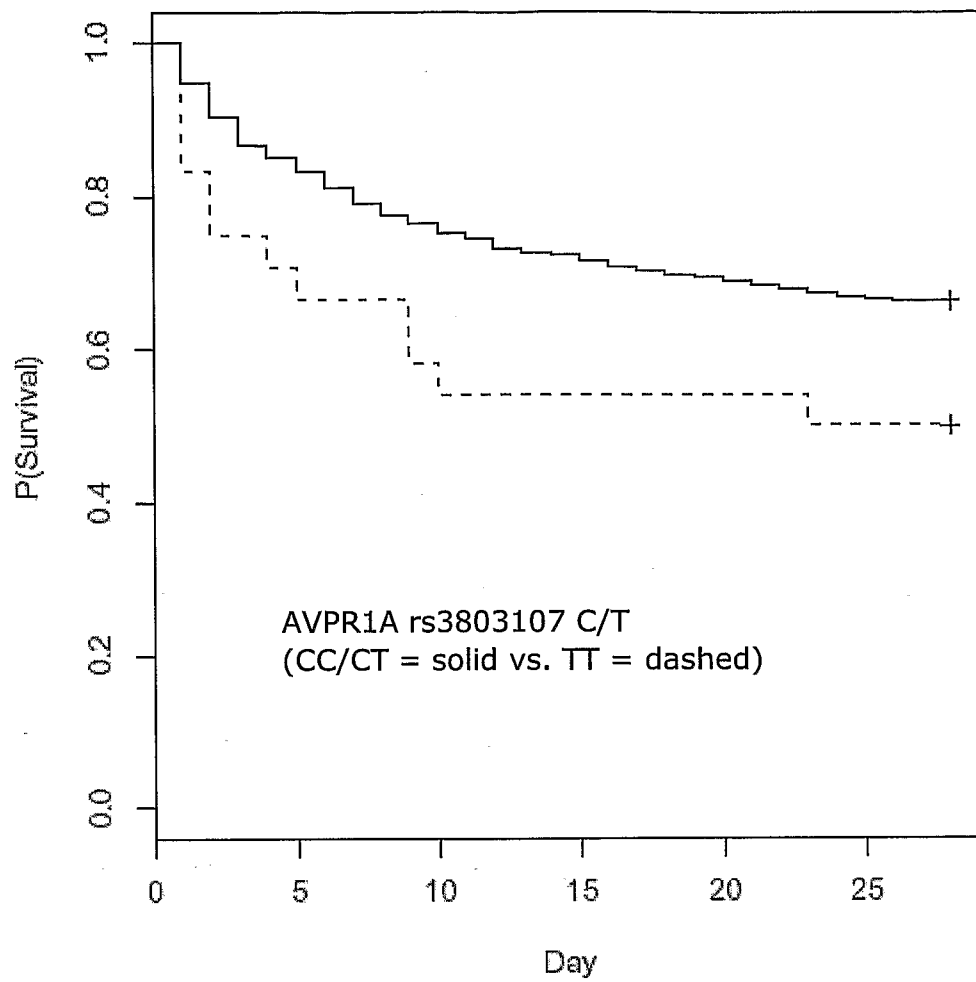
6/10

**FIGURE 6**

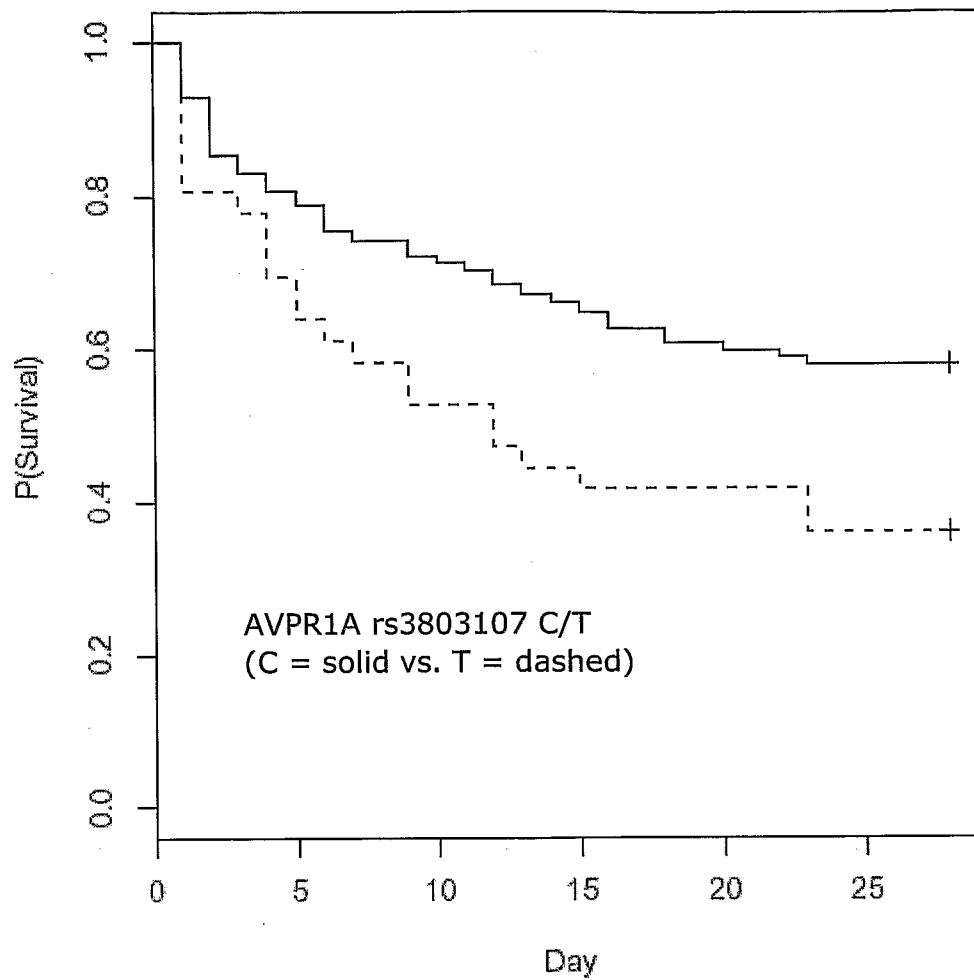
7/10

**FIGURE 7**

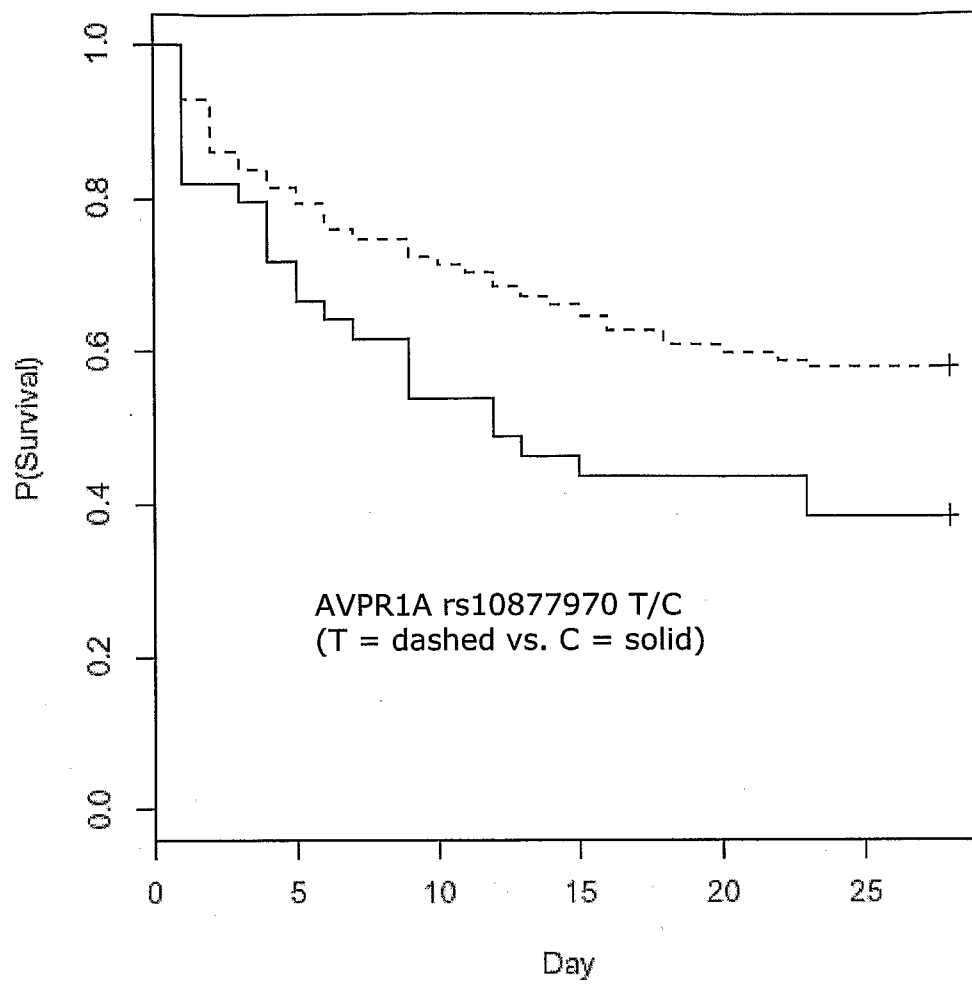
8/10

**FIGURE 8**

9/10

**FIGURE 9**

10/10

**FIGURE 10**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/000111

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **C40B 40/06** (2006.01) , **A61K 31/00** (2006.01) , **A61K 38/00** (2006.01) , **A61K 38/22** (2006.01) , **A61P 29/00** (2006.01) , **C07H 21/00** (2006.01) (more IPCs on the last page)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: **C40B 40/06** (2006.01) , **A61K 31/00** (2006.01) , **A61K 38/00** (2006.01) , **A61K 38/22** (2006.01) , **A61P 29/00** (2006.01) , **C07H 21/00** (2006.01) (more IPCs on the last page)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

STN (Biosis, Caplus, Medline), Delphion, WEST, Canadian Patent Database, GenomeQuest (all nucleotide databases, SEQ ID NOs: 1-264); Keywords: genotyp(e), ing), vasopressin, inflamma(tion, tory), polymorphi(c, sm), AVP, LNPEP, LRAP, AVPR1A, aminopeptidase, neurophysin, otase, oxytocinase.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US2005/0244834 A1 (WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH (US); MILLENNIUM PHARMACEUTICALS INC.(US)) 3 November 2005 - paragraphs 0011, 0015, 0058-0061; Table, page 78	1-10, 13, 14, 19, 21-23
Y		44-49
A		11, 12, 15-18, 20, 24-43
X	CA2498509 A1 (RIKEN(JP)) 27 November 2003 - the entire document, particularly Table 1 SEQ ID NOs: 830-851	1, 2, 4-10, 13, 14, 21-23, 44-49
A		3, 11, 12, 15-20, 24-43
X	SAITO, S. et al. Catalog of 178 variations in the Japanese population among eight human genes encoding G protein-coupled receptors (GPCRs). Nihon Jinrui Iden Gakkai (J. Human Genetics), September 2003, Volume 48, No.9, pages 461-468, ISSN 1434-5161.	1-8
A		9-49

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

28 May 2007 (28-05-2007)

Date of mailing of the international search report

5 June 2007 (05-06-2007)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001-819-953-2476

Authorized officer

Michael W. De Vouge 819- 997-2952

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/000111

C07K 14/575 (2006.01) , *C12N 15/16* (2006.01) , *C12Q 1/00* (2006.01) , *C12Q 1/68* (2006.01) ,
C40B 30/00 (2006.01) , *C12P 19/34* (2006.01)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/000111

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	DELMAS, A. et al. Clinical review: Vasopressin and terlipressin in septic shock patients. Critical Care, April 2005, Volume 9, No. 2, pages 212-222, ISSN 1466-609X. - the entire document	24, 28-43 1-23, 25-27, 44-49
Y A	WO89/11548 A1 (CETUS CORPORATION (US)) 30 November 1989 - Examples 2, 4, 5	44-49 1-43

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/000111

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. ☒ Claim Nos. : 22, 24, 25, 31-43
because they relate to subject matter not required to be searched by this Authority, namely :

method for treatment of the human or animal body by surgery or therapy, are not required to be searched nor is a written opinion required by this Authority. Regardless, this Authority has established a search based on the alleged effect or purpose/use of the product defined in claim 24 (a vasopressin receptor agonist).
2. ☐ Claim Nos. :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :
3. ☐ Claim Nos. :
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

An *a posteriori* analysis has concluded that The National Center for Biotechnology Information (NCBI) single nucleotide polymorphism (SNP) database, from which all of SEQ ID NOs: 1-264 are derived, is known in the art. Furthermore, individual nucleotide sequences of SEQ ID NOs: 1-264 are not sufficiently similar and consequently, cannot serve as special technical features that unify said sequences, as defined in Rule 13.2 PCT. Finally, the products of claims 44-49 are not linked through their utility in prognosis of an individual at risk for, or recovering from an inflammatory condition. Therefore, embodiments of claims 44-49 that are derived from different nucleotide sequences of SEQ ID NOs: 1-264 are considered to represent distinct inventions.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2007/000111

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US2005244834 A1	03-11-2005	AU7119400 A	10-04-2001
		EP1240354 A2	18-09-2002
		US6727063 B1	27-04-2004
		WO0118250 A2	15-03-2001
CA2498509 A1	27-11-2003	AU2003244093 A1	02-12-2003
		CN1692162 A	02-11-2005
		EP1514946 A1	16-03-2005
		US2006240419	26-10-2006
		WO03097877 A1	27-11-2003
WO8911548 A1	30-11-1989	AT 173508T	15-12-1998
		AU 632494B2	07-01-1993
		AU 3754289A	12-12-1989
		CA 1340864C	28-12-1999
		DE 68928853D1	24-12-1998
		DE 68928853T2	05-08-1999
		EP 0451141A1	16-10-1991
		EP 0451141B1	18-11-1998
		IE 891643L	20-11-1989
		IL 90358A	18-08-1993
		IL 90358D0	15-12-1989
		JP 2897959B2	31-05-1999
		JP 3504328T	26-09-1991