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(71) Applicant: **HMNC VALUE GMBH** [DE/DE]; Maximilianstrasse 34, 80539 Munich (DE).

(72) Inventor: **HOLSBOER, Florian**; Rohmeder Strasse 12, 80805 Munich (DE).

(74) Agent: **DF-MP DÖRRIES FRANK-MOLNIA & POHLMAN**; Fünf Höfe, Theatinerstraße 16, 80333 München (DE).

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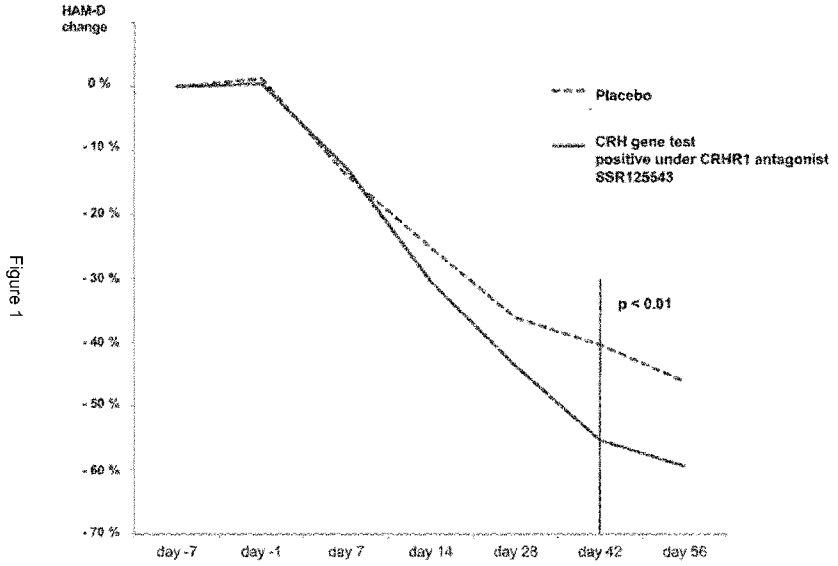

Figure 1

(57) Abstract: The present disclosure provides methods for predicting a treatment response of a subject to a treatment with a CRHR1 antagonist and methods of detecting a polymorphism genotype associated with a treatment response of a subject to treatment with a CRHR1 antagonist. Sets of at least one polymorphism genotype useful in such methods are also disclosed. Further, methods of treating a condition which is treatable by a CRHR1 antagonist in a subject in need thereof are provided. Compositions, kits and arrays and uses thereof are also disclosed, which can be used in the methods of the invention.

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GENETIC PREDICTORS OF A RESPONSE TO TREATMENT WITH CRHR1 ANTAGONISTS

BACKGROUND OF THE INVENTION

[001] Corticotropin-releasing hormone (CRH or corticotropin-releasing factor / CRF) is pivotal in modulating the activity of the hypothalamic–pituitary–adrenal (HPA) axis during stress, stress-response and stress-adaptation, as well as in inflammation. CRH is a 41 aa peptide hormone derived from a 196-amino acid pre-prohormone, produced in the hypothalamus and transported in small vessels to the pituitary from which the peripheral stress hormone corticotropin (also known as adrenocorticotropic hormone / ACTH) is released which, in turn, induces secretion of cortisol from the adrenal gland. CRH containing nerve fibers also project to areas in the CNS implicated in behavioral adaptation to stress, including the amygdala, being implied in fear and anxiety, the prefrontal cortex and the hippocampus. Persistent stress is hypothesized to result in anxiety, depressive symptoms and other stress-related disorders in patients with inherited or acquired vulnerability. Among those patients, antagonists of CRH would appear to be the ideally tailored therapy. The effects of CRH in the brain, where CRH acts like a neurotransmitter, are conveyed via the type 1 CRH receptor (CRHR1, or CRF-R1), which mediates a variety of endocrine, behavioural, and autonomic stress-responses (Heinrichs and Koob, J Pharmacol Exp Ther. 2004 Nov;311(2):427-40), including, but not being limited to, psychiatric conditions such as anxiety disorders and major depression (Holsboer and Ising, Eur J Pharmacol 2008, 583(2-3):350-7; Koob and Zorilla, Neuropsychopharmacology 2012, 37(1):308-9). In murine models, CRHR1 deletions displayed less depression-related behaviors, while CRH overexpression in the CNS lead to an increase of several behaviors that can, within certain limitations, be extrapolated to human depression.

[002] The World Health Organization (WHO) considers depression as one of the top ten causes of morbidity and mortality, with a lifetime prevalence for depression ranging, e.g., from 12-16% in Germany. Depressive disorders account for a worldwide number of over one million suicides annually, and create a significant burden on costs in health care, work leave, disability pension, early retirement, loss of productivity of workers, by far surmounting direct costs such as inpatient and outpatient treatments. Finally,

depression also multiplies the risk for other conditions such as cardiovascular disease, diabetes and neurodegenerative disorders.

[003] Significant effort has been focused on the development of inhibitors of neuropeptide receptor ligands as drugs for psychiatric diseases and related conditions, including CRHR1 antagonists for the treatment of anxiety and depression (Griebel and Holsboer, Nature Reviews Drug Discovery 2012, 11:462-478). However, essentially all randomized controlled trials using CRHR1 antagonists in humans produced negative results, which has lead several originators to stall CRHR1 antagonist development, see Williams, Expert Opin Ther Pat 2013, 23(8):1057-68.

[004] The present invention rests in part on the recognition that several of these earlier trials testing CRHR1 antagonist only failed to show statistically relevant effects due to the lack of appropriate patient stratification and selection according to their individual, underlying pathophysiology. In other words, a CRHR1 antagonist can only be effective in pathologies where the underlying causality is dominated by CRH over-activity or excessive CRH secretion. In the absence of CRH over-activity, a CRHR1-antagonist is not likely to have any significant effect.

[005] Methods and algorithms for predicting an ACTH response to CRHR1 antagonists using the dex/CRH test in patients with depressive symptoms and/or anxiety symptoms, as well as a set of genotypes of single nucleotide polymorphisms (SNPs) for use in such methods and algorithms, have been described in WO 2013/160315 (A2). Correspondingly, CRHR1 antagonists for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH over-activity have been described in WO 2013/160317 (A2), wherein CRH over-activity is detected by determining the status of the same set of genotypes of SNPs as in WO 2013/160315 (A2). However, there remains a need for improved methods of predicting the treatment response to CRHR1 antagonists. In particular, there is a strong need to provide a direct prediction of clinical response in subjects treated with a treatment with a CRHR1 antagonist, e.g., in subjects having depressive symptoms or anxiety symptoms, or another stress-related condition mediated by CRHR1.

[006] The present invention rests on additional evidence unknown in the prior art, according to which many polymorphisms are present in essentially all relevant nodes of the CRH/CRHR1 signaling chain. It is, thus, an object of the present invention to provide a particularly useful set of genomic DNA polymorphisms for predicting a central CRH over-activity and/or a clinical response to treatment with a CRHR1 antagonist, in particular in,

but not being limited to, patients with anxiety symptoms or depressive symptoms. Thus, the present invention provides improved methods for predicting treatment response of patients to a treatment with a CRHR1 antagonist, as well as methods of treatment comprising an CRHR1 antagonist, compositions, kits and arrays comprising polynucleotides and uses thereof in methods of predicting the treatment response.

SUMMARY OF THE INVENTION

[007] The present invention is based, at least in part, on the recognition of polymorphism genotypes, including, but not being limited to, single nucleotide polymorphism (SNP) genotypes that are predictive of a subject's clinical responsiveness or non-responsiveness to treatment with a corticotropin releasing hormone receptor type 1 (CRHR1) antagonist. Specifically, the presence or absence of one or more of the polymorphism genotypes disclosed in Table 2 herein can be used to predict the likelihood that a given subject will or will not respond to treatment with a CRHR1 antagonist. The set and subsets of polymorphism genotypes, compositions, and methods described herein are thus useful in selecting appropriate treatment modalities (e.g., a treatment with a CRHR1 antagonist or a non-CRHR1 antagonist) for a subject having a condition treatable by a CRHR1 antagonist.

[008] Thus, in a first aspect, the invention provides a method for predicting a treatment response of a subject to treatment with a CRHR1 antagonist, the method comprising: providing a biological sample obtained from the subject, and detecting the presence or absence of one or more polymorphism genotypes in the biological sample, wherein the one or more polymorphism genotypes comprise: (a) at least one polymorphism genotype selected from the group consisting of rs34169260 (A/G), rs796287 (A/C), rs56149945 (A/G), rs6190 (T/C), rs7179092 (T/C), rs7614867 (A/G), rs920640 (T/C), rs7167722 (T/C), rs920638 (T/C), rs7165629 (T/C), rs80049044 (T/A), rs16941058 (A/G), rs112015971 (A/G), rs10894873 (T/C), rs117455294 (T/G), rs1170303 (T/C), rs16940681 (C/G), rs968519 (T/C), rs28381866 (T/C), rs79320848 (T/G), rs114653646 (T/G), rs2589496 (T/C), rs10482650 (A/G), rs17614642 (A/G), rs73200317 (T/C), rs1380146 (T/A), rs735164 (T/C), rs730976 (T/G), rs55934524 (T/G), rs4570614 (A/G), rs4458044 (C/G), rs77850169 (A/G), rs35339359 (A/G), rs34800935 (T/C), rs72945439 (T/C), rs113959523 (A/G), rs116798177 (A/G), rs11247577 (T/G), rs75869266 (T/C), rs74372553 (T/C), rs11691508 (A/G), rs6493965 (A/G), rs4869476 (T/C), rs3730170 (T/C), rs2145288 (A/C), rs2935752 (A/C), rs146512400 (A/G), rs62057097 (T/C),

rs115061314 (T/C), rs34113594 (T/G), rs61751173 (A/G), rs74338736 (A/C), rs10851726 (T/C), rs4610906 (T/C), rs59485211 (T/C), rs7060015 (T/G), rs75710780 (T/G), rs6520908 (T/C), rs487011 (T/G), rs1383699 (A/C), rs67516871 (A/G), rs114106519 (T/C), rs7220091 (A/G), rs12489026 (A/G), rs876270 (T/C), rs4968161 (T/C), rs62056907 (A/G), rs2235013 (T/C), rs16878812 (A/G), rs6549407 (A/G), rs28381848 (A/G), rs79723704 (A/C), rs72814052 (A/G), rs10152908 (T/C), rs172769 (A/C), rs78596668 (T/C), rs73307922 (T/C), rs3842 (A/G), rs7210584 (A/C), rs62402121 (T/C), rs55709291 (A/G), rs72747088 (A/G), rs929610 (G/C), rs6766242 (T/C), rs1468552 (G/C), rs78838114 (T/C), rs62489862 (T/C), rs894342 (A/G), rs58882373 (T/C), rs3811939 (A/G), rs6984688 (T/G), rs1018160 (T/C), rs76602912 (A/G), rs80067508 (A/G), rs74888440 (T/C), rs12481583 (T/C), rs66794218 (A/G), rs16946701 (A/G), rs75726724 (A/G), rs67959715 (T/A), rs11871392 (T/G), rs2044070 (A/G), rs77612799 (T/C), rs6743702 (T/C), rs616870 (T/C), rs79590198 (A/G), rs75715199 (A/G), rs13087555 (T/C), rs4869618 (T/C), rs117397046 (A/G), rs8042817 (A/G), rs2258097 (T/C), rs2260882 (C/G), rs532996 (A/G), rs11747040 (T/C), rs10034039 (T/G), rs116909369 (A/G), rs79134986 (A/G), rs117615688 (T/C), rs8032253 (T/C), rs12818653 (T/A), rs4587884 (A/C), rs77122853 (T/C), rs117615061 (T/C), rs74682905 (A/G), rs2257468 (T/C), rs2032582 (T/G), rs2235015 (T/G), rs2729794 (T/C), rs77549514 (A/G), rs74790420 (A/C), rs73129579 (T/C), rs12913346 (A/C), rs117560908 (T/C), rs72747091 (A/G), rs2935751 (A/G), rs4331446 (A/G), rs7523266 (T/C), rs7648662 (T/C), rs117034065 (A/G), rs4836256 (T/C), rs80238698 (T/C), rs3730173 (T/C), rs11687884 (T/C), rs72693005 (T/C), rs2589476 (T/C), rs9813396 (T/C), rs10482667 (A/G), rs72784444 (A/G), rs75074511 (T/C), rs7951003 (A/G), rs79584784 (A/G), rs2214102 (T/C), rs28811003 (A/G), rs6100261 (A/T), rs77152456 (A/G), rs66624622 (T/G), rs140302965 (A/G), rs11653269 (T/C), rs74405057 (A/G), rs7121 (A/G), rs16977818 (A/C), rs12490095 (T/C), rs118003903 (A/G), rs62377761 (T/C), P1_M_061510_6_34_M (-/CACTTACCTTCTTTGTGCCACAGTTTCCCTATCTAAAACAC AAGGTTATCAGTTATCAACATCTCTTGGGATTGTGAGGACTAAAGTAATGCACATAAA G), rs375115639 (-/AAATTACCCTGTTAGGTTTCAATGAAACACCTTTTCTCTTGTAACA AACATCTCCTCC AAGCTAGAATTTCAAAACAG), rs1002204 (A/C), rs10062367 (A/G), rs10482642 (A/G), rs10482658 (A/G), rs1053989 (A/C), rs10851628 (T/C), rs10947562 (T/C), rs11069612 (A/G), rs11071351 (T/C), rs11091175 (A/G), rs11638450 (T/C), rs11715827 (T/G), rs11745958 (T/C), rs11834041 (A/G), rs1202180 (T/C), rs12054781 (A/G), rs12539395 (A/G), rs12720066 (T/G), rs1279754 (A/C), rs12872047 (T/C), rs12876742 (A/C), rs12917505 (A/G), rs13066950 (T/G), rs13229143 (C/G), rs1383707

(T/C), rs1441824 (T/C), rs1652311 (A/G), rs17064 (T/A), rs17100236 (A/G), rs17149699 (A/G), rs1724386 (A/G), rs17250255 (A/G), rs17327624 (T/G), rs17616338 (A/G), rs17687796 (A/G), rs17740874 (T/C), rs17763104 (T/C), rs1880748 (T/C), rs1882478 (A/G), rs1944887 (T/C), rs2028629 (A/G), rs2143404 (A/G), rs2173530 (T/C), rs220806 (T/C), rs2235047 (A/C), rs2242071 (A/G), rs2257474 (T/C), rs2295583 (A/T), rs234629 (T/C), rs234630 (A/G), rs2436401 (A/G), rs258750 (T/C), rs2589487 (T/C), rs28364018 (T/G), rs28381774 (T/C), rs28381784 (A/G), rs2963155 (A/G), rs3133622 (T/G), rs32897 (T/C), rs33388 (A/T), rs3730168 (T/C), rs3735833 (T/G), rs3777747 (A/G), rs3786066 (T/C), rs3798346 (T/C), rs3822736 (A/G), rs389035 (T/C), rs3924144 (A/G), rs4148737 (T/C), rs4148749 (G/C), rs417968 (T/C), rs4458144 (T/C), rs4515335 (T/C), rs4728699 (A/G), rs4758040 (A/G), rs4812040 (A/G), rs4912650 (T/G), rs4957891 (T/C), rs5906392 (A/G), rs6026561 (T/C), rs6026565 (T/A), rs6026567 (A/G), rs6026593 (A/G), rs6092704 (T/G), rs6100260 (A/G), rs6128461 (T/C), rs6415328 (T/C), rs6610868 (T/C), rs6686061 (A/C), rs6730350 (T/G), rs6746197 (T/C), rs6963426 (T/C), rs7121326 (T/C), rs7721799 (A/G), rs7787082 (T/C), rs7799592 (A/C), rs796245 (T/C), rs809482 (A/C), rs8125112 (T/C), rs919196 (A/G), rs920750 (T/C), rs9332385 (A/G), rs930473 (T/G), rs9324921 (A/C), rs9348979 (A/G), rs9571939 (A/C), and rs9892359 (T/C); (b) at least one polymorphism genotype being in linkage disequilibrium with any one of the polymorphism genotypes of (a); or (c) a combination of (a) and (b); and predicting the treatment response from the presence or absence of the one or more polymorphism genotypes of (a), (b), or (c).

[009] In another aspect, the invention provides a method for detecting a polymorphism genotype associated with a treatment response of a subject to treatment with a CRHR1 antagonist, the method comprising providing a biological sample obtained from the subject, and detecting the presence or absence of one or more polymorphism genotypes in the biological sample, wherein the one or more polymorphism genotypes comprise: (a) at least one polymorphism genotype selected from the group consisting of rs34169260 (A/G), rs796287 (A/C), rs56149945 (A/G), rs6190 (T/C), rs7179092 (T/C), rs7614867 (A/G), rs920640 (T/C), rs7167722 (T/C), rs920638 (T/C), rs7165629 (T/C), rs80049044 (T/A), rs16941058 (A/G), rs112015971 (A/G), rs10894873 (T/C), rs117455294 (T/G), rs1170303 (T/C), rs16940681 (C/G), rs968519 (T/C), rs28381866 (T/C), rs79320848 (T/G), rs114653646 (T/G), rs2589496 (T/C), rs10482650 (A/G), rs17614642 (A/G), rs73200317 (T/C), rs1380146 (T/A), rs735164 (T/C), rs730976 (T/G), rs55934524 (T/G), rs4570614 (A/G), rs4458044 (C/G), rs77850169 (A/G), rs35339359 (A/G),

rs34800935 (T/C), rs72945439 (T/C), rs113959523 (A/G), rs116798177 (A/G), rs11247577 (T/G), rs75869266 (T/C), rs74372553 (T/C), rs11691508 (A/G), rs6493965 (A/G), rs4869476 (T/C), rs3730170 (T/C), rs2145288 (A/C), rs2935752 (A/C), rs146512400 (A/G), rs62057097 (T/C), rs115061314 (T/C), rs34113594 (T/G), rs61751173 (A/G), rs74338736 (A/C), rs10851726 (T/C), rs4610906 (T/C), rs59485211 (T/C), rs7060015 (T/G), rs75710780 (T/G), rs6520908 (T/C), rs487011 (T/G), rs1383699 (A/C), rs67516871 (A/G), rs114106519 (T/C), rs7220091 (A/G), rs12489026 (A/G), rs876270 (T/C), rs4968161 (T/C), rs62056907 (A/G), rs2235013 (T/C), rs16878812 (A/G), rs6549407 (A/G), rs28381848 (A/G), rs79723704 (A/C), rs72814052 (A/G), rs10152908 (T/C), rs172769 (A/C), rs78596668 (T/C), rs73307922 (T/C), rs3842 (A/G), rs7210584 (A/C), rs62402121 (T/C), rs55709291 (A/G), rs72747088 (A/G), rs929610 (G/C), rs6766242 (T/C), rs1468552 (G/C), rs78838114 (T/C), rs62489862 (T/C), rs894342 (A/G), rs58882373 (T/C), rs3811939 (A/G), rs6984688 (T/G), rs1018160 (T/C), rs76602912 (A/G), rs80067508 (A/G), rs74888440 (T/C), rs12481583 (T/C), rs66794218 (A/G), rs16946701 (A/G), rs75726724 (A/G), rs67959715 (T/A), rs11871392 (T/G), rs2044070 (A/G), rs77612799 (T/C), rs6743702 (T/C), rs616870 (T/C), rs79590198 (A/G), rs75715199 (A/G), rs13087555 (T/C), rs4869618 (T/C), rs117397046 (A/G), rs8042817 (A/G), rs2258097 (T/C), rs2260882 (C/G), rs532996 (A/G), rs11747040 (T/C), rs10034039 (T/G), rs116909369 (A/G), rs79134986 (A/G), rs117615688 (T/C), rs8032253 (T/C), rs12818653 (T/A), rs4587884 (A/C), rs77122853 (T/C), rs117615061 (T/C), rs74682905 (A/G), rs2257468 (T/C), rs2032582 (T/G), rs2235015 (T/G), rs2729794 (T/C), rs77549514 (A/G), rs74790420 (A/C), rs73129579 (T/C), rs12913346 (A/C), rs117560908 (T/C), rs72747091 (A/G), rs2935751 (A/G), rs4331446 (A/G), rs7523266 (T/C), rs7648662 (T/C), rs117034065 (A/G), rs4836256 (T/C), rs80238698 (T/C), rs3730173 (T/C), rs11687884 (T/C), rs72693005 (T/C), rs2589476 (T/C), rs9813396 (T/C), rs10482667 (A/G), rs72784444 (A/G), rs75074511 (T/C), rs7951003 (A/G), rs79584784 (A/G), rs2214102 (T/C), rs28811003 (A/G), rs6100261 (A/T), rs77152456 (A/G), rs66624622 (T/G), rs140302965 (A/G), rs11653269 (T/C), rs74405057 (A/G), rs7121 (A/G), rs16977818 (A/C), rs12490095 (T/C), rs118003903 (A/G), rs62377761 (T/C), P1_M_061510_6_34_M (-/CACTTACCTTCTTTGTGCCACAGTTTCCCTATCTAAAACACAAGGTTATCAGTTATC AACATCTCTTGGGATTGTGAGGACTAAAGTAATGCACATAAAG), rs375115639 (-/AAATTACCCTGTTAGGTTTCAATGAAACACCTTTTCTCTTGTAACAAACATCTCCTCCA AGCTAGAATTTCAAAACAG), rs1002204 (A/C), rs10062367 (A/G), rs10482642 (A/G), rs10482658 (A/G), rs1053989 (A/C), rs10851628 (T/C), rs10947562 (T/C), rs11069612

(A/G), rs11071351 (T/C), rs11091175 (A/G), rs11638450 (T/C), rs11715827 (T/G), rs11745958 (T/C), rs11834041 (A/G), rs1202180 (T/C), rs12054781 (A/G), rs12539395 (A/G), rs12720066 (T/G), rs1279754 (A/C), rs12872047 (T/C), rs12876742 (A/C), rs12917505 (A/G), rs13066950 (T/G), rs13229143 (C/G), rs1383707 (T/C), rs1441824 (T/C), rs1652311 (A/G), rs17064 (T/A), rs17100236 (A/G), rs17149699 (A/G), rs1724386 (A/G), rs17250255 (A/G), rs17327624 (T/G), rs17616338 (A/G), rs17687796 (A/G), rs17740874 (T/C), rs17763104 (T/C), rs1880748 (T/C), rs1882478 (A/G), rs1944887 (T/C), rs2028629 (A/G), rs2143404 (A/G), rs2173530 (T/C), rs220806 (T/C), rs2235047 (A/C), rs2242071 (A/G), rs2257474 (T/C), rs2295583 (A/T), rs234629 (T/C), rs234630 (A/G), rs2436401 (A/G), rs258750 (T/C), rs2589487 (T/C), rs28364018 (T/G), rs28381774 (T/C), rs28381784 (A/G), rs2963155 (A/G), rs3133622 (T/G), rs32897 (T/C), rs33388 (A/T), rs3730168 (T/C), rs3735833 (T/G), rs3777747 (A/G), rs3786066 (T/C), rs3798346 (T/C), rs3822736 (A/G), rs389035 (T/C), rs3924144 (A/G), rs4148737 (T/C), rs4148749 (G/C), rs417968 (T/C), rs4458144 (T/C), rs4515335 (T/C), rs4728699 (A/G), rs4758040 (A/G), rs4812040 (A/G), rs4912650 (T/G), rs4957891 (T/C), rs5906392 (A/G), rs6026561 (T/C), rs6026565 (T/A), rs6026567 (A/G), rs6026593 (A/G), rs6092704 (T/G), rs6100260 (A/G), rs6128461 (T/C), rs6415328 (T/C), rs6610868 (T/C), rs6686061 (A/C), rs6730350 (T/G), rs6746197 (T/C), rs6963426 (T/C), rs7121326 (T/C), rs7721799 (A/G), rs7787082 (T/C), rs7799592 (A/C), rs796245 (T/C), rs809482 (A/C), rs8125112 (T/C), rs919196 (A/G), rs920750 (T/C), rs9332385 (A/G), rs930473 (T/G), rs9324921 (A/C), rs9348979 (A/G), rs9571939 (A/C), and rs9892359 (T/C); (b) at least one polymorphism genotype being in linkage disequilibrium with any one of the polymorphism genotypes of (a); or (c) a combination of (a) and (b). In one embodiment of this aspect, the method further comprises predicting the treatment response from the presence or absence of the polymorphism genotypes of (a), (b), or (c).

[010] In another aspect, the invention provides a method of treating a condition which is treatable by a CRHR1 antagonist in a subject in need thereof, comprising administering an effective amount of a CRHR1 antagonist to the subject, wherein the subject has been predicted to respond, or has an increased likelihood of responding, to treatment with a CRHR1 antagonist, as determined by the method of predicting a treatment response described above, wherein the CRHR1 antagonist is a compound of Formula I, as defined herein, or any one of “formulae I-VI” as disclosed at pages 2-6 and 12-48 of WO 2013/160317 (A2) (PCT/EP2013/058413). In another aspect, the invention provides a method of treating a condition which is treatable by a CRHR1 antagonist in a

subject in need thereof, comprising administering an effective amount of a CRHR1 antagonist to the subject, wherein at least one polymorphism genotype associated with a treatment response of the subject to treatment with a CRHR1 antagonist has been detected, as determined by the method for detecting a polymorphism genotype associated with a treatment response, wherein the CRHR1 antagonist is a compound of Formula I, as defined herein, or any one of "formulae I-VI" as disclosed at pages 2-6 and 12-48 of WO 2013/160317 (A2) (PCT/EP2013/058413). Likewise, a CRHR1 antagonist for use in treating a condition which is treatable by a CRHR1 antagonist in a subject in need thereof is provided, wherein the subject has been predicted to respond, or has an increased likelihood of responding, to treatment with a CRHR1 antagonist, as determined by the method of predicting a treatment response described above, wherein the CRHR1 antagonist is a compound of Formula I, as defined herein, or any one of "formulae I-VI" as disclosed at pages 2-6 and 12-48 of WO 2013/160317 (A2) (PCT/EP2013/058413). In an alternative aspect, the invention provides a method of treating a condition which is treatable by a CRHR1 antagonist in a subject in need thereof, comprising administering an effective amount of a CRHR1 antagonist to the subject, wherein the subject has been predicted to respond, or has an increased likelihood of responding, to treatment with a CRHR1 antagonist, as determined by the method of predicting a treatment response described above, wherein the CRHR1 antagonist is selected from the group consisting of a Type I CRHR1 antagonist, a bicyclic Type II CRHR1 antagonist, an atypical CRHR1 antagonist, a cyclohexyl amide CRHR1 antagonist. In another aspect, the invention provides a method of treating a condition which is treatable by a CRHR1 antagonist in a subject in need thereof, comprising administering an effective amount of a CRHR1 antagonist to the subject, wherein at least one polymorphism genotype associated with a treatment response of the subject to treatment with a CRHR1 antagonist has been detected, as determined by the method for detecting a polymorphism genotype associated with a treatment response, wherein the CRHR1 antagonist is selected from the group consisting of a Type I CRHR1 antagonist, a bicyclic Type II CRHR1 antagonist, an atypical CRHR1 antagonist, a cyclohexyl amide CRHR1 antagonist. Likewise, a CRHR1 antagonist for use in treating a condition which is treatable by a CRHR1 antagonist in a subject in need thereof is provided, wherein the subject has been predicted to respond, or has an increased likelihood of responding, to treatment with a CRHR1 antagonist, as determined by the method of predicting a treatment response described above, wherein the CRHR1 antagonist is selected from the group consisting of a Type I CRHR1 antagonist, a bicyclic

Type II CRHR1 antagonist, an atypical CRHR1 antagonist, a cyclohexyl amide CRHR1 antagonist.

[011] The above aspects of the invention can be put into practice in any one of the following embodiments.

[012] In one embodiment, providing a biological sample comprises extraction and/or purification of nucleic acids such as DNA or RNA, in particular genomic DNA from the subject's sample. In one embodiment, the detecting step can comprise amplification of nucleic acids extracted and/or purified from the sample obtained from the subject, and optionally clean-up of amplified products. The detecting step can further comprise fragmentation of amplified nucleic acids, or labelling of amplified nucleic acids.

[013] In one embodiment, the detecting step can comprise specific hybridization of at least one polynucleotide to a nucleic acid comprising at least one polymorphism genotype selected from the group disclosed in Table 2 herein. Hybridization can be achieved by mixing and heating the at least one polynucleotide and the sample nucleic acid to a temperature at which denaturation occurs, e.g., at about 90-95°C and subsequent incubation at a temperature at which hybridization occurs, e.g., at about 45-55°C in buffer conditions suitable for specific hybridization. In one embodiment the polynucleotide is labelled. The polynucleotide can be a primer or probe. Specifically, in some embodiments, the detecting step comprises a method selected from the group consisting of allele-specific oligonucleotide (ASO)-dot blot analysis, primer extension assays, iPLEX polymorphism / SNP genotyping, dynamic allele-specific hybridization (DASH) genotyping, the use of molecular beacons, tetra primer ARMS PCR, a flap endonuclease invader assay, an oligonucleotide ligase assay, PCR-single strand conformation polymorphism (SSCP) analysis, quantitative real-time PCR assay, polymorphism / SNP microarray based analysis, restriction enzyme fragment length polymorphism (RFLP) analysis, targeted resequencing analysis and/or whole genome sequencing analysis.

[014] In one embodiment, the predicting step comprises: (a) determining whether the subject will respond, or has an increased likelihood of responding to the treatment with a CRHR1 antagonist; and/or (b) determining whether the subject will not respond, or has a decreased likelihood of responding to the treatment with a CRHR1 antagonist. The determining step may further comprise, but is not limited to, one or more statistical analysis methods selected from the group consisting of artificial neural network learning, decision tree learning, decision tree forest learning, linear discriminant analysis, non-linear discriminant analysis, genetic expression programming, relevance vector machines, linear

models, generalized linear models, generalized estimating equations, generalized linear mixed models, the elastic net, the lasso support vector machine learning, Bayesian network learning, probabilistic neural network learning, clustering, and regression analysis. The predicting step may also comprise providing a value indicative of the subject being responsive, or having an increased likelihood of responding to the treatment with a CRHR1 antagonist; and/or providing a value indicative of the subject being non-responsive, or having a decreased likelihood of responding to the treatment with a CRHR1 antagonist.

[015] In one embodiment, the one or more polymorphism genotypes comprise at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least 15, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90, at least 100, at least 200, or all (a) polymorphism genotypes selected from the group consisting of the polymorphism genotypes disclosed in Table 2, (b) polymorphism genotypes being in linkage disequilibrium with the polymorphism genotypes disclosed in Table 2; or (c) a combination of (a) and (b).

[016] In a specific embodiment, the one or more polymorphism genotypes comprise (a) at least two polymorphism genotypes selected from the group consisting of the polymorphism genotypes disclosed in Table 2, (b) at least two polymorphism genotypes being in linkage disequilibrium with the polymorphism genotypes disclosed in Table 2; or (c) a combination of (a) and (b). Exemplary sets of at least two polymorphism genotypes useful in the methods of the invention are disclosed in Table 5. Therefore, the specific combinations of at least two polymorphism genotypes disclosed in Table 5 are used in specific embodiments of the invention, while further combinations of at least two polymorphism genotypes are expressly contemplated.

[017] In another specific embodiment, the one or more polymorphism genotypes comprise (a) at least four polymorphism genotypes selected from the group consisting of the polymorphism genotypes disclosed in Table 2, (b) at least four polymorphism genotypes being in linkage disequilibrium with the polymorphism genotypes disclosed in Table 2, or (c) a combination of (a) and (b). Exemplary sets of at least four polymorphism genotypes useful in the methods of the invention are disclosed in Table 6. Therefore, the specific combinations of at least four polymorphism genotypes disclosed in Table 6 are used in specific embodiments of the invention, while further combinations of at least four polymorphism genotypes are expressly contemplated.

[018] In another specific embodiment, the one or more polymorphism genotypes comprise (a) at least eight polymorphism genotypes selected from the group consisting of the polymorphism genotypes disclosed in Table 2, (b) at least eight polymorphism genotypes being in linkage disequilibrium with the polymorphism genotypes disclosed in Table 2, or (c) a combination of (a) and (b). Exemplary sets of at least eight polymorphism genotypes useful in the methods of the invention are shown in Table 7. Therefore, the specific combinations of at least eight polymorphism genotypes disclosed in Table 7 are used in specific embodiments of the invention, while further combinations are expressly contemplated.

[019] In another embodiment, the one or more polymorphism genotypes comprise (a) at least 16 polymorphism genotypes selected from the group consisting of the polymorphism genotypes disclosed in Table 2, (b) at least 16 polymorphism genotypes being in linkage disequilibrium with the polymorphism genotypes disclosed in Table 2, or (c) a combination of (a) and (b). In another embodiment, the one or more polymorphism genotypes comprise (a) at least 32 polymorphism genotypes selected from the group consisting of the polymorphism genotypes disclosed in Table 2, (b) at least 16 polymorphism genotypes being in linkage disequilibrium with the polymorphism genotypes disclosed in Table 2, or (c) a combination of (a) and (b). In another embodiment, the one or more polymorphism genotypes comprise at least 150 polymorphism genotypes selected from the group consisting of the polymorphism genotypes disclosed in Table 2, (b) at least 16 polymorphism genotypes being in linkage disequilibrium with the polymorphism genotypes disclosed in Table 2, or (c) a combination of (a) and (b). In another embodiment, the one or more polymorphism genotypes comprise all polymorphism genotypes disclosed in Table 2.

[020] In some embodiments, the method can include detecting the presence or absence of (a) one or more of the polymorphism genotypes disclosed in Tables 2, 5, 6, or 7, (b) one or more polymorphism genotypes being in linkage disequilibrium with the polymorphism genotypes disclosed in Tables 2, 5, 6, or 7, or (c) a combination of (a) and (b), predicting that the subject will respond, or is likely to respond to treatment with a CRHR1 antagonist and selecting a treatment with a CRHR1 agent for the subject. The method can further include administering the CRHR1 antagonist to the subject.

[021] In some embodiments, the predicting step can include creating a record indicating that the subject will respond, or is likely to respond to treatment with a CRHR1 antagonist. The record can be created on a computer readable medium.

[022] In some embodiments, the method can include detecting the presence or absence of (a) one or more of any of the polymorphism genotypes disclosed in Tables 2, 5, 6 or 7, (b) one or more polymorphism genotypes being in linkage disequilibrium with the polymorphism genotypes disclosed in Tables 2, 5, 6, or 7, or (c) a combination of (a) and (b), predicting that the subject will not respond, or is not likely to respond to a treatment with a CRHR1 antagonist and selecting a treatment with treatment with a non-CRHR1 antagonist for the subject. The method can further include administering the treatment with the non-CRHR1 antagonist to the subject.

[023] In some embodiments, the method can include creating a record indicating that the subject will not respond, or is not likely to respond to a treatment with a CRHR1 antagonist. The record can be created on a computer readable medium.

[024] In one embodiment, the subject is a mammal. Preferably, in all aspects of the invention, the subject is human.

[025] In one embodiment, the subject has a condition which is treatable by a treatment with a CRHR1 antagonist, as described herein. The condition can be characterized, caused or accompanied by CRH overproduction or over-activity. The condition can be characterized, caused or accompanied by ACTH overproduction or over-activity. The condition can be characterized, caused or accompanied by over-activity of the Hypothalamic–pituitary–adrenal (HPA) axis.

[026] In another embodiment, the subject has and/or the treatment is a treatment of a condition selected from the group consisting of anxiety symptoms, generalized anxiety disorder, panic, phobias, obsessive-compulsive disorder, post-traumatic stress disorder, sleep disorders such as insomnia, hypersomnia, narcolepsy, idiopathic hypersomnia, excessive amounts of sleepiness, lack of alertness, lack of attentiveness, absentmindedness and/or lack of or aversion to movement or exercise, sleep disorders induced by stress, pain perception such as fibromyalgia, mood disorders such as depressive symptoms, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression, dysthymia, bipolar disorders, cyclothymia, chronic fatigue syndrome, stress-induced headache, eating disorders such as anorexia and bulimia nervosa, hemorrhagic stress, stress-induced psychotic episodes, endocrine disorders involving ACTH overproduction, ACTH over-activity, e.g., adrenal disorders, including, but not limited to congenital adrenal hyperplasia (CAH), euthyroid sick syndrome, syndrome of inappropriate antidiarrhetic hormone (ADH), obesity, infertility,

head traumas, spinal cord trauma, ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia), excitotoxic neuronal damage, epilepsy, senile dementia of the Alzheimers type, multi-infarct dementia, amyotrophic lateral sclerosis, chemical dependencies and addictions (e.g., dependencies on alcohol, nicotine, cocaine, heroin, benzodiazepines, or other drugs), drug and alcohol withdrawal symptoms, hypertension, tachycardia, congestive heart failure, osteoporosis, premature birth, and hypoglycaemia, inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies, irritable bowel syndrome, Crohn's disease, spastic colon, post-operative ileus, ulcer, diarrhea, stress-induced fever, human immunodeficiency virus (HIV) infections, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease, gastrointestinal diseases, stroke, stress induced immune dysfunctions, muscular spasms, urinary incontinence.

[027] In a specific embodiment, the subject has and/or the treatment is a treatment of depressive symptoms, anxiety symptoms or both depressive symptoms and anxiety symptoms. In another specific embodiment, the subject has and/or the treatment is a treatment of depressive disorder, anxiety disorder or both depressive disorder and anxiety disorder. In another specific embodiment, the subject has and/or the treatment is a treatment of a sleep disorder.

[028] In contrast to the prior art, the present invention identifies sets of polymorphisms indicative of a clinical response in subjects which are in need of a treatment with a CRHR1 antagonist. Therefore, in all aspects of the invention, the treatment response to treatment with the CRHR1 antagonist is preferably a clinical response. Generally, the clinical response can be a prevention, alteration, alleviation or complete remission of a clinical parameter in any of the above conditions. In particular, the clinical response can be a prevention, alteration, alleviation or complete remission of depressive symptoms and/or anxiety symptoms, or a decrease in adverse effects resulting from the treatment.

[029] In some embodiments, the clinical response is a prevention, alteration, alleviation or complete remission of depressive symptoms, as determined using a scale selected from the group consisting of the Hamilton Depression Rating Scale (HAM-D), the Beck Depression Inventory (BDI), the Montgomery-Asberg Depression Scale (MADRS), the Geriatric Depression Scale (GDS), and/or the Zung Self-Rating Depression Scale (ZSRDS).

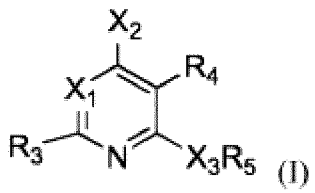
[030] In some embodiments, the clinical response is a prevention, alteration, alleviation or complete remission of anxiety symptoms, as determined using a scale selected from the group consisting of Hamilton Anxiety Rating Scale (HAM-A) and/or the State-Trait Anxiety Rating Scale (STAI).

[031] Any of the methods described herein can further include a step of prescribing a treatment with a CRHR1 antagonist or non-CRHR1 antagonist (the choice of which depends upon the outcome of the predictive methods described herein) for the subject.

[032] In all aspects, the sample obtained from the subject can comprise any type of cells containing nucleic acids from the subject, in particular genomic DNA. Specifically, the sample can be, e.g., a buccal sample, a blood sample, a tissue sample, a formalin-fixed, paraffin-embedded tissue sample, or a hair follicle. The sample obtained from the subject can comprise purified nucleic acids, such as purified genomic DNA.

[033] In any of the above aspects, a CRHR1 antagonist can be any compound capable of binding directly or indirectly to a CRHR1 so as to modulate any of its known biological activity receptor mediated activity, as is commonly known in the art. For instance, CRHR1 antagonists will specifically bind to CRHR1 with a K_D of 1 μM or less, preferably with a K_D of 100 nM or less and/or specifically inhibit CRH binding to CRHR1 *in vitro* with K_i values of 1 μM or less, preferably with K_i values of 100 nM or less. Alternatively or in addition, a CRHR1 antagonist will also inhibit cAMP accumulation and adrenocorticotropic hormone (ACTH) production *in vitro* and/or attenuate CRH and ACTH production *in vivo*.

[034] In some embodiments of any of the above aspects, the CRHR1 antagonist can be a compound of Formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

X_1 is $-CR_6$ or N;

X_2 is $-NR_1R_2$, $-CR_1R_2R_9$, $-C(=CR_2R_{10})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_{10}$, $-CHR_2SR_{10}$, $-C(S)R_2$ or $-C(O)R_2$;

X_3 is NH, O, S, -N(C_1-C_2 alkyl) or -C($R_{11}R_{12}$), wherein R_{11} and R_{12} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{11} and R_{12} is cyano and the other is hydrogen or methyl, or

X_3 is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5;

R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), - NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, C_1-C_{12} alkoxyalkyl, aryl or -(C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl;

3- to 8-membered cycloalkyl or -(C_1-C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl;

and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR_1R_2 or -$CR_1R_2R_9$ may form a saturated 5- to 8-membered ring which may optionally contain one or two carbon-carbon double bonds and/or in which one or two of the ring carbons may optionally be replaced by an oxygen, nitrogen or sulfur atom and which may be substituted with at least one substituent;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH, or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2OCF_3$, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), $-N(CH_3)_2$, $-NHCOCH_3$ $-NHCONHCH_3$, $-SO_n$(C_1- C_4 alkyl) wherein n is 0, 1 or 2, hydroxy, -CO(C_1-C_4 alkyl), -CHO, cyano or -COO(C_1-C_4 alkyl) wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and/or may optionally be substituted with one substituent selected from hydroxy, amino, $-NHCOCH_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each of the above groups R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, (C_1-C_6 alkyl)O(C_1-C_6)alkyl, $-NHCH_3$, $-N(CH_3)_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), $-SO_2NH$(C_1-C_4 alkyl), - SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), $-SO_2NH_2$, $-NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and SO_2(C_1-C_6 alkyl), and wherein the C_1-C_4 alkyl and the C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R_6 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C_1-C_4 alkyl), -C(O)(C_1-C_4 alkyl), -C(O)O(C1-C_4 alkyl), $-OCF_3$, CF_3, $-CH_2OH$, - CH_2OCH_3 or - $CH_2OCH_2CH_3$;

R_9 is hydrogen, hydroxy, fluoro, or methoxy;

R_{10} is hydrogen or C_1-C4 alkyl.

[035] Further, CRHR1 antagonists can encompass compounds of Formula (I) as defined above, wherein X_1 is $-CR_6$. Optionally, X_1 is $-CR_6$, wherein R_6 is hydrogen.

[036] In a further embodiment, the 5- to 8- membered ring formed by $-NR_1R_2$ or - $CR_1R_2R_9$ of the compound of Formula (I) as defined above is substituted with at least one substituent selected from C_1-C4 alkyl or with a 4-8 membered ring, which may be saturated or may contain one to three double bonds and in which one carbon atom may be replaced by CO or SO_2 and one to four carbon atoms may optionally be replaced by nitrogen.

[037] In a specific embodiment, X_2 of the compound of Formula (I) as defined above is $-NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

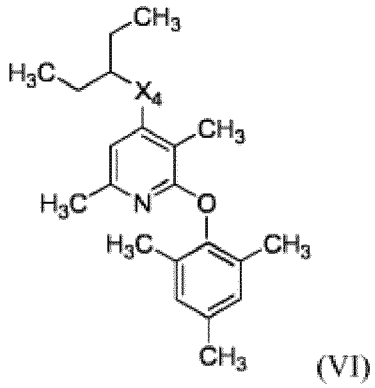
[038] Optionally, in the compounds of Formula (I) as defined above $-NHCHR_1R_2$ is $-NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$, $-NHCH(CH_2CH_2OCH_3)_2$ or $-NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, or $-NR_1R_2$ is $-N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), $-N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$, or $-OCHR_1R_2$ is $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$, $-OCH(CH_2CH_3)(CH_2OCH_3)$.

[039] In another embodiment, R_3 and R_4 of the compound of Formula (I) as defined above are methyl.

[040] In a further embodiment, X_3 of the compound of Formula (I) as defined above is O.

[041] In another embodiment, R_5 of the compound of Formula (I) as defined above is phenyl substituted with from one to three substituent(s) independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, CF_3.

[042] In a specific embodiment of any of the above aspects, the CRHR1 antagonist is a compound of the Formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein

X_4 is O or NH.

[043] In some embodiments of the methods of predicting, or the methods of detecting as described herein, the CRHR1 antagonist is a compound of Formulae I or VI, as defined above, or any one of "formulae I-VI" as disclosed at pages 2-6 and 12-48 of WO 2013/160317 (A2) (PCT/EP2013/058413) or a pharmaceutically acceptable salt thereof.

[044] In alternative embodiments of the methods of predicting, or the methods of detecting as described herein, the CRHR1 antagonist is selected from the group consisting

of GW876008 (Emicerfont), GSK-561679 (NBI-77860, Verucerfont), GSK586529, BMS-562,086 (Pexacerfont), NBI-30775 (R-121919), NBI-34101, CP-316,311, CP-376,395, PF-00572778, NVP-AAG561, Ono-2333MS, E2508, E2009, R317573 (JNJ19567470, CRA5626), R278995 (CRA0450), CRA-1000, CRA-1001, CP154,526, Antalarmin, DMP-695, DMP-696, DMP-904, SC-241, BMS-561388, NBI30545, PD-171729, NBI34041, NBI35965, SN003, NBI-27914, *trans*-2-chloro-N-(4-((5-fluoro-4-methyl-pyridin-2-ylamino)-methyl)-cyclohexyl)-5-(trifluoromethyl)-benzamide, SSR-125543, or a pharmaceutically acceptable salt thereof.

[045] In preferred embodiments of the methods of predicting, or the methods of detecting, as described herein, the CRHR1 antagonist is selected from the group consisting of BMS-562,086 (Pexacerfont), CP-316,311, Ono-2333MS, GW876008 (Emicerfont), GSK-561679 (NBI-77860, Verucerfont), NBI-30775 (R-121919), DMP-696, and SSR-125543, or a pharmaceutically acceptable salt thereof. In preferred embodiments of the methods of predicting, or the methods of detecting, as described herein, the CRHR1 antagonist is SSR-125543. In one embodiment of the method of treatment, the CRHR1 antagonist is not SSR-125543. In a preferred embodiment of all aspects, the CRHR1 antagonist is BMS-562,086 (Pexacerfont). In another preferred embodiment of all aspects, the CRHR1 antagonist is CP-316,311. In another preferred embodiment of all aspects, the CRHR1 antagonist is ONO-2333MS. In another preferred embodiment of all aspects, the CRHR1 antagonist is GW876008 (Emicerfont). In another preferred embodiment of all aspects, the CRHR1 antagonist is GSK-561679 (Verucerfont). In another preferred embodiment of all aspects, the CRHR1 antagonist is NBI-30775 (R121919). In another preferred embodiment of all aspects, the CRHR1 antagonist is DMP-696.

[046] In another aspect, the disclosure provides a composition comprising at least one polynucleotide capable of specifically hybridizing to nucleic acids comprising: (a) at least one polymorphism genotype selected from the group consisting of rs34169260 (A/G), rs796287 (A/C), rs56149945 (A/G), rs6190 (T/C), rs7179092 (T/C), rs7614867 (A/G), rs920640 (T/C), rs7167722 (T/C), rs920638 (T/C), rs7165629 (T/C), rs80049044 (T/A), rs16941058 (A/G), rs112015971 (A/G), rs10894873 (T/C), rs117455294 (T/G), rs1170303 (T/C), rs16940681 (C/G), rs968519 (T/C), rs28381866 (T/C), rs79320848 (T/G), rs114653646 (T/G), rs2589496 (T/C), rs10482650 (A/G), rs17614642 (A/G), rs73200317 (T/C), rs1380146 (T/A), rs735164 (T/C), rs730976 (T/G), rs55934524 (T/G), rs4570614 (A/G), rs4458044 (C/G), rs77850169 (A/G), rs35339359 (A/G), rs34800935 (T/C), rs72945439 (T/C), rs113959523 (A/G), rs116798177 (A/G), rs11247577 (T/G),

rs75869266 (T/C), rs74372553 (T/C), rs11691508 (A/G), rs6493965 (A/G), rs4869476 (T/C), rs3730170 (T/C), rs2145288 (A/C), rs2935752 (A/C), rs146512400 (A/G), rs62057097 (T/C), rs115061314 (T/C), rs34113594 (T/G), rs61751173 (A/G), rs74338736 (A/C), rs10851726 (T/C), rs4610906 (T/C), rs59485211 (T/C), rs7060015 (T/G), rs75710780 (T/G), rs6520908 (T/C), rs487011 (T/G), rs1383699 (A/C), rs67516871 (A/G), rs114106519 (T/C), rs7220091 (A/G), rs12489026 (A/G), rs876270 (T/C), rs4968161 (T/C), rs62056907 (A/G), rs2235013 (T/C), rs16878812 (A/G), rs6549407 (A/G), rs28381848 (A/G), rs79723704 (A/C), rs72814052 (A/G), rs10152908 (T/C), rs172769 (A/C), rs78596668 (T/C), rs73307922 (T/C), rs3842 (A/G), rs7210584 (A/C), rs62402121 (T/C), rs55709291 (A/G), rs72747088 (A/G), rs929610 (G/C), rs6766242 (T/C), rs1468552 (G/C), rs78838114 (T/C), rs62489862 (T/C), rs894342 (A/G), rs58882373 (T/C), rs3811939 (A/G), rs6984688 (T/G), rs1018160 (T/C), rs76602912 (A/G), rs80067508 (A/G), rs74888440 (T/C), rs12481583 (T/C), rs66794218 (A/G), rs16946701 (A/G), rs75726724 (A/G), rs67959715 (T/A), rs11871392 (T/G), rs2044070 (A/G), rs77612799 (T/C), rs6743702 (T/C), rs616870 (T/C), rs79590198 (A/G), rs75715199 (A/G), rs13087555 (T/C), rs4869618 (T/C), rs117397046 (A/G), rs8042817 (A/G), rs2258097 (T/C), rs2260882 (C/G), rs532996 (A/G), rs11747040 (T/C), rs10034039 (T/G), rs116909369 (A/G), rs79134986 (A/G), rs117615688 (T/C), rs8032253 (T/C), rs12818653 (T/A), rs4587884 (A/C), rs77122853 (T/C), rs117615061 (T/C), rs74682905 (A/G), rs2257468 (T/C), rs2032582 (T/G), rs2235015 (T/G), rs2729794 (T/C), rs77549514 (A/G), rs74790420 (A/C), rs73129579 (T/C), rs12913346 (A/C), rs117560908 (T/C), rs72747091 (A/G), rs2935751 (A/G), rs4331446 (A/G), rs7523266 (T/C), rs7648662 (T/C), rs117034065 (A/G), rs4836256 (T/C), rs80238698 (T/C), rs3730173 (T/C), rs11687884 (T/C), rs72693005 (T/C), rs2589476 (T/C), rs9813396 (T/C), rs10482667 (A/G), rs72784444 (A/G), rs75074511 (T/C), rs7951003 (A/G), rs79584784 (A/G), rs2214102 (T/C), rs28811003 (A/G), rs6100261 (A/T), rs77152456 (A/G), rs66624622 (T/G), rs140302965 (A/G), rs11653269 (T/C), rs74405057 (A/G), rs7121 (A/G), rs16977818 (A/C), rs12490095 (T/C), rs118003903 (A/G), rs62377761 (T/C), P1_M_061510_6_34_M (-/CACTTAC CTTCTTTGTGCCACAGTTTCCCTATCTAAAACACAAGGTTATCAGTTATCAACATCTCT TGGGATTGTGAGGACTAAAGTAATGCACATAAAG), rs375115639 (-/AAATTACCCTGTTAGGTTTCAATGAAACACCTTTTCTCTTGTAACAAACATCTCC TCCAAGCTAGAATTTCAAAACAG), rs1002204 (A/C), rs10062367 (A/G), rs10482642 (A/G), rs10482658 (A/G), rs1053989 (A/C), rs10851628 (T/C), rs10947562 (T/C),

rs11069612 (A/G), rs11071351 (T/C), rs11091175 (A/G), rs11638450 (T/C), rs11715827 (T/G), rs11745958 (T/C), rs11834041 (A/G), rs1202180 (T/C), rs12054781 (A/G), rs12539395 (A/G), rs12720066 (T/G), rs1279754 (A/C), rs12872047 (T/C), rs12876742 (A/C), rs12917505 (A/G), rs13066950 (T/G), rs13229143 (C/G), rs1383707 (T/C), rs1441824 (T/C), rs1652311 (A/G), rs17064 (T/A), rs17100236 (A/G), rs17149699 (A/G), rs1724386 (A/G), rs17250255 (A/G), rs17327624 (T/G), rs17616338 (A/G), rs17687796 (A/G), rs17740874 (T/C), rs17763104 (T/C), rs1880748 (T/C), rs1882478 (A/G), rs1944887 (T/C), rs2028629 (A/G), rs2143404 (A/G), rs2173530 (T/C), rs220806 (T/C), rs2235047 (A/C), rs2242071 (A/G), rs2257474 (T/C), rs2295583 (A/T), rs234629 (T/C), rs234630 (A/G), rs2436401 (A/G), rs258750 (T/C), rs2589487 (T/C), rs28364018 (T/G), rs28381774 (T/C), rs28381784 (A/G), rs2963155 (A/G), rs3133622 (T/G), rs32897 (T/C), rs33388 (A/T), rs3730168 (T/C), rs3735833 (T/G), rs3777747 (A/G), rs3786066 (T/C), rs3798346 (T/C), rs3822736 (A/G), rs389035 (T/C), rs3924144 (A/G), rs4148737 (T/C), rs4148749 (G/C), rs417968 (T/C), rs4458144 (T/C), rs4515335 (T/C), rs4728699 (A/G), rs4758040 (A/G), rs4812040 (A/G), rs4912650 (T/G), rs4957891 (T/C), rs5906392 (A/G), rs6026561 (T/C), rs6026565 (T/A), rs6026567 (A/G), rs6026593 (A/G), rs6092704 (T/G), rs6100260 (A/G), rs6128461 (T/C), rs6415328 (T/C), rs6610868 (T/C), rs6686061 (A/C), rs6730350 (T/G), rs6746197 (T/C), rs6963426 (T/C), rs7121326 (T/C), rs7721799 (A/G), rs7787082 (T/C), rs7799592 (A/C), rs796245 (T/C), rs809482 (A/C), rs8125112 (T/C), rs919196 (A/G), rs920750 (T/C), rs9332385 (A/G), rs930473 (T/G), rs9324921 (A/C), rs9348979 (A/G), rs9571939 (A/C), and rs9892359 (T/C), as disclosed in Table 2; (b) at least one polymorphism genotype being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or (c) a combination of (a) and (b). In one embodiment, the composition comprises less than 100,000, less than 90,000, less than 80,000, less than 70,000, less than 60,000, less than 50,000, less than 40,000, less than 30,000, less than 20,000, less than 15,000, less than 10,000, less than 5,000, less than 4,000, less than 3,000, less than 2,000, less than 1,500, less than 1,000, less than 750, less than 500, less than 200, less than 100, or less than 50 different polynucleotides in total. In some embodiments, the composition comprises at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least 10, at least 11, at least 12, at least 15, at least 20, or at least 30, or at least 50, or at least 100, or at least 200, or 274 polynucleotides capable of specifically hybridizing to nucleic acids comprising each of at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least 10, at least 11, at least 12, at least 15, at least 20, or at least

30, or at least 50, or at least 100, or at least 200, or 274 (a) polymorphism genotypes as disclosed in Table 2, (b) polymorphism genotypes being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or (c) a combination of (a) and (b).

[047] In a specific embodiment, the disclosure provides a composition containing at least two polynucleotides capable of specifically hybridizing to nucleic acids comprising (a) each of at least two polymorphism genotypes selected from the group consisting of the polymorphism genotypes as disclosed in Table 2, (b) each of at least two polymorphism genotypes being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or (c) a combination of (a) and (b). In another specific embodiment, the disclosure provides a composition containing at least four polynucleotides capable of specifically hybridizing to (a) each of at least four polymorphism genotypes selected from the group consisting of the polymorphism genotypes as disclosed in Table 2, (b) each of at least four polymorphism genotypes being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or (c) a combination of (a) and (b). In another specific embodiment, the disclosure provides a composition containing at least eight polynucleotides capable of specifically hybridizing to (a) each of at least eight polymorphism genotypes selected from the group consisting of the polymorphism genotypes as disclosed in Table 2, (b) each of at least eight polymorphism genotypes being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or (c) a combination of (a) and (b). In another specific embodiment, the disclosure provides a composition containing at least 16 polynucleotides capable of specifically hybridizing to each of at least 16 polymorphism genotypes selected from the group consisting of the polymorphism genotypes as disclosed in Table 2, (b) each of at least 16 polymorphism genotypes being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or (c) a combination of (a) and (b). In another specific embodiment, the disclosure provides a composition containing at least 32 polynucleotides capable of specifically hybridizing to (a) each of at least 32 polymorphism genotypes selected from the group consisting of the polymorphism genotypes as disclosed in Table 2, (b) each of at least 32 polymorphism genotypes being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or (c) a combination of (a) and (b). In another specific embodiment, the disclosure provides a composition containing at least 150 polynucleotides capable of specifically hybridizing to (a) each of at least 150 polymorphism genotypes selected from the group consisting of the polymorphism genotypes as disclosed in Table 2, (b) each of at least 150 polymorphism genotypes being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or (c) a combination of (a) and (b). In

another specific embodiment, the disclosure provides a composition containing 274 polynucleotides capable of specifically hybridizing to each of the 274 polymorphism genotypes as disclosed in Table 2.

[048] In some embodiments, the at least one polynucleotide capable of specifically hybridizing to the polymorphism genotypes is selected from the group consisting of the polynucleotides disclosed as “AlleleA Probe” in Table 2. In particular, the composition can comprise all of the polynucleotides disclosed as “AlleleA Probe” in Table 2.

[049] In any of the compositions described above, the at least one polynucleotide can be bound to a solid support. The solid support can be in the form of an array on a microarray chip, a particle (e.g., an encoded, magnetic, or magnetic and encoded particle), or any other solid support described herein.

[050] In yet another aspect, the disclosure provides a kit useful in determining the presence or absence of one or more polymorphism genotypes. The kit can include any of the compositions described above and, optionally, instructions for detecting one or more polymorphism genotypes. The kit can also include, e.g., one or more additional reagents for detecting the presence or absence of the one or more polymorphism genotypes described herein. For example, the kit can include primers (e.g., random hexamers or oligo(dT) primers), reverse transcriptase, a DNA polymerase (e.g., Taq polymerase), T4 polynucleotide kinase, one or more detectable labels (such as any described herein), or any other reagents described herein.

[051] In some embodiments, the compositions, kits or arrays described above contain less than 100,000 different polynucleotides. In some embodiments, the compositions, kits or arrays described above contain less than 90,000; less than 80,000; less than 70,000; less than 60,000; less than 50,000; less than 40,000; less than 30,000; less than 20,000; less than 15,000; less than 10,000; less than 5,000; less than 4,000; less than 3,000; less than 2,000; less than 1,500; less than 1,000; less than 750; less than 500, less than 200, less than 100, or less than 50 different polynucleotides.

[052] In yet another aspect, the disclosure provides a use of a composition, kit or array as described herein for predicting the treatment response of a subject to a treatment with a CRHR1 antagonist, wherein the composition, kit or array is used to detect the presence or absence of one or more polymorphism genotypes within a sample obtained from a subject. In some embodiments, the composition, kit or array is used in a method of predicting a treatment response of a subject to a treatment with a CRHR1 antagonist as

described herein. In some embodiments, the composition, kit or array is used in a method of detecting a polymorphism genotype associated with a treatment response of a subject to treatment with a CRHR1 antagonist as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[053] Figure 1 shows a time course curve of the clinical response of depressive patients as measured by the HAM-D scale upon treatment using placebo, or using an exemplary CRHR1 antagonist, wherein the surveyed subjects were predicted to positively respond to CRHR1 antagonist treatment using the method of prediction. The dashed line indicates a significant effect in treatment response at day 42 (p-value < 0.01).

DETAILED DESCRIPTION OF THE INVENTION

General definitions

[054] The term "comprise" or "comprising" as used herein is to be construed as “containing” or “including” and does generally not exclude other elements or steps, but encompasses the term "consisting of” as an optional, specific embodiment. Thus, a group defined as comprising a certain number of embodiments, is also to be construed as a disclosure of a group which optionally consists only of these embodiments. Where an indefinite or a definite article is used when referring to a singular noun such as "a" or "an" or "the", it includes a plural form of that noun unless specifically stated. *Vice versa*, when the plural form of a noun is used it refers also to the singular form. For example, when polymorphism genotypes are mentioned, this is also to be understood as a single polymorphism genotype.

[055] Furthermore, the terms “first”, “second”, “third” or “(a)”, “(b)”, “(c)” and the like in the description and in the claims are used for distinguishing between elements and not necessarily for describing a sequential or chronological order. It is to be understood that the terms so used can be interchangeable under appropriate circumstances and that the embodiments of the invention described herein are capable of operation in other sequences than described or illustrated herein.

[056] "Corticotropin releasing hormone” or "CRH" is used synonymously to the term "corticotropin releasing factor” or “CRF” herein, and refers to the known human 41 aa peptide or its mammalian homologues. The term "corticotropin releasing hormone receptor

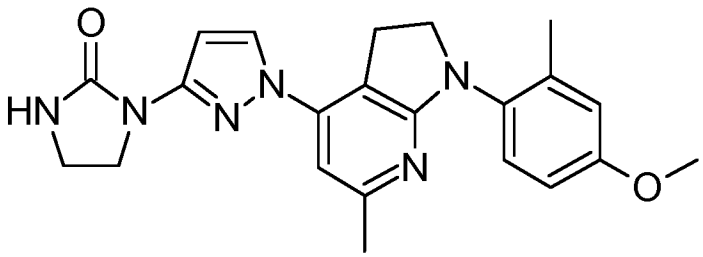
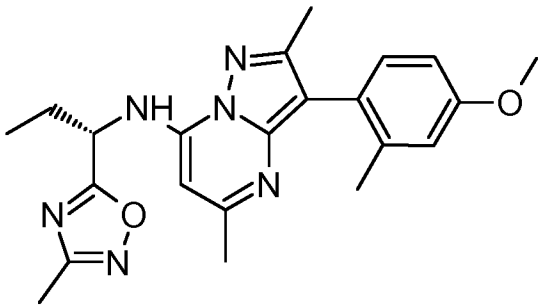
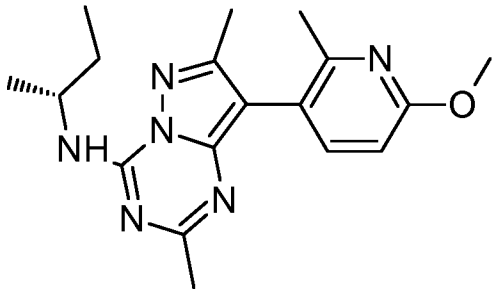
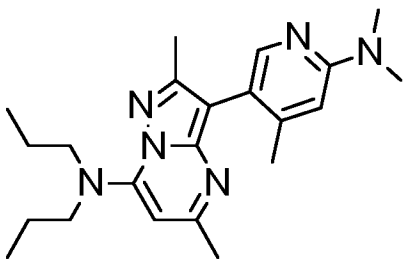
1" or "CRHR1" refers to the receptor which binds to CRH and is used synonymously to the term “corticotropin-releasing factor receptor 1”, or CRF-R1, or CRFR-1 herein.

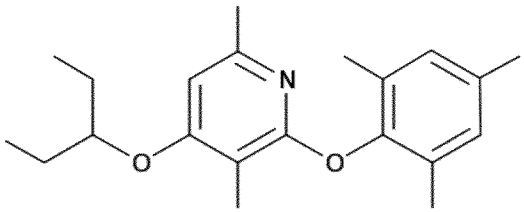
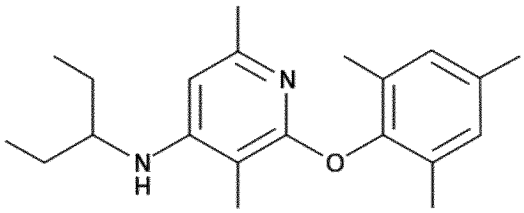
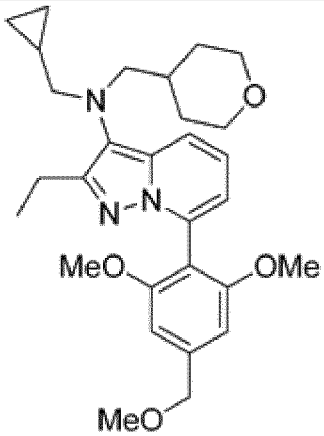
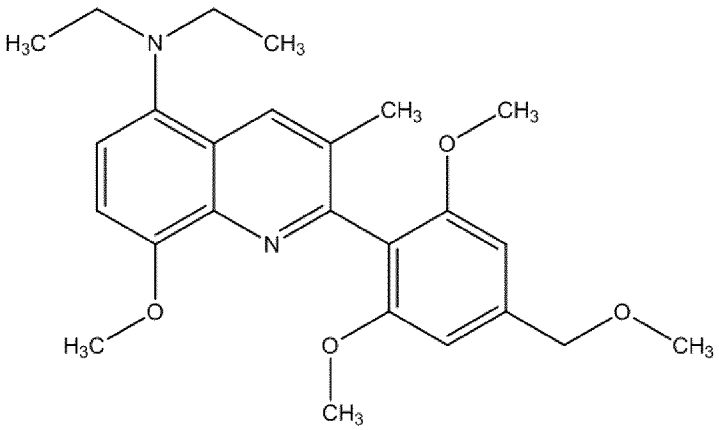
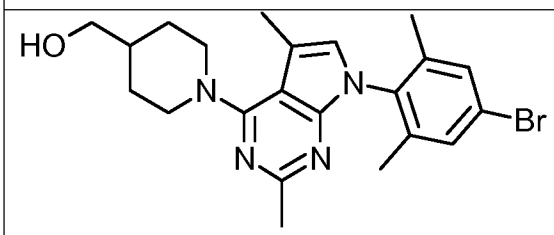
[057] A “CRHR1 antagonist”, as used herein, refers to a compound capable of binding directly or indirectly to CRHR1 so as to modulate the receptor mediated activity. The CRHR1 mediated activity may be exerted on a downstream target within the signalling pathway of CRHR1. A "downstream target" may refer to a molecule such as an endogenous molecule (e.g. peptide, protein, lipid, nucleic acid or oligonucleotide), that is regulated by CRHR1 directly or indirectly, comprising direct or indirect modulation of the activity and/or expression level and/or localization, degradation or stability of the downstream target. A CRHR1 antagonist can be tested by any *in vitro* or *in vivo* test known in the art to be indicative of CRHR1 inhibition. For instance, CRHR1 antagonists will specifically bind to CRHR1 with a K_D of 1 μM or less, preferably with a K_D of 100 nM or less and/or specifically inhibit CRH binding to CRHR1 *in vitro* with an IC_{50} value of 1 μM or less, preferably with IC_{50} value of 100 nM or less. Alternatively or in addition, a CRHR1 antagonist can inhibit cellular, CRHR1-mediated cAMP accumulation and/or attenuate CRH and ACTH production *in vivo*.

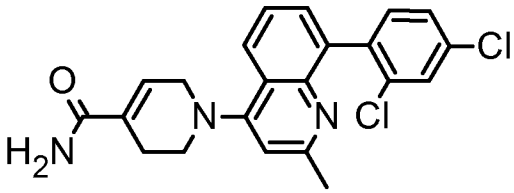
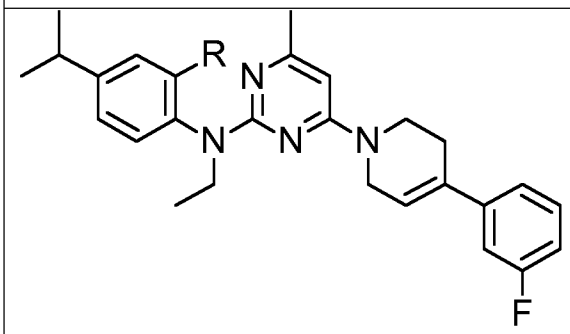
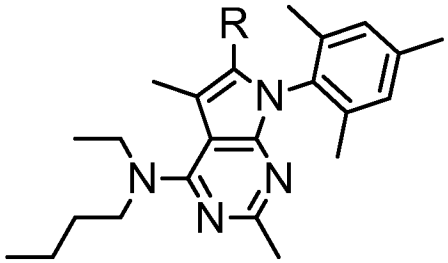
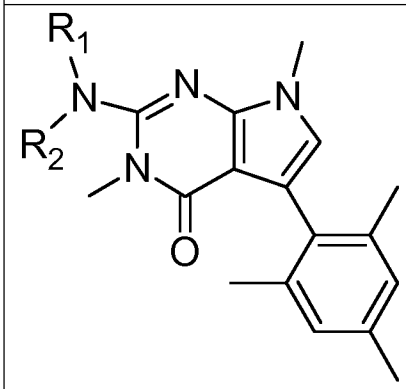
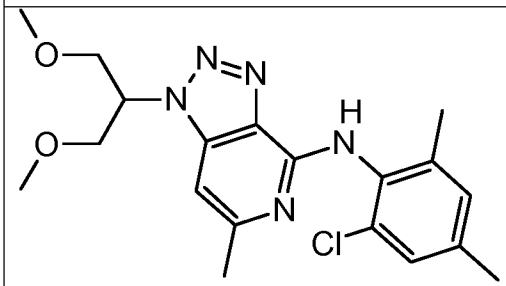
[058] Several groups of CRHR1 antagonists are well known in the literature and are disclosed in the patent literature, e.g., in WO 94/13676, EP 0 773 023, WO 2004/047866, WO 2004/094420, WO 98/03510, WO 97/029109, WO 2006/044958, WO 2001/005776 and WO 95/033750, WO 2009/008552, WO 2010/015655 all of which are herein incorporated by reference. Further exemplary groups of CRHR1 antagonists are reviewed and disclosed in the scientific literature, e.g., in Williams, Expert Opin Ther Pat. 2013; 23(8):1057-68 (in particular compounds 1-48 as disclosed therein); Zorilla and Koob, Drug Discovery Today, 2010, 371-383 (in particular Figure 1 and Tables 1-3 thereof); all of which are herein incorporated by reference in their entirety. Exemplary CRHR1 antagonist comprise, but are not limited to, GW876008 (Emicerfont), GSK-561679 (NBI-77860, Verucerfont), GSK586529, BMS-562,086 (Pexacerfont), NBI-30775 (R-121919), NBI-34101, CP-316,311, CP-376,395, PF-00572778, NVP-AAG561, Ono-2333MS, E2508, E2009, R317573 (JNJ19567470, CRA5626), R278995 (CRA0450), CRA-1000, CRA-1001, CP154,526, Antalarmin, DMP-695, DMP-696, DMP-904, SC-241, BMS-561388, NBI30545, PD-171729, NBI34041, NBI35965, SN003, NBI-27914, *trans*-2-chloro-N-(4-((5-fluoro-4-methyl-pyridin-2-ylamino)-methyl)-cyclohexyl)-5-(trifluoromethyl)-benzamide, SSR-125543. Ono-2333Ms, NBI-34101, PF-00572778, GSK-561579 and GSK586529 are described by Zorilla and Koob (Drug Discovery Today, 2010, 371-383) as corticotropin

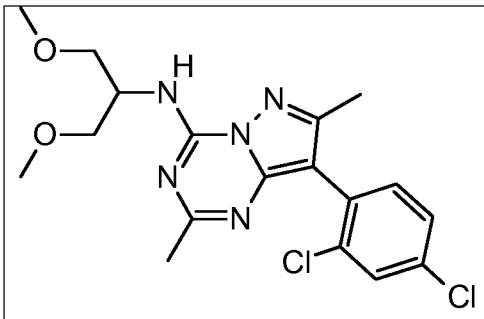
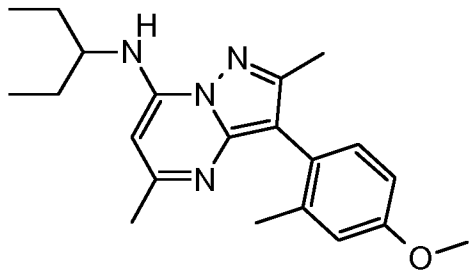
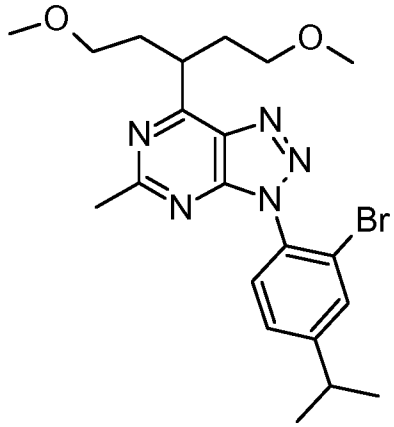
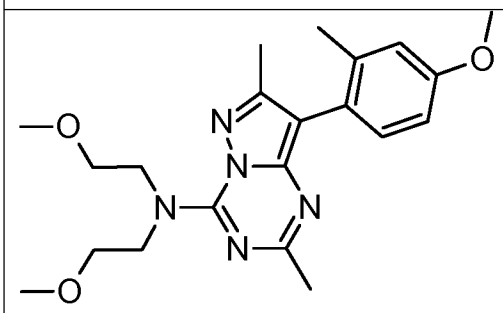
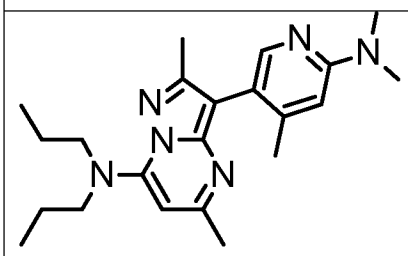
releasing factor receptor antagonists tested in clinical trials. Exemplary CRHR1 antagonists are depicted in Table 1.

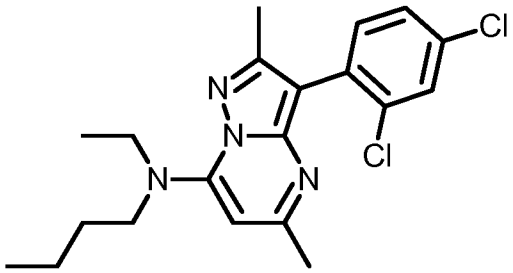
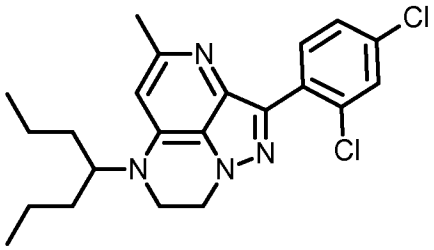
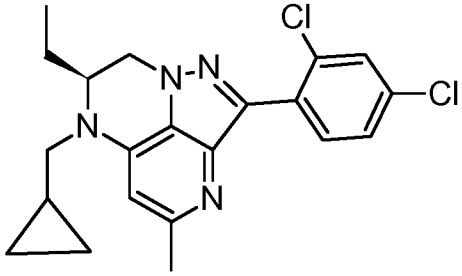
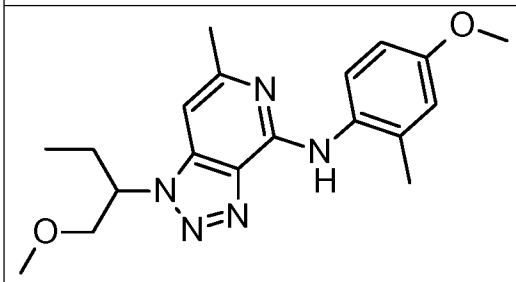
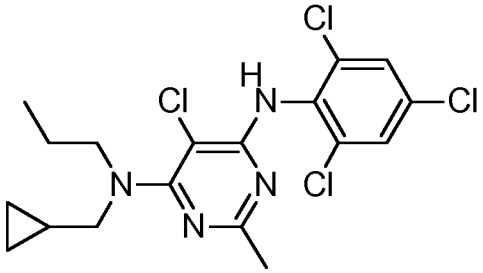
Table 1 – Exemplary CRHR1 antagonists

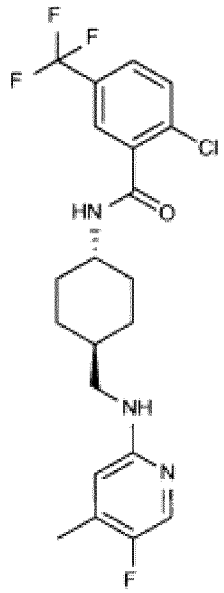
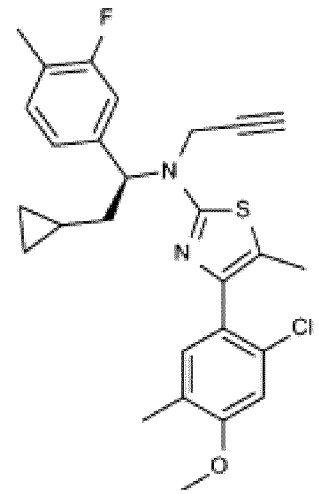
Structure	Name (synonym) / reference
	GW876008 (Emicerfont)
	GSK-561679 (NBI-77860, Verucerfont)
	BMS-562,086 (Pexacerfont)
	NBI-30775 (R-121919)

	CP-316,311
	CP-376,395
	E2508
	E2009 Terauchi et al., 244th ACS National Meeting, Aug. 19-23, 2012, Poster Presentation & Abstract, 2 pp.
	R317573 (JNJ19567470, CRA5626, TAI-041)

	R278995 (CRA0450)
	CRA-1000 (R = S-CH_3) CRA-1001 (R = Br)
	CP154,526 (R = H) Antalarmin (R = CH3)
	Compounds 16a-e K. Aso et al. / Bioorg. Med. Chem. Lett. 21 (2011) 2365–2371
	DMP-695

	DMP-696
	DMP-904
	SC-241
	BMS-561388
	NBI30545

	PD-171729
	NBI34041
	NBI35965
	SN003
	NBI-27914

	*trans*-2-chloro-N-(4-((5-fluoro-4-methyl-pyridin-2-ylamino)-methyl)-cyclohexyl)-5-(trifluoromethyl)-benzamide Compound 46 in Williams Expert Opin Ther Pat, 2013, 23(8):1057-68); WO 2010/015655
	SSR-125543

[059] Most of the non-peptidic CRHR1 antagonists can be described by a pharmacophore model comprising a lipophilic top group, a heterocyclic core containing an invariable hydrogen bond acceptor, which is almost always a heterocyclic nitrogen, and a lipophilic, usually aromatic, bottom group. The terms “Type I CRHR1 antagonist”, “Type II CRHR1 antagonist”, “monocyclic Type II CRHR1 antagonist”, “bicyclic Type II CRHR1 antagonist”, “atypical CRHR1 antagonist” or “cyclohexyl amide CRHR1 antagonist”, as used herein, is synonymous to “Type I CRF_1 antagonist”, “Type II CRF_1 antagonist”, “monocyclic Type II CRF_1 antagonist”, “bicyclic Type II CRF_1 antagonist”, “atypical CRF_1 antagonist” or “cyclohexyl amide CRF_1 antagonist”, respectively, referring to known and readily available compounds as defined in Williams, Expert Opin Ther Pat. 2013; 23(8):1057-68, incorporated herein by reference in its entirety. In specific embodiments,

Type I CRHR1 antagonists are compounds 1-33, monocyclic Type II CRHR1 antagonists are compounds 34-36, bicyclic Type II CRHR1 antagonists are compounds 37-41, atypical CRHR1 antagonists are compounds 42-45, or cyclohexyl amide CRHR1 antagonists are compounds 46-48, respectively, as disclosed in Figures 1-11 of Williams, Expert Opin Ther Pat. 2013; 23(8):1057-68, incorporated herein by reference in its entirety. Exemplary "Type I CRHR1 antagonists" may be characterized in that the heterocyclic hydrogen bond acceptor and the bottom group are connected by a two-atom linker as exemplified by CRHR1 antagonists R-121919, NBI-30545, CP-154526, DMP-696, pexacerfont (BMS-562086), emicerfont (GW876008), or verucerfont (GSK561679). Type II CRH1R antagonists may be characterized by a one-atom linker between hydrogen bond acceptor and the bottom group. Any pharmaceutically acceptable salt of a CRHR1 antagonist described herein is encompassed by the present disclosure.

Methods of predicting treatment response to CRHR1 treatment

[060] In one aspect, the present invention provides methods for predicting a treatment response of a subject (such as a human patient) to a treatment with a CRHR1 antagonist, which can include one or more CRHR1 antagonists. Thus, methods of the invention are useful in selecting appropriate therapeutic modalities (e.g., a treatment with a CRHR1 antagonist or a treatment with a non-CRHR1 antagonist) for subjects suffering from conditions generally treatable by a CRHR1 antagonist, for instance psychiatric disorders such as depressive symptoms or anxiety symptoms.

[061] Specifically, in this aspect, the method of the invention can be used for predicting a treatment response of a subject to treatment with a CRHR1 antagonist, the method comprising providing a biological sample obtained from the subject, detecting the presence or absence of one or more polymorphism genotypes in the biological sample, wherein the one or more polymorphism genotypes comprise: (a) at least one polymorphism genotype selected from the group consisting of the polymorphism genotypes disclosed in Table 2, (b) at least one polymorphism genotype being in linkage disequilibrium with any one of the polymorphism genotypes of (a); or (c) a combination of (a) and (b), and predicting the treatment response from the presence or absence of the one or more polymorphism genotypes of (a), (b), or (c).

[062] A "subject", as used herein, can generally be any mammal, in which one or more polymorphism genotypes as disclosed in Table 2 or polymorphism genotypes being in linkage disequilibrium with any one of the polymorphism genotypes of Table 2 are

conserved or homologous. In particular, the term “subject” includes a human subject, and any model organism such as mice, rats, cats, dogs, simians, cattle. Preferably, the subject is a human subject.

[063] A “treatment with a CRHR1 antagonist”, as used herein, refers to the treatment of a condition in the subject which can be treated by administration of a CRHR1 antagonist, as is made plausible herein or in the prior art. “Conditions treatable with a CRHR1 antagonist”, as used herein, are conditions which can generally be treated by administration of a CRHR1 antagonist and/or are commonly characterized, caused or accompanied by CRH over-activity, by ACTH over-activity and/or by over-activity of the Hypothalamic–pituitary–adrenal (HPA) axis.

[064] The term "CRH over-activity" is used herein synonymously to the terms "CRH system over-activity", "CRH hyperactivity", "CRH hyperdrive" or "central CRH hyperdrive". An indication for CRH over-activity may be an increase in activity or concentration of CRH or of one or several molecules downstream of the CRHR1 receptor, that are activated or whose concentration is increased based on the activation of CRHR1 receptor upon CRH binding, for instance, but not being limited to, ACTH. A further indication for CRH over-activity may be a decrease in activity or concentration of one or several molecules downstream of the CRHR1 receptor, that are inactivated or whose concentration is decreased resulting from the activation of CRHR1 receptor upon CRH binding. For instance, the concentrations or activities of adrenocorticotrophin (ACTH) and/or cortisol can be used for determining a value indicative for CRH over-activity. The CRH over-activity in each patient may be determined by a CRH test as described in Holsboer *et al.,* N Engl J Med. 1984;311(17):1127, or by a combined dexamethasone suppression/CRH stimulation test (dex/CRH test) as described in Heuser *et al.*, J Psychiatr Res 1994, 28(4):341-56; both incorporated herein by reference in their entirety.

[065] In particular, conditions which can be treated using a CRHR1 antagonist in a subject comprise, but are not limited to, behavioural disorders, neuropsychiatric disorders, mood disorders, neurological disorders, neurodegenerative disorders, endocrine disorders, inflammatory or stress-induced immune disorders, CRH-related cardiovascular diseases or metabolic diseases. Specifically, such conditions comprise anxiety symptoms, generalized anxiety disorder, panic, phobias, obsessive-compulsive disorder, post-traumatic stress disorder, sleep disorders such as insomnia, hypersomnia, narcolepsy, idiopathic hypersomnia, excessive amounts of sleepiness, lack of alertness, lack of attentiveness, absentmindedness and/or lack of or aversion to movement or exercise,

sleep disorders induced by stress, pain perception such as fibromyalgia, mood disorders such as depressive symptoms, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression, dysthymia, bipolar disorders, cyclothymia, chronic fatigue syndrome, stress-induced headache, eating disorders such as anorexia and bulimia nervosa, hemorrhagic stress, stress-induced psychotic episodes, endocrine disorders involving ACTH overproduction, ACTH over-activity, e.g., adrenal disorders, including, but not limited to congenital adrenal hyperplasia (CAH), euthyroid sick syndrome, syndrome of inappropriate antidiarrhetic hormone (ADH), obesity, infertility, head traumas, spinal cord trauma, ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia), excitotoxic neuronal damage, epilepsy, senile dementia of the Alzheimers type, multi-infarct dementia, amyotrophic lateral sclerosis, chemical dependencies and addictions (e.g., dependencies on alcohol, nicotine, cocaine, heroin, benzodiazepines, or other drugs), drug and alcohol withdrawal symptoms, hypertension, tachycardia, congestive heart failure, osteoporosis, premature birth, and hypoglycaemia, inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies, irritable bowel syndrome, Crohn's disease, spastic colon, post-operative ileus, ulcer, diarrhea, stress-induced fever, human immunodeficiency virus (HIV) infections, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease, gastrointestinal diseases, stroke, stress induced immune dysfunctions, muscular spasms, urinary incontinence. In a specific embodiment, the subject has and/or the treatment is a treatment of depressive symptoms, anxiety symptoms or both depressive symptoms and anxiety symptoms. The depressive and/or anxiety symptoms can be symptoms of a depressive disorder, an anxiety disorder or both a depressive disorder and anxiety disorder. In another specific embodiment, the subject has and/or the treatment is a treatment of a sleep disorder.

[066] A “treatment response”, as used herein, generally refers to any measurable response specific for the treatment with one or more CRHR1 antagonist and/or the condition being treated, during and/or shortly after treatment as compared to before said treatment. Generally, the treatment response can be a biological response or a clinical response. A biological response would include, for example, any alteration in CRH over-activity, as defined above.

[067] Preferably, according to the invention, the treatment response is a clinical treatment response. A “clinical treatment response”, as used herein, refers to a prevention,

alteration, alleviation or complete remission, as measured by the alteration in severity and/or frequency of relapse of individual symptoms and/or the mean change on a diagnostic marker or scale of any type commonly used in assessing clinical responses in the conditions described herein, see, for instance, Harrison's Principles of Internal Medicine, 18th ed. / editors Longo *et al.,* Mcgraw-Hill Publ. Comp, NY, US (2011), as incorporated herein by reference in its entirety. A clinical treatment response can also include an alteration, increase or decrease in adverse effects resulting from the treatment with a CRHR1 antagonist. Predicting a clinical response, or lack thereof, is expressly distinguished from predicting merely biological responses, since a clinical response is to be seen as target variable directly linked to treatment success, or failure, respectively. Therefore, while biological responses can also be predicted by the methods described herein, the methods of the invention are particularly suited for predicting a clinical response, as defined above.

[068] In preferred embodiments, the clinical response can be a prevention, alteration, alleviation or complete remission of depressive symptoms and/or anxiety symptoms. In preferred embodiments, the clinical response can be a prevention, alteration, alleviation or complete remission of a sleep disorder. Depressive symptoms comprise, but are not limited to, low mood, low self-esteem, loss of interest or pleasure, psychosis, poor concentration and memory, social isolation, psychomotor agitation/retardation, thoughts of death or suicide, significant weight change (loss/gain), fatigue, and feeling of worthlessness. The depressive symptoms can last for weeks to lifelong with periodic reoccurring depressive episodes. For the diagnosis of the depression mode (e.g. moderate or severe depression) the Hamilton Depression Rating Scale (HAM-D) (Hamilton, J Neurol Neurosurg Psychiatry, 1960) may be used. In addition or alternatively, the depression mode may be also rated by alternative scales as the Beck Depression Inventory (BDI), the Montgomery-Asberg Depression Scale (MADRS), the Geriatric Depression Scale (GDS), and/or the Zung Self-Rating Depression Scale (ZSRDS). Therefore, in some embodiments, the clinical response is a prevention, alteration, alleviation or complete remission of depressive symptoms as determined using a scale selected from the group consisting of HAM-D, BDI, MADRS, GDS, ZSRDS.

[069] Anxiety symptoms comprise, but are not limited to, panic disorders, generalized anxiety disorder, phobias and posttraumatic stress disorder, avoidance behavior which may lead to social isolation, physical ailments like tachycardia, dizziness and sweating, mental apprehension, stress and/or tensions. The severity of anxiety

symptoms ranges from nervousness and discomfort to panic and terror in subjects. Anxiety symptoms may persist for several days, weeks, or even months and years, if not suitably treated. The severity of anxiety symptoms may be measured by the Hamilton Anxiety Rating Scale (HAM-A) and/or the State-Trait Anxiety Rating Scale (STAI). Therefore, in some embodiments, the clinical response is a prevention, alteration, alleviation or complete remission of anxiety symptoms as determined using a scale selected from the group consisting of HAM-A and STAI. Sleep disorders comprise, but are not limited to, insomnia, hypersomnia, narcolepsy, idiopathic hypersomnia, excessive amounts of sleepiness, lack of alertness, lack of attentiveness, absentmindedness and/or lack of or aversion to movement or exercise, sleep disorders induced by stress.

[070] “Alteration”, as used herein, refers to any change in a clinical response as defined above. “Alleviation”, as used herein, refers to any amelioration in a clinical response, including partial amelioration of one or more symptoms, temporary disappearance of one or more symptoms, wherein relapse is not excluded, as well as complete remission of one or more symptoms. “Complete remission” refers to disappearance of all manifestations and symptoms of a disease to be treated, as described herein.

[071] The present disclosure identifies sets of polymorphism genotypes that are predictive for the treatment response of a subject to treatment with a CRHR1 antagonist. Thus, the presence of one or more of these polymorphism genotypes can be used to predict the likelihood of responding or not responding to treatment with a CRHR1 antagonist in a subject.

[072] The term "polymorphism", as used herein, refers to a sequential variation of a genomic allele at the same locus within a population of subjects and having a certain frequency in the population, including deletions / insertions (designated “[-/I]” herein), point mutations and translocations. The term “polymorphism”, as used herein, in particular includes, but is not limited to, single nucleotide polymorphisms (SNPs). For instance, as used herein, the term “polymorphism” can also include polymorphic deletions, or insertions, respectively, of more than one nucleotide. The term "single nucleotide polymorphism" or “SNP” is well understood by the skilled person and refers to a point mutation of a genomic allele at the same locus within a population of subjects and having a certain frequency in a population. The term “genotype”, as used herein, encompasses one or both genomic alleles at the same locus of a subject. The term “polymorphism genotype” or “SNP genotype”, as used herein, refers to the presence of a polymorphism or SNP

within the genotype of a subject, either in one or both genomic alleles at the same locus. The allele being present in the majority of the population, is also referred to herein as wild-type allele or major allele. As used herein, this state is defined as the "absence of one or more polymorphism genotypes". The nucleotide being present in the minority of the population is also referred to herein as the variation, point mutation, mutated nucleotide or minor allele. As used herein this state is defined as "presence of one or more polymorphism genotype". For instance, P_ID 1 as identified in Table 2 below, (rs34169260, TOP, [A/G]) exhibits a variation to nucleotide G instead of the wild-type nucleotide A. Typically, a polymorphism or SNP genotype occurs in a certain percentage of a population, for example in at least 5 % or at least 10% of a population. In other words, the minor allele frequency (MAF) is equal or higher than about 0.05 or about 0.10 (MAF > 0.05 or MAF > 0.10).

[073] Theoretically, a wild-type allele could be mutated to three alternative nucleotides. However, a mutation to a first nucleotide within germline cells of an individual which persists within a population occurs very rarely. The chance of the same nucleotide being mutated to yet another nucleotide and again persisting within a population is virtually non-existent and can be therefore neglected. Therefore, as used herein, a certain nucleotide position in the genome of an individual can only have the above two states, namely the wild-type state (absence of a polymorphism genotype from both alleles of a single subject) and the mutated state (presence of a polymorphism genotype in one or both alleles of a single subject). The presence of a polymorphism genotype in both alleles may have a higher predictive value than the presence of a polymorphism genotype in one allele only, the other allele comprising a wild-type genotype. The presence or absence of a polymorphism genotype on one or two alleles may be associated with an algorithm for predicting the treatment response to CRHR1 antagonists as described herein.

[074] Sets of polymorphism genotypes useful in methods for predicting a treatment response are disclosed in Table 2. Table 2 provides a consecutively numbered identifier (P_ID) for internal reference, an rs-identifier (rs_ID), as commonly known in polymorphism databases such as NCBI's dbSNP, the polymorphism (P, indicated in bold and defined as [wild-type / variation]), the strand designation (Str, see, e.g., Illumina Inc. *"TOP/BOT" Strand and "A/B" Allele - A guide to Illumina's method for determining Strand and Allele for the GoldenGate® and Infinium™ Assays"*, Technical Note, © 2006; http://www.illumina.com/documents/products/technotes/technote_topbot.pdf; incorporated by reference herein in its entirety), specific probe sequences for the respective allele in

humans (AlleleA Probe, see also SEQ ID NOs: 275-548), a human chromosomal identifier (Chr), and a reference to the sequence of the genomic flanking sequence in humans (TopGenomicSequence), as disclosed in SEQ ID NOs: 1-274. A person skilled in the art is able to derive the exact position and polymorphism genotype sequence from the rs-nomenclature identified in Table 2 from suitable database entries and associated information systems, e.g. the NCBI's Single Nucleotide Polymorphism database (dbSNP; http://www.ncbi.nlm.nih.gov/SNP/), even where the nomenclature, or the surrounding sequence elements were subject to alterations over time.

Table 2 – Polymorphism genotypes as used herein

P_ID	rs_ID	Str	P	AlleleA Probe	Chr	TopGenomic Sequence
1	rs34169260	TOP	**[A/G]**	AGGACTCTATGGCTTCCTTCATGTCATCGTCCA CTCTGCCAAGGGATTTA	17	SEQ ID NO: 1
2	rs796287	TOP	**[A/C]**	ACGACAGAGATGAATTGAGGGGACAAATGTCAG AGCTCACAGACGACTGT	2	SEQ ID NO: 2
3	rs56149945	TOP	**[A/G]**	TCAGAAGCCTATTTTTAATGTCATTCCACCAAT TCCCGTTGGTTCCGAAA	5	SEQ ID NO: 3
4	rs6190	BOT	**[T/C]**	TCACAGTAGCTCCTCCTCTTAGGGTTTTATAGA AGTCCATCACATCTCCC	5	SEQ ID NO: 4
5	rs7179092	BOT	**[T/C]**	TTGCATTCTCTCCTAGCACTCCAGTAAATAAAC TATAGTCCTGGTCAAGT	15	SEQ ID NO: 5
6	rs7614867	TOP	**[A/G]**	ATTCCCAATATTCGTATATGTATTTATAAATTA CATAATGGGCAGGGTGC	3	SEQ ID NO: 6
7	rs920640	BOT	**[T/C]**	AGTGCTTTTTGAGAGGTATGAACTTACTCCATA CTACTTACATCTGCTAA	15	SEQ ID NO: 7
8	rs7167722	BOT	**[T/C]**	TGACTTCTAATTACAGGCAAAATCAACCTTAAT AAGAACAGGCGTTACTA	15	SEQ ID NO: 8
9	rs920638	BOT	**[T/C]**	TACTATTCTGTTCATAAGGTACACTTCTTTTTA GGGCACACTACCTTGGG	15	SEQ ID NO: 9
10	rs7165629	BOT	**[T/C]**	AGGTGGGATAAACAGAAGCAGCATAACGTGTCT TGATGTGTGCTGTTTAG	15	SEQ ID NO: 10
11	rs80049044	BOT	**[T/A]**	TTGTCATGCAGCAGGTTAACTATGCTTTCTGGA GAAGGTGTCAGCCAACT	4	SEQ ID NO: 11
12	rs16941058	TOP	**[A/G]**	CCCTCCAGCTGAATGATTTTTGTCTGTGCCTGG CCCAGTCCCTGAGTCCA	17	SEQ ID NO: 12
13	rs112015971	TOP	**[A/G]**	GTGAAAATGCATTTTCCCCCTATTCCTTCTGGA AAGCAACATTAGGGTCC	20	SEQ ID NO: 13
14	rs10894873	BOT	**[T/C]**	TGCTCACCACAGTCCTCATATCCTTAAAGGGAC ACCCTAGTGATTACTGA	11	SEQ ID NO: 14
15	rs117455294	BOT	**[T/G]**	CAGTCCCGCCTGCTTGGATCTGACGAGCGTGCC GATTCGGTCCGAAAATC	20	SEQ ID NO: 15
16	rs1170303	BOT	**[T/C]**	AGAGCACTAACTCTGGAGAGTAAGGATCTGAGT GTAAGTCACCGCTGTGT	4	SEQ ID NO: 16
17	rs16940681	TOP	**[C/G]**	AAGCAGTCCACAGCAGTCTGAGCTGGCAGGTCA TGGAGCAGCCCCCAAAC	17	SEQ ID NO: 17
18	rs968519	BOT	**[T/C]**	GTAAAGAACAGGGGGAGATAATGATCAGTAAAA TCACAGCAGGGTGAGGG	20	SEQ ID NO: 18

19	rs28381866	BOT	**[T/C]**	TATTTAGGTAGTTGACCACTTCAGCATTCTAGGTACAATAACGTTAGCCC	7	SEQ ID NO: 19
20	rs79320848	BOT	**[T/G]**	AGAACAAAGCCAGGACAAGGTACAAGGTGACCCCAGCAAATTTCCTTTTC	20	SEQ ID NO: 20
21	rs114653646	BOT	**[T/G]**	TGCTAGAAGCTTATCAACTGCATTAATCTTTTTAAAAACACTTTTAGTTT	7	SEQ ID NO: 21
22	rs2589496	BOT	**[T/C]**	TCTCACCTTCTCCAGGTGCACGGTAGGTGCTGTGTAAATTAACGACTTCA	17	SEQ ID NO: 22
23	rs10482650	TOP	**[A/G]**	GCCTCCTGCTAGACAATTAGCTTTATCCATGAGTTACCAAAGAGGGAGCC	5	SEQ ID NO: 23
24	rs17614642	TOP	**[A/G]**	ACCAAAATCTATAAACAATAAGGAACTGTGGTTGTTTGCTGCAAATAACT	6	SEQ ID NO: 24
25	rs73200317	BOT	**[T/C]**	TCAAGAGTTGGGAATGATGAGGGCATGTACTGTGACTGGCACACAGAATG	7	SEQ ID NO: 25
26	rs1380146	BOT	**[T/A]**	AGTGCCTACTATGTGCTAGTCCCTAGTGACATGAGAGTGAGGAAGGCAGT	12	SEQ ID NO: 26
27	rs735164	BOT	**[T/C]**	CCTTATTTCAAGGTCGGGGTCAAGGTGGTCAAAAGAACTGTTTTGCTCTC	16	SEQ ID NO: 27
28	rs730976	BOT	**[T/G]**	AAGGGTATTTATACCTTTGCCTTTCCGCCTCAACCATTGGAACCTGGGAC	5	SEQ ID NO: 28
29	rs55934524	BOT	**[T/G]**	AGCCTCTCTGGGTCCTTGGGGAGCATGAGGATCCTGCAGAAAGCAGAGTG	17	SEQ ID NO: 29
30	rs4570614	TOP	**[A/G]**	ATGCTCTCTGAACACTATGACCTCTGATTATTTATCAACCTCCAAGAGCT	11	SEQ ID NO: 30
31	rs4458044	TOP	**[C/G]**	CCCCTCTTCTGTGAGAGCCAAACAGAGCCCTTCCTGAGTCCCATCCATTC	17	SEQ ID NO: 31
32	rs77850169	TOP	**[A/G]**	TCTGGGTCCTTTTCATTGCTCTACAAAGAATCCTTTCTTCCTCCCAGGCC	17	SEQ ID NO: 32
33	rs35339359	TOP	**[A/G]**	CATCAATGCCCACGCTACACGAGGCATACTAGACAGTCGCTGCCTAAGCC	17	SEQ ID NO: 33
34	rs34800935	BOT	**[T/C]**	TCAAGAGTAACAGTATGCCCTGCATTAACAGGGATAATATATAAGAAAAA	7	SEQ ID NO: 34
35	rs72945439	BOT	**[T/C]**	GAATTTATTACTCCTGGGAGGATTCTGCTCACCACTGGCAACTATGACCA	2	SEQ ID NO: 35
36	rs113959523	TOP	**[A/G]**	CATCATGATGTAATGTAGTCATATAGACTAGGACACTTAGATTAGCCCCC	20	SEQ ID NO: 36
37	rs116798177	TOP	**[A/G]**	GGTTTTAGTATTGCAATGTGGAATCCAAAACTGTTATCAATGAACTTTTG	5	SEQ ID NO: 37
38	rs11247577	BOT	**[T/G]**	TGGGTGAGGGAACCGTTAGTGCCATCCTGAGGCCCCGTGTCAGGAAATAT	17	SEQ ID NO: 38
39	rs75869266	BOT	**[T/C]**	ACTGAACTCCCCATCACAAATCTGTATGCTTTATTAGAAAGTAAAACTCT	15	SEQ ID NO: 39
40	rs74372553	BOT	**[T/C]**	AGTAAAACAGACGACGGGATCCCCAGACGCTGCACATCAGCACCAGGAGC	17	SEQ ID NO: 40
41	rs11691508	TOP	**[A/G]**	CACACTAATATTCAAACATCCTTGACCTCATCTCATATAAATAAATCCAA	2	SEQ ID NO: 41
42	rs6493965	TOP	**[A/G]**	CCAAGATTCTGGATGTCTTTAAGGTAACAAGTGTCCATGTTGTTCCTTGA	15	SEQ ID NO: 42
43	rs4869476	BOT	**[T/C]**	GAAGCGAAAATAGCTATGCACCAAATCTCTGCAGGCATTTCATTGAGTAC	5	SEQ ID NO: 43
44	rs3730170	BOT	**[T/C]**	TGAATGACAGTGTTGTTGATTAGTTCAAGCTCTTGCCTTTCTCTAAACTT	20	SEQ ID NO: 44
45	rs2145288	TOP	**[A/C]**	GATCTTAGCCAAGGCAGGAAAGCACACGATCAGGTAACCTCCAGATTCAC	20	SEQ ID NO: 45
46	rs2935752	TOP	**[A/C]**	TTACTCGCATTAACTCTTTCAATTTCACAACAAATCTAAGAAAAATGCAA	8	SEQ ID NO: 46

47	rs146512400	TOP	**[A/G]**	AGTCTAAAACACTATCATCTCCTCCTGGATTACTGCAACAGACTCCTTCT	7	SEQ ID NO: 47
48	rs62057097	BOT	**[T/C]**	TCTGCCCTAAATATTCCCTGTTCGGTGGGGTTTGGCGGTCCAGCAGCCCT	17	SEQ ID NO: 48
49	rs115061314	BOT	**[T/C]**	CCATGCGTGTTGGAAGTATTTCTCTTGTTCTCCTGCTTTTAGAAAGCCAT	6	SEQ ID NO: 49
50	rs34113594	BOT	**[T/G]**	CTTCTGACCCTCGCCGTCCTAGAACCAACGGCCCCTCGGTGTCTGGTCCT	17	SEQ ID NO: 50
51	rs61751173	TOP	**[A/G]**	AAAGCTCTAATACCACCTAAAACCATTTCTGTTCTCTACCTCTGTCATTA	5	SEQ ID NO: 51
52	rs74338736	TOP	**[A/C]**	ACAGGTTCTATATCTTTAGATGGTAAATTAAAAATTCCTGGCTGAATTTG	20	SEQ ID NO: 52
53	rs10851726	BOT	**[T/C]**	AATGTGAGTAGATTCCAACCTTTATCCATTCCATTCACATTTACCTTCTC	15	SEQ ID NO: 53
54	rs4610906	BOT	**[T/C]**	TTGTTTAAAGCTGCTGCAGGTATACTCTTTGGAGGCTAATAATAAAGAAC	X	SEQ ID NO: 54
55	rs59485211	BOT	**[T/C]**	TGGAGTAGTCTTCTTCTAGCCCTTGCATGACCTCTCTTACTTCACCCATA	X	SEQ ID NO: 55
56	rs7060015	BOT	**[T/G]**	CTTCCACCTGCTGCACTCCAATATAGCCACTATGTTCGGCTATATATATA	X	SEQ ID NO: 56
57	rs75710780	BOT	**[T/G]**	TAGAGAGTAATGTGGTGGGTGTGCTGTGTCAGAAAGGCTTCACTAGCAGT	6	SEQ ID NO: 57
58	rs6520908	BOT	**[T/C]**	CTAATTTGATCAATGAATCACTGCTAGCATGTGAATGTCCATAATGGATA	X	SEQ ID NO: 58
59	rs487011	BOT	**[T/G]**	TTATTAGAGGTAAACATAGAGATAAGCCCCTAATAAAATAGTAGCTGGAG	X	SEQ ID NO: 59
60	rs1383699	TOP	**[A/C]**	AGTGTTAATTCTCTAAGAGGAAAATGTCATTTCTCCAAAACAAAACTTTA	4	SEQ ID NO: 60
61	rs67516871	TOP	**[A/G]**	GTAACAAGGTTACCTCCAGAAAAAAAGGCTATTGCTGAACAGAGGCTTTC	X	SEQ ID NO: 61
62	rs114106519	BOT	**[T/C]**	AAGAGAGAAAAATATTTTTAAGTGAAAAGGAACAAAACTATTCTATACGA	7	SEQ ID NO: 62
63	rs7220091	TOP	**[A/G]**	GGCTCACACCGAGATCAATCCATGATGACAGCACTTCATGGCCCGTCTCA	17	SEQ ID NO: 63
64	rs12489026	TOP	**[A/G]**	GATAATCTAATTCATCTAACTTGCTTTACAAATGAGGAAACTGATAATCC	3	SEQ ID NO: 64
65	rs876270	BOT	**[T/C]**	GTGGACCCTTTGAGTGGTTACAGACGGGCCTCAGGATTGGTGTTATTTAA	12	SEQ ID NO: 65
66	rs4968161	BOT	**[T/C]**	AACAGGGGCCACTGTCTGTTTCCCATGGTATCTATAGGGCCTGGTGGACA	17	SEQ ID NO: 66
67	rs62056907	TOP	**[A/G]**	AGGGGTCAAGATACAAGGAGTCACCAAAGAATGCAGAAGAGACAAGTTCA	17	SEQ ID NO: 67
68	rs2235013	BOT	**[T/C]**	CCTTTTCTAAGACCAATATTAACAAGAATTAGTAGTAGAATGTTCTTATG	7	SEQ ID NO: 68
69	rs16878812	TOP	**[A/G]**	TGTTGCTAATCCCAACCAGCATGATTTACGGGAAGTAAATCATCTATGAC	6	SEQ ID NO: 69
70	rs6549407	TOP	**[A/G]**	GCCTGTCTCACAAACATTGGGTTCTATAGACGCTCCTAGATTGCATTTTC	3	SEQ ID NO: 70
71	rs28381848	TOP	**[A/G]**	CCCAGTGCCTTGACAGGGTATGGGGGGACCTGCATGACTAGCATTAAATG	7	SEQ ID NO: 71
72	rs79723704	TOP	**[A/C]**	TAACCAGGGATCTGTGCGTTTTGCTATAATTCAGAAAGTAGCAGACTACT	20	SEQ ID NO: 72
73	rs72814052	TOP	**[A/G]**	AAAAGTCGGTTCGAGAACCCAGGTGGAAAATAGATTGAGGGAAGCAAAAC	17	SEQ ID NO: 73
74	rs10152908	BOT	**[T/C]**	GAGTAAGAGTTAATCACTTCCACTGTGCACTTGTTTATTCCAAGTAGAAA	15	SEQ ID NO: 74

75	rs172769	TOP	**[A/C]**	CTCTGGACATCTTCAGAGGGTCCCACTTTAGACTTCACTGATCTCTTTTT	2	SEQ ID NO: 75
76	rs78596668	BOT	**[T/C]**	TCACACTTTACATTTATTATTTCCAGTAAGGGATATAGCTAAGATAGTTA	6	SEQ ID NO: 76
77	rs73307922	BOT	**[T/C]**	CAGTTTGATGAATGGCAAAATCGTTCAAATGGAAAAGAGGAGAGAGATAG	20	SEQ ID NO: 77
78	rs3842	TOP	**[A/G]**	TTCGTAATTAAAGGAACAGAGTGAGAGACATCATCAAGTGGAGAGAAATC	7	SEQ ID NO: 78
79	rs7210584	TOP	**[A/C]**	AGCCAGGGTTGAAGTCACTCACGGGTCCTCTCCGAGAACTCGAGTGGTGA	17	SEQ ID NO: 79
80	rs62402121	BOT	**[T/C]**	CAAAGGTGATATGCATTTTAAATTTGATAGTTATTGCCCAACTGTCTTTA	6	SEQ ID NO: 80
81	rs55709291	TOP	**[A/G]**	CCCTCAGGCTGCTTGTTACCGTGGAAGCTTCCTGAACTCTCTCCAGACCC	17	SEQ ID NO: 81
82	rs72747088	TOP	**[A/G]**	TTTTCATTTTTCTCTTCCCAACCCAATCCCCTCTCTCTAAATCTTGGTAT	15	SEQ ID NO: 82
83	rs929610	BOT	**[G/C]**	TTCAATATATGTTTTCTGAACACCTTCTGTGTTCAAGGCACCATGCTGGG	14	SEQ ID NO: 83
84	rs6766242	BOT	**[T/C]**	CCCTTGCATGTTCACCTTGTTATGTGTACTTTCATCTCAATTGCCAGTTA	3	SEQ ID NO: 84
85	rs1468552	BOT	**[G/C]**	AAAGTATCTCCCCAAATCATTCCCAAACACTACAAAGGTAGTGCCATCAG	16	SEQ ID NO: 85
86	rs78838114	BOT	**[T/C]**	TGCTCTAAAACTAATTTGCTTGAAGTGTACAGAATGGAATTCGGGAAGGA	15	SEQ ID NO: 86
87	rs62489862	BOT	**[T/C]**	ATCACTTTTCCATGAAATTGTCTTTGCATTAGCAAAATGAATCAAGCATA	7	SEQ ID NO: 87
88	rs894342	TOP	**[A/G]**	TTGGTGATGCTGATAGTTGGAGATACCCAGACAGATAAGGTATATTGCCC	15	SEQ ID NO: 88
89	rs58882373	BOT	**[T/C]**	ATCAATATGACTGGTGTCCTTCAGGAATGTGGTAGCACAGTGAAAAAGGT	3	SEQ ID NO: 89
90	rs3811939	TOP	**[A/G]**	GCAGTAGGGGACTGGCTGCCGAGGGGGCATCTAGATTGAGATAGGTGGGA	5	SEQ ID NO: 90
91	rs6984688	BOT	**[T/G]**	ATTGGCAAAAGTGCTCATTCTGGAAAAACAAAGAAGTGAGAAAGTGGATG	8	SEQ ID NO: 91
92	rs1018160	BOT	**[T/C]**	ATTCTAAAGCTTTGTGTGGTCCACCATGATCACCTTTTCCTGCTTCCCCC	5	SEQ ID NO: 92
93	rs76602912	TOP	**[A/G]**	GCTCCATTTTCTTTGAGGTACATCAACATCAATAACAGATCAATGGACCC	20	SEQ ID NO: 93
94	rs80067508	TOP	**[A/G]**	AGCCTGACCTCATGGCTTAGCTGTGCCTCCTGGACACCATCCCTCTCTGC	17	SEQ ID NO: 94
95	rs74888440	BOT	**[T/C]**	TTCTGAAAGTCACAGCCCAGGGATTCAGACCCACTAAAAAAAACTGAGAT	5	SEQ ID NO: 95
96	rs12481583	BOT	**[T/C]**	ACTACATTACATCATGATGTATTGATTGCCTCTGGCCTAGGAATCTGCAG	20	SEQ ID NO: 96
97	rs66794218	TOP	**[A/G]**	CCACTCATATGTCTGTTCTCACTCAGAGGTGAGGCCCTGTGTCTTCAGCC	17	SEQ ID NO: 97
98	rs16946701	TOP	**[A/G]**	GGGGGACAGAGAAGTAACGTCACAAGATTTTAAGCTTGGGCCAGATATGG	15	SEQ ID NO: 98
99	rs75726724	TOP	**[A/G]**	AAGTAGAGCAGAAAGGGCAAGCAGAGAACTAGACAGAGAAGACAGATGAC	15	SEQ ID NO: 99
100	rs67959715	BOT	**[T/A]**	TGGCTGCCTCTAGGGCAAGAAGACTGGGGATATCACCATGGGCTCAATGT	13	SEQ ID NO: 100
101	rs11871392	BOT	**[T/G]**	CCAAGTCCTTCTACCTCCCTGGGTGAGGGAACCGTTAGTGCCATCCTGAG	17	SEQ ID NO: 101
102	rs2044070	TOP	**[A/G]**	AATCTTGGGGAATCTGAGTTTATTAGAGGAATGTAGGGAGGAAGCAGGCT	15	SEQ ID NO: 102

103	rs77612799	BOT	**[T/C]**	TATCATATGCTCTAGTGACTTCATCAAGACAGT CTAAAGGAAGATGGGCC	6	SEQ ID NO: 103
104	rs6743702	BOT	**[T/C]**	CAGAAACACCTTTAATGTTTTTATTTCTATGAA TATTCTCCTAATGATTA	2	SEQ ID NO: 104
105	rs616870	BOT	**[T/C]**	TTAAAATGAGATCCCTTCCAACATGCTTTGCTG AGCCAGATTTATAAAAT	3	SEQ ID NO: 105
106	rs79590198	TOP	**[A/G]**	TAGTACAGTAAGGGCAAAGGGCACTGCAATTGC TATTAAACTGTAAGAAG	5	SEQ ID NO: 106
107	rs75715199	TOP	**[A/G]**	ATCCCCCGGAACTGGGGGAATTTCCAGGCACAT GAGGCTCTGTCAACCCA	17	SEQ ID NO: 107
108	rs13087555	BOT	**[T/C]**	AGCCACTTAAAATAAATTTTTCCAGCAGTTATT CATTTAGTGCCAAAATA	3	SEQ ID NO: 108
109	rs4869618	BOT	**[T/C]**	GCAGGGGCACATGCAATTGCCATTTAAAAATGA GGTCTGGCATGGCCAGA	5	SEQ ID NO: 109
110	rs117397046	TOP	**[A/G]**	GTACCACAGCTCCCAGCTGCATGTACTTTAAAA ATGTGTCTAAGCCAGGC	17	SEQ ID NO: 110
111	rs8042817	TOP	**[A/G]**	TGCAAACAGAAAAATCAGAACCTGCTCATGCTG CCATATTAATAGGAACC	15	SEQ ID NO: 111
112	rs2258097	BOT	**[T/C]**	TAACTACACACTCAAGGCTCCCTCTCAAAGTCT CAAACCTTACAACTTCC	17	SEQ ID NO: 112
113	rs2260882	TOP	**[C/G]**	AATACAGCCATGCGCTACCTACTGGCATTCCCG TCAGTGCGTACACGATC	17	SEQ ID NO: 113
114	rs532996	TOP	**[A/G]**	AACTGCTTTCCTCATTGGCTTGGTCTCCATAGT GATTCATTTTGCTGTAA	13	SEQ ID NO: 114
115	rs11747040	BOT	**[T/C]**	TGGAAATTTTTTTGTAATTAGAAATGACCTAAA GGATAGTTTCTATTCTT	5	SEQ ID NO: 115
116	rs10034039	BOT	**[T/G]**	ATTGATTTTTATGTCAGCAATCTTCCAATCTTG TTAATTCTAAAATACTT	4	SEQ ID NO: 116
117	rs116909369	TOP	**[A/G]**	GCCTAAGCTGAACCTGAGAGGTGAGGAAAACAG ACCAAGCTGACCAAACC	17	SEQ ID NO: 117
118	rs79134986	TOP	**[A/G]**	GCGAACTGTGGAGTATCTCAGTAAGAGTGTTAG GAGGAATATTTTATAGG	6	SEQ ID NO: 118
119	rs117615688	BOT	**[T/C]**	ACAACAACAAATCTCAAACAACTGTTCTGCCAA TGGGGTGGAGCACCTTT	17	SEQ ID NO: 119
120	rs8032253	BOT	**[T/C]**	TGATGATTTTCCAGCATGGCAATGGTAAAGCTG CAAATAAAAAGCAGCCA	15	SEQ ID NO: 120
121	rs12818653	BOT	**[T/A]**	TTCTTTTCTCCAAGCAAAAGAGAGAAGAGTTTA TTTCATTCTCAGCAGCT	12	SEQ ID NO: 121
122	rs4587884	TOP	**[A/C]**	GGCAAAAGCAGAGATGTGAGCTGTAAATTTGAA TGAAGGACCAGATAGAA	14	SEQ ID NO: 122
123	rs77122853	BOT	**[T/C]**	TAGGAACATAAAAGTTCAGATGTTAGTAGGACT AATAAAAAGTTATTGTT	20	SEQ ID NO: 123
124	rs117615061	BOT	**[T/C]**	TTTTTCAGGTCTAGCTTAACCAAAACACTTAAA ACTGTTACCAAAAAACT	20	SEQ ID NO: 124
125	rs74682905	TOP	**[A/G]**	CAAATAAATAAACTTTAAAGAAATGGCCAACTT GGGAAGGACATTAGGCC	7	SEQ ID NO: 125
126	rs2257468	BOT	**[T/C]**	CAGTCCAACAACCAGTTCCAGAAGATCTCAGAG GTAGGCCGCTCCCCACA	17	SEQ ID NO: 126
127	rs2032582	BOT	**[T/G]**	TGAAAATGTTGTCTGGACAAGCACTGAAAGATA AGAAAGAACTAGAAGGT	7	SEQ ID NO: 127
128	rs2235015	BOT	**[T/G]**	GATTCATTTTTACATGTTTATTTTTAATGGAGA CTAAAGAGACATAAATG	7	SEQ ID NO: 128
129	rs2729794	BOT	**[T/C]**	TCTTGATTCAATTGGAAGTAACTGAGAGGTATA TCACATGTTGTGATTCA	15	SEQ ID NO: 129
130	rs77549514	TOP	**[A/G]**	TGCTCCATAACACAAATAATTTCATTCTTCTTC CTTTCTTGCCGAGTAGT	2	SEQ ID NO: 130

131	rs74790420	TOP	**[A/C]**	ATGAGCAAGGAGGCCAAAACCCTGCGTGGACGGTCTGCTTCCCTGCCCTT	17	SEQ ID NO: 131
132	rs73129579	BOT	**[T/C]**	GAGTGCCAAATATGTGCCCTTCCCCGTGGGGAAGACAAAAGTATGAGACA	20	SEQ ID NO: 132
133	rs12913346	TOP	**[A/C]**	TATTTTTAGCAGCCTATGGATTCTAGGAGTGACCCAGCTCCAGGGATAGG	15	SEQ ID NO: 133
134	rs117560908	BOT	**[T/C]**	CATGAGGAAAGGCTGCAACTTTGAGCTCCCTCTTTAGCTAGGGAGCCTCC	17	SEQ ID NO: 134
135	rs72747091	TOP	**[A/G]**	AGCATTAATGAAGCACAGGGCCTATCACGCAGTCAGGCTCAGTATAAGGT	15	SEQ ID NO: 135
136	rs2935751	TOP	**[A/G]**	CATACTCAAATTGATACACAGCCTTTGTCCTGAGTGTTTGTCTTCCAAAA	8	SEQ ID NO: 136
137	rs4331446	TOP	**[A/G]**	AGAGTAGTATTGCTTAAAAACTGCTCCAACCACTTCTTAAACCTGAAACC	2	SEQ ID NO: 137
138	rs7523266	BOT	**[T/C]**	TCGGCCAAAATCAGGGACAAGGATGACATGCCATTGCTTACCAACTGCTA	1	SEQ ID NO: 138
139	rs7648662	BOT	**[T/C]**	CCGTTGTGCAAACTCCAGAAAGGGCATCTCTCTGTCCCACTCCCCCATTA	3	SEQ ID NO: 139
140	rs117034065	TOP	**[A/G]**	ATCTGCGTAAATTGCTGCATCTCTCTTGGCCTCAGTTTTCTTAGCCACAC	15	SEQ ID NO: 140
141	rs4836256	BOT	**[T/C]**	GTAAGTGCCAGCTACTATTATTTAGGAGGCTAAGGCTCTAGGTGATGAGG	5	SEQ ID NO: 141
142	rs80238698	BOT	**[T/C]**	TGCCACCCTATGGCATTCTTGTTGTGTAATGAAATAACTCTCCTATGAAA	7	SEQ ID NO: 142
143	rs3730173	BOT	**[T/C]**	CTGCGCTTGCCCAGGAGGCCCTGGTCTGCACTGTTTATAGAGAAGAACCC	20	SEQ ID NO: 143
144	rs11687884	BOT	**[T/C]**	TTAGGAAAGTTCTGTACAGATATGTGTAATCCAGCATCTGTTTATCTATT	2	SEQ ID NO: 144
145	rs72693005	BOT	**[T/C]**	AATGATGGAAAAAACTGCAGCGCACGGTGGAAATGTCTACTTTGTATGCA	4	SEQ ID NO: 145
146	rs2589476	BOT	**[T/C]**	CTCCTCATTATTCGCTTCTGCTGTAACTGCACCTATGGTAACCCAGGTGC	17	SEQ ID NO: 146
147	rs9813396	BOT	**[T/C]**	AAGTGCTCTGTAACCAAATATTTTGGAAATGCTGAGTTGTACCAAGTTGG	3	SEQ ID NO: 147
148	rs10482667	TOP	**[A/G]**	TTTTGAAATTTCCATTATATGCAAAGCCCATGAAAGGCTAAATATCAGTT	5	SEQ ID NO: 148
149	rs72784444	TOP	**[A/G]**	GTTTGTAAATGCACACTGTTGGGGGAACCCTCTTCCTAGTCCTTGTTTCC	5	SEQ ID NO: 149
150	rs75074511	BOT	**[T/C]**	TGGGCGAGAACTTATTCCTCAGGCCATTAGATTCCCTAATGCTGCACCTT	17	SEQ ID NO: 150
151	rs7951003	TOP	**[A/G]**	GCCATGGGCAAAAACAGCTCAGGTAGTAATGAAGGTGTGGCTATAGCTGA	11	SEQ ID NO: 151
152	rs79584784	TOP	**[A/G]**	ACATCAAACTAAATTACATCATCAGAGTAAAGAGACAATTTACAAAAAGG	7	SEQ ID NO: 152
153	rs2214102	BOT	**[T/C]**	AAAAAGTTCTTCTTCTTTGCTCCTCCATTGCGGTCCCCTTCAAGATCCAT	7	SEQ ID NO: 153
154	rs28811003	TOP	**[A/G]**	CTGGCTCCAGGCAAAGAATACTACCAGCAACAAAGAGGAACATTTCAGAT	15	SEQ ID NO: 154
155	rs6100261	TOP	**[A/T]**	GGACTAGCCTGCTGCTTCATTTCCCCCCTCCTCTGCAGCCGATTTCAGAA	20	SEQ ID NO: 155
156	rs77152456	TOP	**[A/G]**	ATATTAGTAACCTGGAAAACATACATGGAGGTATGTTCATTAACGGCAGT	15	SEQ ID NO: 156
157	rs66624622	BOT	**[T/G]**	ATGGGAAGAGCTGGATTTTTGTCGTGGAGTAAAGGAGAGGGAATCAAGAA	5	SEQ ID NO: 157
158	rs140302965	TOP	**[A/G]**	AAAATCATAGAAATTGTGTCTAAGGATATGCTTTGGGATATTTGGACTTC	7	SEQ ID NO: 158

159	rs11653269	BOT	**[T/C]**	CATAAACCAAAGGGATCTTCTCTACTCGTGCGTCCCTAGTCTCTCTCCCC	17	SEQ ID NO: 159
160	rs74405057	TOP	**[A/G]**	GCTGCCTGTACTAGTGATAGTGAGGCTCACTACCATCCACCACCTAAATT	20	SEQ ID NO: 160
161	rs7121	TOP	**[A/G]**	GTGTAGCTTACGGGAGGGAAGTCAAAGTCAGGCACGTTCATCACACTCAG	20	SEQ ID NO: 161
162	rs16977818	TOP	**[A/C]**	CTCATTGTAAGATTCAAAAACATTCCAGCTTACAAAACATATCCAGCTTA	15	SEQ ID NO: 162
163	rs12490095	BOT	**[T/C]**	TTTGCAAGGCAATTTGTTCTACTGCTGGACAGCTTCATGTTTAATGTTTT	3	SEQ ID NO: 163
164	rs118003903	TOP	**[A/G]**	CTATATTTGAACAAGCTTCTGGGTAATATTTATGACAGGGAAGTCTTGAG	17	SEQ ID NO: 164
165	rs62377761	BOT	**[T/C]**	CTGTGAACCAGGCACTGTTTGAAATGTTCCATTTATTGACTTATTTAAGT	5	SEQ ID NO: 165
166	P1_M_061510_6_34_M	MINUS	**[-/I*]**	ACTACTACTAATGTTGAAAGTATACCATGTAACAGGCACTGTACAAAGCC	6	SEQ ID NO: 166
167	rs375115639	MINUS	**[-/I*]**	TTTTGGGTTTTGTTGCTAGCATAAAAATTATTACCTAGTGGATGGTAACA	6	SEQ ID NO: 167
168	rs1002204	TOP	**[A/C]**	TTTTTTTTTCATTTGAAGTAAATATCCACCTTTGTATCTAATTTTGCATT	7	SEQ ID NO: 168
169	rs10062367	TOP	**[A/G]**	TTATTTTTTAATAGTGTTCTTGCACATGAGGAGAAAGACTGAATTCAATT	5	SEQ ID NO: 169
170	rs10482642	TOP	**[A/G]**	CGTGTCACTTCGTTTGACTTCAGCTGGGAACATGCATATCAGTCGACTCA	5	SEQ ID NO: 170
171	rs10482658	TOP	**[A/G]**	ATCGTCACACAGTTTTAAGACAAATGTTTTTACCTATTTGACCTAGTCTG	5	SEQ ID NO: 171
172	rs1053989	TOP	**[A/C]**	TGTGCTACAAACCTGAAACTGGTAAGACAAGCACAAAGCAACGTGCAATA	5	SEQ ID NO: 172
173	rs10851628	BOT	**[T/C]**	CTTGGATGGAGGCTCAGGGAGCCAAAGGCAAATGTCTTCATAGAACCAGG	15	SEQ ID NO: 173
174	rs10947562	BOT	**[T/C]**	ATCATGAATTAAACAAATTAATTTATGTATTTTGTTTTGAGTCAGTGTCT	6	SEQ ID NO: 174
175	rs11069612	TOP	**[A/G]**	ACATGTGACCAACAAGATAATTATGAAACCTGACTGCTGGATATGCTGAT	13	SEQ ID NO: 175
176	rs11071351	BOT	**[T/C]**	GTCTTTTGGAAAATGCAATCTGCCACTCTGTGCAATGGAAAACCACTGCA	15	SEQ ID NO: 176
177	rs11091175	TOP	**[A/G]**	TTATTAATATTAGCCTTTCTTCTCTCCCCGTTTATGCTTTGGTGGGTACT	X	SEQ ID NO: 177
178	rs11638450	BOT	**[T/C]**	TTTGGTTTGGGTTTTGTTTGGCAGAGGCAGAATAGAATAAAGAACATGGG	15	SEQ ID NO: 178
179	rs11715827	BOT	**[T/G]**	AGAATTATTGCTGCACAATTCTTATGAAACCGAACTAGAGCTACACTATT	3	SEQ ID NO: 179
180	rs11745958	BOT	**[T/C]**	CAGGCAGATCACTTGACGTGAGGAGTTCAAGTGAGGAGTTCAAGTCCAGC	5	SEQ ID NO: 180
181	rs11834041	TOP	**[A/G]**	ACAAACAAACTGAGGTTTAGGTTTAGGTAGCTGGAGTTTATAGGCATGGC	12	SEQ ID NO: 181
182	rs1202180	BOT	**[T/C]**	TCTGGAATAATAGTTACATTTGCTACATCCCTTTCTAGCGTCAACTCACT	7	SEQ ID NO: 182
183	rs12054781	TOP	**[A/G]**	CATAATGTGATGCCATATTAAACTGTAATCACCTTTCCACCAAACTAATA	5	SEQ ID NO: 183
184	rs12539395	TOP	**[A/G]**	CAAAATTCATATGTTGATACCTAATCTCCAAAGCAATAGTATTAAGGGTG	7	SEQ ID NO: 184
185	rs12720066	BOT	**[T/G]**	AATACTGTTTGGTATGGCAAGACAGTATTGGTTTTGGTTCAAGTGCTCCT	7	SEQ ID NO: 185
186	rs1279754	TOP	**[A/C]**	TTGGTTTTCCTGGGTGGGGAAGGGTGCTGGCCT	5	SEQ ID NO: 186

				CATTCACAACAGCAGAT		
187	rs12872047	BOT	**[T/C]**	GGGAAAGACAGAGTGAGAGAAAGAGAGAGTTAG CCTCTACATATTATAAG	13	SEQ ID NO: 187
188	rs12876742	TOP	**[A/C]**	GCAGAGAGAGCCCTGTCTCAAAACAGATTTCTG AGTGTGGCTTCTGTCCA	13	SEQ ID NO: 188
189	rs12917505	TOP	**[A/G]**	TCTCGTAGCTGAGAGAGTCATGACTATGGCGTG TTCTCTGTACTCTGAGG	15	SEQ ID NO: 189
190	rs13066950	BOT	**[T/G]**	CTCAAGCAGAAGGAATCTCTCCCCATAGCCGCT ATAGTTTCAAATGTGCT	3	SEQ ID NO: 190
191	rs13229143	TOP	**[C/G]**	GTGAGGATAGGTAGCTTTTCTTACTCACTGTTG TTACCAGTACCTAGAAC	7	SEQ ID NO: 191
192	rs1383707	BOT	**[T/C]**	ACGAGCTTGTCATTCTGTAAATGACATATTCAT ATTCTTGGTATTGTACA	4	SEQ ID NO: 192
193	rs1441824	BOT	**[T/C]**	CAAGGTTAAAATTCCCGCATTGTGGGCCTTGTA GCTTTCATGTCTTAATG	15	SEQ ID NO: 193
194	rs1652311	TOP	**[A/G]**	GGATTTTGGCCATTCTAAGAGATGTGCAGTAGT AACTCAGTGTTTTATTT	2	SEQ ID NO: 194
195	rs17064	BOT	**[T/A]**	CTGAAGACTCTGAACTTGACTGAGGAAATGTTA AACAGATACCTCTTCAT	7	SEQ ID NO: 195
196	rs17100236	TOP	**[A/G]**	AACATTCCATTATCCTATTGTTCATTCTTTGGA GCTGTGATTTGTTTAAT	5	SEQ ID NO: 196
197	rs17149699	TOP	**[A/G]**	AGCTTCGGTGAATATTAGAATGGCCTCAAGAGC TAGTAAAAAACACAGCC	7	SEQ ID NO: 197
198	rs1724386	TOP	**[A/G]**	AGGCATATGGGGAAAAAATAAGGCAGGAAAGGA AGACGGAAAATGCTGTG	17	SEQ ID NO: 198
199	rs17250255	TOP	**[A/G]**	TTGGTTTTATAAAGGATCTAAGTGTTTGGAAAG GTGTGGGACCATGTACT	7	SEQ ID NO: 199
200	rs17327624	BOT	**[T/G]**	ACATGCTCTGCATGCTTTGACAGTACAGTGTAT AGAATAGACACAAAACT	7	SEQ ID NO: 200
201	rs17616338	TOP	**[A/G]**	TAAGGTTGTATCATCTACCTGTAGTCACTGCAG TCAGCTGAATTTTACCA	4	SEQ ID NO: 201
202	rs17687796	TOP	**[A/G]**	CTCTGTAGCCACACAGATGCCAACAGCTGGCAC TTGTCCAAGAAACATGT	17	SEQ ID NO: 202
203	rs17740874	BOT	**[T/C]**	AGAATGGGTCACTTGTTAGAAACAGTCAAGGAT ACATACAAACAGTGGAA	2	SEQ ID NO: 203
204	rs17763104	BOT	**[T/C]**	CCAAGAGTGGTGAAGCCTTCCTGTTTACAGAGG ATTTTCATATCTGTTAT	17	SEQ ID NO: 204
205	rs1880748	BOT	**[T/C]**	ACACCCATGGGGCCAAGCCAGGAGCAGTCACCA CAGCCAACCTGCAGGCT	17	SEQ ID NO: 205
206	rs1882478	TOP	**[A/G]**	TATTCTAAGGAAGTGCCCCCTAAAACAAAGCTC AGGAGCCTCAACCCGGC	7	SEQ ID NO: 206
207	rs1944887	BOT	**[T/C]**	TCCCAACATCAAAAGGCAAATTCTTGCCCCACT TTTACAGATGAGAGCGC	11	SEQ ID NO: 207
208	rs2028629	TOP	**[A/G]**	TACCATGGGAAACAGACAGTGGCCCCTGTTCTC AAGTGGCTTAGACTCTA	17	SEQ ID NO: 208
209	rs2143404	TOP	**[A/G]**	CTTATTGGCCCTAAGTAAATCTTAGGTTAGGTA GAGCTCAGTTCCCAGGG	6	SEQ ID NO: 209
210	rs2173530	BOT	**[T/C]**	GTATTTTTAGGAACATTCAGGAAAACAGGTAAA GGGTATTCAGGAATTCA	13	SEQ ID NO: 210
211	rs220806	BOT	**[T/C]**	GGCCTTCCTCACTCTGACGGTGAGTTCCAGAGG ACAGGGATTTGTGGTTG	6	SEQ ID NO: 211
212	rs2235047	TOP	**[A/C]**	TGGTTGCTAATTTCTCTTCACTTCTGGGAAACC AGCCCCTTATAAATCAA	7	SEQ ID NO: 212
213	rs2242071	TOP	**[A/G]**	AACACAGAGCAGTATGTACAGGACAGCGTTAGA ATATACCAGAGAACAAG	2	SEQ ID NO: 213

214	rs2257474	BOT	**[T/C]**	AAACACACCTGTCACCCACGACCCTGGCATAGG GCATCGTGAACCCATCA	17	SEQ ID NO: 214
215	rs2295583	TOP	**[A/T]**	ATAGTATTCTGTTCTTCAGGGAGTTGTGGGTTC GGATCTGTGCAAAGATA	20	SEQ ID NO: 215
216	rs234629	BOT	**[T/C]**	TAGGAATCAGGGAACTCTAGATGCGTCTAGCAG CTAGCCTGTGGCCTCGA	20	SEQ ID NO: 216
217	rs234630	TOP	**[A/G]**	TTCAAATTGCTTGATTAAAATGGCAAACAGTTT GAAAATTGTATACCTCT	20	SEQ ID NO: 217
218	rs2436401	TOP	**[A/G]**	GGATAATGGAAAAGGGGGTTTCTCCCAAGTAGA GAACTTAAACAGTGTGA	5	SEQ ID NO: 218
219	rs258750	BOT	**[T/C]**	CACCTAGTCATGTGTATATAAAATCACCATGTT ATTACAGAATTTAGTAA	5	SEQ ID NO: 219
220	rs2589487	BOT	**[T/C]**	CAATCTATTTTCCACCTGGGTTCTCGAACCGAC TTTTCCTCCCTCTCTTC	17	SEQ ID NO: 220
221	rs28364018	BOT	**[T/G]**	GGGTCTTCCTACGGGACTGCCTTAGACGTGCTG GGCTTTGGCCTCAGTGA	8	SEQ ID NO: 221
222	rs28381774	BOT	**[T/C]**	AGTTTTGGTTGGGGAGGACAATGCCAGGTTAAC AGACACTTAATATACAT	7	SEQ ID NO: 222
223	rs28381784	TOP	**[A/G]**	AAAGAGAGTGGAAGTACCAGGTGGGCAAAGTTT ACAATTTTAAGTAGGAT	7	SEQ ID NO: 223
224	rs2963155	TOP	**[A/G]**	ATGATTCTTTCCATGACACCTAGTGCCCTTCTC CATCTAGAGCTACCTCT	5	SEQ ID NO: 224
225	rs3133622	BOT	**[T/G]**	AAATGAACTCAGCAATGAAATGGAACAAGCTAT CCATACATGCAGCAATT	8	SEQ ID NO: 225
226	rs32897	BOT	**[T/C]**	CCATCATTGCCTGGCTGTTGAAGCAGTTCTTGA CATTTTAAAGTAATATG	5	SEQ ID NO: 226
227	rs33388	TOP	**[A/T]**	TTGCTACAAGGAGGATTATGGGTGAAAGTCATG GATGGATTATGAGTTAA	5	SEQ ID NO: 227
228	rs3730168	BOT	**[T/C]**	GATGGACATCACTGAAATGTAGTTTTGCCTGAA GTGTGGTTTGGATGCTC	20	SEQ ID NO: 228
229	rs3735833	BOT	**[T/G]**	CTTGTTTGTGTATGATACATGAAGTAGAATTCA TACAGCACAAGTACTTT	8	SEQ ID NO: 229
230	rs3777747	TOP	**[A/G]**	GAAATTCTCCATAATTTCTGATCCACTCTTACA TTCCTCTCCTTTCCAGC	6	SEQ ID NO: 230
231	rs3786066	BOT	**[T/C]**	GGGGGCTGGGGGGAAGTCCCGGGACAGGTGCAT GTCATCAACACGACTGT	17	SEQ ID NO: 231
232	rs3798346	BOT	**[T/C]**	AGATCTTTTCAGGCATAAAAGTTGTCAATAGGT TTTCATAAATTTCTAGG	6	SEQ ID NO: 232
233	rs3822736	TOP	**[A/G]**	CCCTTGCACAGGCACAGCTATAATTTTTGTCTC TCTTCTGTTGGAAAGGT	5	SEQ ID NO: 233
234	rs389035	BOT	**[T/C]**	GTGGTTTCTAATGATTTAATACCATCCCCCAGG GTGCTCTTCTTGTGATA	2	SEQ ID NO: 234
235	rs3924144	TOP	**[A/G]**	GAATATTGAAGGTAGCCAGAAAAGAAAAAAAGG CACATTGCATGCAGAGG	2	SEQ ID NO: 235
236	rs4148737	BOT	**[T/C]**	ATGGCAGTTCATTGCTTTACTATTTGGACATTT CAAACTGTCCCAAGGTG	7	SEQ ID NO: 236
237	rs4148749	BOT	**[G/C]**	TTTTTTCAAACCTTTAAACAACAGTCCCACTTG GATAAAGTCTGAGAGCG	7	SEQ ID NO: 237
238	rs417968	BOT	**[T/C]**	ATAGCCTAACTTTCCCCCCGAAGCTTCCCAAGC CCTCATGATATCTATTA	17	SEQ ID NO: 238
239	rs4458144	BOT	**[T/C]**	ACCTGAGAATTCTCACCCATCCAATTCTACTTG ATATGGGATTCCTCTAA	2	SEQ ID NO: 239
240	rs4515335	BOT	**[T/C]**	AATGGGCATGATCTCACTCACATGGAACAGGAT CTCTTTCCTTGTTAGCA	5	SEQ ID NO: 240
241	rs4728699	TOP	**[A/G]**	AGTCACAGAAACATAGCAAGCCCTTGAAATCAG GCTTTCTGACTTTGTCT	7	SEQ ID NO: 241

242	rs4758040	TOP	**[A/G]**	CACCTACACACATGCATGCACACACACATGGCC TCTCTCTCCAGGCTTCT	11	SEQ ID NO: 242
243	rs4812040	TOP	**[A/G]**	CGTACAGACCTGGTCCAAAAATTCCAATTTCAT AGGTGTGGAGTTTTCAT	20	SEQ ID NO: 243
244	rs4912650	BOT	**[T/G]**	CAAACAACCACCACATCAAAATAATAGCAAAGA CAACAACTAATACTAAT	5	SEQ ID NO: 244
245	rs4957891	BOT	**[T/C]**	ATAGTAAGTTTTAAAGTAAGAGGTCAGAAACAT ATGTTACTTTACAAACA	5	SEQ ID NO: 245
246	rs5906392	TOP	**[A/G]**	TTATGTAGCAGGTCCTGATGTAACAGAATTAAG ATTGCAGGTGGGATTGG	X	SEQ ID NO: 246
247	rs6026561	BOT	**[T/C]**	TCCCTAGAACAGCAGGACCTGCGAAACTCTGAG GCCGCTTTGTGAGGTCC	20	SEQ ID NO: 247
248	rs6026565	BOT	**[T/A]**	TTGAAAAGAGAAACCCACAGGGCTTTCTGCTTA AATCCCTCGGACACAGT	20	SEQ ID NO: 248
249	rs6026567	TOP	**[A/G]**	TAAGGATGGGACCCCTACTGTCCATCTCAGGCT CAGCACTGCCTTGGGGC	20	SEQ ID NO: 249
250	rs6026593	TOP	**[A/G]**	CTTCTACATCTTAGCTCACCTGTCCTCACAAAT AAACATCACTCTTGAAT	20	SEQ ID NO: 250
251	rs6092704	BOT	**[T/G]**	TTGTTGAAATGTGACCACGAACTAGGTCTTAAC CTAGCAAATTCACAAAT	20	SEQ ID NO: 251
252	rs6100260	TOP	**[A/G]**	CTTTCTAAACACTAGCAGCCCAGAATTCTCAGG CCACTTTTGGGCATTGT	20	SEQ ID NO: 252
253	rs6128461	BOT	**[T/C]**	GTCTATGAATTGGTGAATCAGCCAAGTGAATGC TTCAAAAACTGGGACTC	20	SEQ ID NO: 253
254	rs6415328	BOT	**[T/C]**	CCTCCTGAGATGAACATCGTGAGGAGTAAATAG AGATGCTATTCTCAGCT	7	SEQ ID NO: 254
255	rs6610868	BOT	**[T/C]**	AACTCCGATTAATCACTAGTTGTTCACACCAAA AACCCAAGTGCCATTAC	X	SEQ ID NO: 255
256	rs6686061	TOP	**[A/C]**	TCACCAAGTCTGGTTGTCCCAGTCTCCTATCTC TGTCTGTTCCTCTCCTC	1	SEQ ID NO: 256
257	rs6730350	BOT	**[T/G]**	ATGAGTTGGAATTGCATAATGGGTAGATGCTGA TGCTGGAGAACTTTGAG	2	SEQ ID NO: 257
258	rs6746197	BOT	**[T/C]**	GTCATTGACTCGACTATAATTTTCCAAACTACC TAAACGTGTTATATCAT	2	SEQ ID NO: 258
259	rs6963426	BOT	**[T/C]**	TGATGATTAGGAGTCTGATGGAGGAAAGTAATT TTAAAACAACTTAATGG	7	SEQ ID NO: 259
260	rs7121326	BOT	**[T/C]**	TGGGGTTTTATTTGCTTTTTTCCCAGTTTCTTA GATGTAAAGTTAGGTTA	11	SEQ ID NO: 260
261	rs7721799	TOP	**[A/G]**	GGAACTCTGACGCAATCCAGGGCCGAGGAAAAA TGATTAAAACCCAACAA	5	SEQ ID NO: 261
262	rs7787082	BOT	**[T/C]**	TACTGCAGTGAGTTCAAGTGTTGTACCTGCTTA AAATGCAGTGACACTAA	7	SEQ ID NO: 262
263	rs7799592	TOP	**[A/C]**	GGCAGAGGGAACAGCTTGTGCAAAGGCCCTGGG GCAGGCCAAGGGCAGAG	7	SEQ ID NO: 263
264	rs796245	BOT	**[T/C]**	AAAAGAGGATGGCTGGTTTATCTCAAGTAATCA GACATTTAATAATAATA	2	SEQ ID NO: 264
265	rs809482	TOP	**[A/C]**	GTGCTATTTTGTTGCTGTTAGGTCTATTTTCTT CATCTGTTATTTCGCAT	2	SEQ ID NO: 265
266	rs8125112	BOT	**[T/C]**	GCCTGGGGGAGCGGGGAATCGCTTTTCGCCGGC CTCCGCGTAACCTTGTT	20	SEQ ID NO: 266
267	rs919196	TOP	**[A/G]**	GGCTCAACGGAAGTGACCGTCCCACAGTTATGC AGCACTAAGTCAATGGC	20	SEQ ID NO: 267
268	rs920750	BOT	**[T/C]**	TTGTGACAGGTCCCAGCGTGAACACGCACGCCC TAGCCGGGCCCCAAACC	17	SEQ ID NO: 268
269	rs9332385	TOP	**[A/G]**	AAGGGGACCGCAATGGAGGAGCAAAGAAGAAGA ACTTTTTTAAACTGAAC	7	SEQ ID NO: 269

270	rs930473	BOT	**[T/G]**	GCTGACTTCTTGACTGCAGCCACAGGAAGGACT CAACCCAGGACCATCCA	15	SEQ ID NO: 270
271	rs9324921	TOP	**[A/C]**	AATTTTTCAATGGTAAACAGACCAGAGTTATTC TAAGAAATTATGAAAAG	5	SEQ ID NO: 271
272	rs9348979	TOP	**[A/G]**	AGGATTTCAAGACTTGCCTGAGCAACATAATGA GATGCCCTCTCTCAAAA	6	SEQ ID NO: 272
273	rs9571939	TOP	**[A/C]**	AGCAAGCAGAAAACAAACAACTTCATTAAAAAT GAGCAGAGGACCTGAAC	13	SEQ ID NO: 273
274	rs9892359	BOT	**[T/C]**	TTCTGAGACCTTCTTGCCCCTTTGTTTCTAAGC CCAGGGCCACAATTCCC	17	SEQ ID NO: 274
***[-/I]** designates an allelic deletion/insertion polymorphism as defined in the respective SEQ ID NOs: 166 and 167						

[075] Further useful combinations of more than one polymorphism genotype are disclosed in Tables 5, 6, and 7 below, which all refer to the consecutively numbered, internal polymorphism-identifier (P_ID) of Table 2 to specify the genotype identity.

[076] For the purposes of the present invention, the one or more polymorphism genotypes described above may be represented, for instance, within a nucleic acid of a length of, e.g., 1 nt, 2 nt, 3 nt, 4 nt, 5 nt, 10 nt, 15 nt, 20 nt, 25 nt, 30 nt, 35 nt, 40 nt, 45 nt, 50 nt, 60 nt, 70 nt, 80 nt, 90 nt, 100 nt, 200 nt, 300 nt, 400 nt, 500 nt, 1000 nt, 2000 nt, or more or any length in between these lengths. The nucleic acid may be any nucleic acid molecule, e.g. a DNA molecule, e.g., a genomic DNA molecule or a cDNA molecule, an RNA molecule, or a derivative thereof. The one or more polymorphism genotypes may further be represented by translated forms of the nucleic acid, e.g. a peptide or protein, as long as the polymorphic modification leads to a corresponding modification of the peptide or protein. Corresponding information is readily available in the art, e.g., from databases such as the NCBI dbSNP repository or the NCBI Genbank.

[077] The polymorphism genotypes as described herein may be present on both strands of genomic DNA or its derivatives, i.e. on the chromosomal / genomic 5'→3' strand and/or the chromosomal / genomic 3'→5' strand. For example, a polymorphism can be present on the 5'→3' strand as A, it is present on the 3'→5' strand as T and *vice versa*. Also the insertion or deletion of bases may be detected on both DNA strands, with correspondence as defined above. For analytic purposes, the strand identity may be defined, or fixed, or may be chosen at will, e.g. in dependence on factors such the availability of binding elements, GC-content etc. Furthermore, for more universally applicable designation, a polymorphism genotype may be defined on both strands at the same time, or using the commonly known designations, such as the "probe/target"-designation, the "plus(+)/minus(-)"-designation, the "TOP/BOT"-designation or the "forward/reverse"-designation, as described in Nelson et al., Trends Genet. 2012, 28(8):361-3, or Illumina Inc. *"TOP/BOT" Strand and "A/B" Allele - A guide to Illumina's*

method for determining Strand and Allele for the GoldenGate® and Infinium™ Assays", Technical Note, © 2006; http://www.illumina.com/documents/products/technotes/technote_topbot.pdf, both incorporated by reference herein in their entirety. For the sake of unambiguity in polymorphism genotype designation, e.g., the "TOP/BOT"-designation can be used to identify the polymorphism genotypes in Table 2 above. In the alternative, the probe sequence or the genomic flanking sequences can be used to identify the polymorphism genotypes in Table 2 above.

[078] A "polymorphic site" or "polymorphic variant" as used herein relates to the position of a polymorphism or SNP as described herein within the genome or portion of a genome of a subject, or within a genetic element derived from the genome or portion of a genome of a subject.

[079] "Linkage disequilibrium" as used herein refers to co-inheritance of two or more alleles at frequencies greater than would be expected from the separate frequencies of occurrence of each allele in the corresponding control population. The expected frequency of occurrence of two or more alleles that are inherited independently is the population frequency of the first allele multiplied by the population frequency of the second allele. Alleles or polymorphisms that co-occur at expected frequencies are said to be in linkage equilibrium. Polymorphisms in linkage disequilibrium with a polymorphism of Table 2 can be identified by methods known to one skilled in the art. For example, Devlin and Risch (Genomics 1995, 29(2):311-22; incorporated herein by reference in its entirety) provide guidance for determining the parameter delta (also referred to as "r") as a standard measure of the linkage disequilibrium. Gabriel *et al.* (Science 2002, 296(5576):2225-9; incorporated herein by reference in its entirety) provides instructions for finding the maximal r^2 value in populations for disease gene mapping. Further, Carlson et al. (Am J Hum Genet 2004; 74(1): 106–120) disclose methods for selecting and analyzing polymorphisms based on linkage disequilibrium for disease gene association mapping. Stoyanovich and Pe'er (Bioinformatics, 2008, 24(3):440-2; incorporated herein by reference in its entirety) show that polymorphisms in linkage disequilibrium with identified polymorphisms have virtually identical response profiles. Currently, several databases provide datasets that can be searched for polymorphisms in strong linkage disequilibrium, which can be accessed by the following addresses: http://1000.genomes.org, http://www.hapmap.org, http://www.broadinsitute.org/mpg/snap. An example workflow for determining polymorphisms in linkage disequilibrium to a specific polymorphism is outlined in Uhr *et al.* (Neuron 2008, 57(2):203-9; incorporated herein by reference in its entirety).

Preferably, the linkage disequilibrium referred to herein is strong linkage disequilibrium. “Strong linkage disequilibrium”, as used herein, means that the polymorphism is in linkage disequilibrium with an r^2 higher than 0.7 or higher than 0.8 in the tested population or an ethnically close reference population with the identified polymorphism.

[080] A "sample obtained from a subject" as used herein may be any sample any biological sample comprising a bodily fluid, cell, tissue, or fraction thereof, which includes analyte biomolecules of interest such as nucleic acids (e.g., DNA or RNA). For instance, the sample obtained from the subject can be a buccal sample, a blood sample, plasma, serum, semen, sputum, cerebral spinal fluid, tears, a tissue sample, a formalin-fixed, paraffin-embedded tissue sample, or a hair follicle. Such samples are routinely collected, processed, preserved and/or stored by methods well known in the art. A biological sample can be further fractionated, if desired, to a fraction containing particular cell types. If desired, a sample can be a combination of samples from a subject such as a combination of a tissue and fluid sample.

[081] In some embodiments, the subject’s nucleic acid or DNA is extracted, isolated, and/or purified from the sample by any method commonly known in the art prior to polymorphism and/or SNP genotyping analysis. The term "isolated nucleic acid molecule", as used herein, refers to a nucleic acid entity, e.g. DNA, RNA etc, being substantially free of other biological molecules, such as, proteins, lipids, carbohydrates, other nucleic acids or other material, such as cellular debris and growth media. Generally, the term "isolated" is not intended to refer to the complete absence of such material, or to the absence of water, buffers, or salts, unless they are present in amounts which substantially interfere with the methods of the present invention. In alternative embodiments, detection of one or more polymorphism genotypes may also be performed by using a non-extracted, non-isolated or non-purified sample. In some embodiments, DNA amplification by any suitable method known in the art is used prior to the detection of one or more polymorphism genotypes.

[082] The term “detecting the presence or absence of one or more polymorphism / SNP genotypes” is used herein synonymously to a “polymorphism / SNP genotyping analysis” and refers to a step of determining in one or several patients the presence or absence of at least one polymorphism / SNP genotype, typically several polymorphism / SNP genotypes, or all polymorphism / SNP genotypes disclosed in Table 2, or, in some embodiments, all (known) polymorphism / SNP genotypes of the human genome, including endogenous and exogenous regions. In particular, detecting the presence or absence of

one or more polymorphism genotypes as used herein may not be limited to the CRHR1 gene or to genes of the CRH pathway, but can encompass a genome-wide screening for polymorphism genotypes.

[083] A detection step or polymorphism / SNP genotyping analysis can be performed by any suitable method known in the art. Such methods include, but are not limited to, PCR-related methods using polymorphism / SNP-specific primers and/or probes, a primer extension reaction, polymorphism / SNP microarrays analysis, sequencing analysis, mass spectrometry, 5'-nuclease assays, allele specific hybridization, high-throughput / multiplex variants of these techniques or combinations thereof, as described in the prior art, for example in Rampal, DNA Arrays: Methods and Protocols (Methods in Molecular Biology) 2010; Graham & Hill, DNA Sequencing Protocols (Methods in Molecular Biology) 2001; Schuster, Nat. Methods, 2008 and Brenner, Nat. Biotech., 2000; Mardis, Annu Rev Genomics Hum Genet., 2008, which are incorporated herein by reference. Genome-wide arrays can be purchased from different suppliers such as Illumina or Affymetrix. For primer selection, multiplexing and assay design, and the mass-extension for producing primer extension products the MassARRAY Assay Designer software may be used using the sequences presented in Table 2 as input. The MassARRAY Typer 3.4 software may be used for genotype calling.

[084] For example, the presence or absence of a polymorphism genotype can be detected by determining the nucleotide sequence at the respective locus and may be carried out by allele-specific oligonucleotide (ASO)-dot blot analysis, primer extension assays, iPLEX polymorphism / SNP genotyping, dynamic allele-specific hybridization (DASH) genotyping, the use of molecular beacons, tetra primer ARMS PCR, a flap endonuclease invader assay, an oligonucleotide ligase assay, PCR-single strand conformation polymorphism (SSCP) analysis, quantitative real-time PCR assay, polymorphism / SNP microarray based analysis, restriction enzyme fragment length polymorphism (RFLP) analysis, targeted resequencing analysis and/or whole genome sequencing analysis. In some embodiments, any of the methods described herein can comprise the determination of the haplotype for two copies of the chromosome comprising the polymorphism genotypes identified herein.

[085] In another example, genomic DNA isolated from a biological sample can be amplified using PCR as described above. The amplicons can be detectably-labeled during the amplification (e.g., using one or more detectably labeled dNTPs) or subsequent to the amplification. Following amplification and labeling, the detectably-labeled-amplicons are

then contacted with a plurality of polynucleotides, containing one or more of a polynucleotide (e.g., an oligonucleotide) being capable of specifically hybridizing to a corresponding amplicon containing a specific polymorphism, and where the plurality contains many probe sets each corresponding to a different, specific polymorphism. Generally, the probe sets are bound to a solid support and the position of each probe set is predetermined on the solid support. The binding of a detectably-labeled amplicon to a corresponding probe of a probe set indicates the presence of a nucleic acid containing the polymorphism so amplified in the biological sample. Suitable conditions and methods for detecting a polymorphism or SNP using nucleic acid arrays are further described in, e.g., Lamy et al. (2006) Nucleic Acids Research 34(14): e100; European Patent Publication No. 1234058; U.S. Publication Nos. 2006/0008823 and 2003/0059813; and U.S. Patent No. 6,410,231; the disclosures of each of which are incorporated herein by reference in their entirety.

[086] In yet another example, MALDI-TOF (matrix-assisted laser desorption ionization time of flight) mass spectrometry on the Sequenom platform (San Diego, USA) may be used to detect one or more polymorphism genotypes.

[087] Polynucleotides for use in detection of one or more of the polymorphism genotypes disclosed in Tables 2, 5, 6 or 7 are capable of specifically hybridizing to nucleic acids comprising said one or more polymorphism genotypes and can comprise the nucleic acid sequences of the polymorphism genotypes themselves, including up and/or downstream, flanking sequences, e.g., as hybridization polynucleotide probes or primers (e.g., for amplification or reverse transcription). “Capable of specifically hybridizing”, as used herein, refers to capability of hybridization under stringent conditions in any one of the methods of detection involving hybridization disclosed herein, as known to one skilled in the art. In that sense, primers and probes useful in such detection methods are particular polynucleotides capable of specifically hybridizing.

[088] Primers or probes should contain a sequence of sufficient length and complementarity to a corresponding polymorphism locus to specifically hybridize with that locus under suitable hybridization conditions. For example, the polymorphism probes can include at least one (e.g., at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least 10, at least 11, at least 12, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, or 55 or more) nucleotides 5’ or 3’ to the polymorphism of interest. The polymorphic site of each probe (i.e., the polymorphism region) is generally flanked on one or both sides by

sequence that is common among the different alleles. In specific embodiments, the polynucleotides capable of specifically hybridizing to the polymorphism genotypes are selected from the group consisting of the polynucleotides disclosed as “AlleleA Probe” in Table 2. The term "primer" may denote an oligo- or polynucleotide that acts as an initiation point of nucleotide synthesis under conditions in which synthesis of a primer extension product complementary to a nucleic acid strand is induced. The term "probe" may denote an oligonucleotide that is capable of specifically hybridizing to a target nucleic acid under suitable conditions, e.g., stringent conditions suitable for allele-specific hybridization. Primers and probes can be designed such are suitable for discriminating between wild-type allele or mutated allele of the position of a polymorphism to be analyzed, as described, e.g., by Coleman, and Tsongalis, Molecular Diagnostics: For the Clinical Laboratorian, 2007; Weiner et al. Genetic Variation: A Laboratory Manual, 2010, which are incorporated herein by reference.

[089] Any of the methods of detecting a polymorphism can, optionally, be performed in multiplex formats that allow for rapid preparation, processing, and analysis of multiple samples, see above.

[090] The detected polymorphism genotypes may be represented by values 0, 1 or 2. The value "0" may indicate that the polymorphism is present on none of the two homologous chromosomes, or in no allele, or is absent. The value "1" may indicate that the polymorphism is present on one of the two homologous chromosomes, or in one allele, or that the polymorphism genotype is heterozygous. The value "2" may indicate that the polymorphism is present on both homologous chromosomes, or in both alleles, or that the polymorphism genotype is homozygous.

[091] The term "predicting a treatment response from the presence or absence of the one or more polymorphism genotypes", as used herein, generally refers to a prediction step that provides a reasonably high prediction performance by associating the presence or absence of a polymorphism genotype with a treatment response. Similarly, the term “polymorphism genotype associated with a treatment response of a subject to treatment with a CRHR1 antagonist”, as used herein, generally refers to a polymorphism genotype being predicted to be associated with a treatment response with a reasonably high prediction performance. Specifically, the predicting step may comprise determining whether the subject will respond, or has an increased likelihood of responding to the treatment with a CRHR1 antagonist; and/or (b) determining whether the subject will not respond, or has a decreased likelihood of responding to the treatment with a CRHR1

antagonist. This is generally achieved herein by associating the presence or absence of the one or more polymorphism genotypes as a variable with a value indicative for treatment response within an algorithm for predicting a treatment response to a treatment with a CRHR1 antagonist, which is commonly a computer-implemented algorithm. The evaluation of the performance of the algorithm may depend on the problem the algorithm is applied for. If the algorithm is used to identify patients that are likely to respond to treatment with CRHR1 antagonists, the performance is preferably expressed by a high accuracy and/or sensitivity and/or precision. If patients should be identified which are likely not to respond to the treatment with CRHR1 antagonists, specificity and/or negative predictive value can be statistical measures to describe the performance of the prediction algorithm. For optimizing the prediction performance of the method of predicting a treatment response, a step of determining and/or optimizing the algorithm by a machine-learning method in a first subset of the test set and testing the prediction performance in an second independent subset of the test set may be carried out and repeated based on different numbers and groups of polymorphism genotypes, until the desired prediction performance is reached. Specifically, the algorithm for predicting may comprise a classification function (also known as binary classification test), which can comprise one or more statistical analysis methods and/or machine learning methods which are available to one of skill in the art. Specifically, statistical analysis methods and/or machine learning methods to be used in the invention may be selected from the group consisting of artificial neural network learning, decision tree learning, decision tree forest learning, linear discriminant analysis, non-linear discriminant analysis, genetic expression programming, relevance vector machines, linear models, generalized linear models, generalized estimating equations, generalized linear mixed models, the elastic net, the lasso support vector machine learning, Bayesian network learning, probabilistic neural network learning, clustering, and regression analysis, e.g., as described and exemplified herein. Statistical methods and/or machine learning methods from the group mentioned above may exist in different variants, especially applying or not applying prior and posterior weights in the analysis leading to solutions which may be applicable in different settings and may lead to models with more or less explanatory variables. The results of single methods may be used in a method called “ENSEMBLE learning” in which the results of several single analysis with one of the methods mentioned above are combined to arrive at a better prediction using either simply majority vote or using one of the machine learning algorithms with the results of the single analyses again as input to that specific algorithm..

[092] In an exemplary embodiment of the method of the invention, the number of minor alleles for both polymorphism rs74888440 (P1) and rs9813396 (P2) is coded as a numeric variable, which can take one of the following values: 0, 1 or 2, denoting the two variables thus created as V1 for rs74888440 and V2 for rs9813396. Each subject is designated a value of the predictive quantitative variable PQV such that PQV = 0.3205619 + (0.2923413*V1) + (0.2362708 *V2) + (-0.0104643 *V1*V2). Depending on whether a subject's PQV is above or below a value of 0.5, that person is then predicted to not to respond, or to have a decreased likelihood of responding to a treatment with a CRHR1 antagonist (if PQV <= 0.5), or to respond, or to have an increased likelihood of responding to a treatment with a CRHR1 antagonist (if PQV > 0.5). For example, a subject who has no minor alleles at either of the two polymorphisms (homozygous for the common allele at both loci, such that V1 = V2 = 0) is designated a PQV of 0.3205619 and is consequently predicted to be a non-responder. In another example, a subject who is heterozygous at P1 (V1=1) and homozygous for P2 (V2=2) is then designated a PQV of (0.3205619) + (0.2923413 *1) + (0.2362708 *2) + (-0.0104643 *1*2) = 1.064516 and is, in consequence, predicted to be a responder. In this example, a sensitivity of 0.6285714 and a specificity of 0.6626506 is reached.

[093] In another exemplary embodiment of the method of the invention, the number of minor alleles for both SNPs rs74888440 (P1) and rs220806 (P2) is coded as a numeric variable, which can take one of the following values: 0, 1 or 2, denoting the two variables thus created as V1 for rs74888440 and V2 for rs220806. Each subject is designated a value of the predictive quantitative variable PQV such that PQV = 0.539548 + (0.460452 *V1) + (-0.1765537 *V2) + (-0.1567797 *V1*V2). Depending on whether a subject's PQV is above or below a value of 0.5, that subject is then predicted to not to respond, or to have a decreased likelihood of responding to a treatment with a CRHR1 antagonist (if PQV <= 0.5), or to respond, or to have an increased likelihood of responding to a treatment with a CRHR1 antagonist (if PQV > 0.5). For example, a subject who has no minor alleles at either of the two SNPs (homozygous for the common allele at both loci, such that V1 = V2 = 0) is designated a PQV of 0.539548 and is consequently predicted to be a responder. In another example, a subject who is heterozygous at SNP1 (V1=1) and homozygous for SNP2 (V2=2) is then designated a PQV of (0.539548) + (0.460452 *1) + (-0.1765537 *2) + (-0.1567797 *1*2) = 0.3333333 and is, in consequence, predicted to be a non-responder. In this example, a sensitivity of 0.6857143 and a specificity of 0.626506 is reached.

[094] In a similar manner, one of skill in the art, having the polymorphisms of Table 2 and the additional information above at hand, will readily derive suitable methods, combinations of methods, parameters and/or coefficients such as those exemplified herein, for use in the methods of the invention, achieving a high performance of prediction.

[095] Preferably, the prediction of the treatment response is made with a high accuracy, sensitivity, precision, specificity and/or negative predictive value.

[096] “Accuracy”, “sensitivity”, “precision”, “specificity” and “negative predictive value” are exemplary statistical measure of the performance of the prediction algorithm. In the following, examples are given for determining the performance of the prediction algorithm.

[097] As used herein, accuracy may be calculated as (number of true positives + number of true negatives) / (number of true positives + number of false positives + number of true negatives + number of false negatives), e.g., (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients correctly diagnosed as not responding to CRHR1 antagonist) / (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients wrongly diagnosed as responding to CRHR1 antagonist + number of patients correctly diagnosed as not responding to CRHR1 antagonist + number of patients wrongly diagnosed as not responding to CRHR1 antagonist). In some embodiments, the accuracy of prediction is higher than 50%, at least 60%, at least 70%, at least 80% or at least 90%.

[098] As used herein, sensitivity may be calculated as (true positives) / (true positives + false negatives), e.g., (number of patients correctly diagnosed as responding to CRHR1 antagonist) / (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients wrongly diagnosed as not responding to CRHR1 antagonist). In some embodiments, the sensitivity of prediction is higher than 50%, at least 60%, at least 70%, at least 80% or at least 90%.

[099] As used herein, precision (also referred to as positive predictive value) may be calculated as (true positives) / (true positives + false positives), e.g.: (number of patients correctly diagnosed as responding to CRHR1 antagonist) / (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients wrongly diagnosed as responding to CRHR1 antagonist). In some embodiments, the precision of prediction is higher than 50%, at least 60%, at least 70%, at least 80% or at least 90%.

[0100] As used herein, specificity is calculated as (true negatives) / (true negatives + false positives), e.g.: (number of patients correctly diagnosed as not responding to

CRHR1 antagonist) / (number of patients correctly diagnosed as not responding to CRHR1 antagonist + number of patients wrongly diagnosed as responding to CRHR1 antagonist). In some embodiments, the specificity of prediction is higher than 50%, at least 60%, at least 70%, at least 80% or at least 90%.

[0101] As used herein, negative predictive value is calculated as (true negatives) / (true negatives + false negatives), e.g.: (number of patients correctly diagnosed as not responding to CRHR1 antagonist) / (number of patients correctly diagnosed as not responding to CRHR1 antagonist + number of patients wrongly diagnosed as not responding to CRHR1 antagonist). In some embodiments, the negative predictive value is higher than 50%, at least 60%, at least 70%, at least 80% or at least 90%.

[0102] Other statistical measures useful for describing the performance of the prediction algorithm are geometric mean of sensitivity and specificity, geometric mean of positive predictive value and negative predictive value, F-measure and area under ROC curve, and the positive and negative likelihood ratios, the false discovery rate and Matthews correlation coefficient. These measures and method for their determination are well known in the art.

[0103] In general, a prediction algorithm with high sensitivity may have low specificity and *vice versa*. For the purposes of the present invention, it is generally preferable that the prediction algorithm is based on a number of polymorphism genotypes selected from Table 2 sufficient to achieve a sensitivity and specificity of higher than 50% each, optionally at least 60% each, at least 70% each, at least 80% each, or at least 90% each.

[0104] For a prediction whether a patient will respond, or has an increased likelihood of responding to a treatment with a CRHR1 antagonist, the prediction algorithm may be based on a number of polymorphisms sufficient to achieve a prediction sensitivity and/or precision of higher than 50%, optionally at least 60%, at least 70%, at least 80%, or at least 90%.

[0105] For the prediction whether the subject will not respond, or has a decreased likelihood of responding to a treatment with a CRHR1 antagonist, the prediction algorithm may be based on a number of polymorphisms sufficient to achieve a prediction specificity and/or negative predictive value of higher than 50%, optionally at least 60%, at least 70%, at least 80%, or at least 90%.

[0106] For a prediction whether a patient responds to a treatment with CRHR1 antagonists or not, the prediction algorithm may be based on a number of polymorphisms

sufficient to achieve sensitivity and/or precision and/or specificity and/or negative predictive value of higher than 50%, optionally at least 60%, at least 70%, at least 80%, or at least 90%.

[0107] Based on the disclosure of the present invention, in particular of the highly useful set of polymorphism genotypes disclosed in Table 2, the skilled person in the art is enabled to employ the statistical analysis methods and/or machine-learning methods disclosed herein and to identify suitable parameters for further improving the prediction performance, as defined above. The whole statistical work-flow can be automated by the use of an algorithm as described above, implemented and/or stored on a machine-readable medium, e.g., implemented and/or stored on a computer.

[0108] Typically, at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 20, at least 30, at least 50, at least 100, at least 100, at least 200 or all polymorphism genotypes disclosed in Table 2 are used for predicting the treatment response to a CRHR1 antagonist.

[0109] Using various such polymorphism genotype sets and statistical analysis methods as described above, the present invention consistently achieves a high predictive performance in directly predicting a clinical response. For instance, Example 1 describes a study with clinical data from 300 enrolled patients, wherein 150 polymorphism genotypes were used in a method for predicting the clinical treatment response of subjects to a treatment with a CRHR1 antagonist. Therein, a sensitivity of about 78% and a specificity of about 73% was observed, which is considered to reflect a superior reliability in predicting both true positive responses and true negative responses. Further, Example 2 provides examples of minimal subsets of only one, two, four or eight polymorphism genotypes selected from the group of polymorphism genotypes disclosed in Table 2, achieving a performance of predicting a clinical treatment response with values for specificity and sensitivity which are still higher than 60%, or even higher than 70%. Predictive performance in terms of sensitivity and specificity can be further increased to at least 75% each, e.g., by including specific combinations of 32 polymorphism genotypes, as is also shown in Example 2.

[0110] Furthermore, in patients with depressive symptoms and/or anxiety symptoms, another embodiment of the method for predicting a treatment response to CRHR1 antagonists, the method of predicting a treatment response as described above may be also accompanied by analyzing the rapid-eye- movement (REM) sleep, e.g. during night sleep of a patient in a sleep EEC. In some embodiments, an alteration in REM sleep may

serve as an additional biomarker to identify subjects who would benefit from treatment with a CRHR1 antagonist. REM sleep typically comprises a characteristic coincidence of nearly complete muscle atonia, a waking-like pattern of brain oscillations and rapid eye movements (REMs). The amount of REMs during consecutive REM sleep episodes is usually increasing throughout the night. Single and short REMs with low amplitude can be characteristic for initial parts of REM sleep. The amount of REMs, in particular within the first REM sleep episode, can be of clinical relevance. Recent clinical and animal data supports the correlation of REM density with an increased CRH activity. For example, Kimura et al. (Mol. Psychiatry, 2010) showed that mice overexpressing CRH in the forebrain exhibit constantly increased rapid eye movement (REM) sleep compared to wildtype mice. In addition, it could be shown that treatment with the CRHR1 antagonist DMP696 could reverse the REM enhancement. Further, the polymorphism analysis and REM density analysis as described herein may be combined for predicting the response of patients with depressive symptoms and/or anxiety symptoms to treatment with a CRHR1 antagonist. The REM analysis may be carried out before, concomitant or after the polymorphism analysis. For example, the REM density analysis may be carried out on subjects that where identified by the polymorphism analysis as responding, or having an increased likelihood of responding to the treatment with a CRHR1 antagonist; or as not responding, or having a decreased likelihood of responding to the treatment with a CRHR1 antagonist. The recording of a "sleep-EEG" (also referred to "polysomatic recordings") may comprise electroencephalography (EEG), vertical and horizontal elecrooculography (EOG), electromyography (EMG) and/or electrocardiography (ECG). In EOG, muscle activities of right and left eye may be recorded by electrooculograms (one or typically two channels) in order to visualize the phasic components of REM sleep. "REM analysis" or "analyzing the rapid-eye-movement (REM)" may refer to a method comprising recoding of muscle activities of right and left eye by EOG and then analyzing the electrooculogram. The recognition of REM in the electrooculogram may be done manually, for example by standard guidelines Rechtschaffen and Kales, 1968, Bethesda, MD: National Institute of Neurological Diseases and Blindness, incorporated herein by reference in its entirety.

Methods of Treatment

[0111] In a further aspect, the present invention also provides methods of treating a condition treatable by treatment with a CRHR1 antagonist in a subject in need thereof, comprising administering an effective amount of a CRHR1 antagonist to a subject in need

thereof, wherein the subject has been predicted to respond, or has an increased likelihood of responding, to treatment with a CRHR1 antagonist, as determined by the method described above, and wherein the CRHR1 antagonist is a compound of Formula I, as defined herein, or any one of "formulae I-VI" as disclosed at pages 2-6 and 12-48 of WO 2013/160317 (A2) (PCT/EP2013/058413). Likewise the invention features a CRHR1 antagonist for use in treating a condition treatable by treatment with a CRHR1 antagonist in a subject in need thereof, wherein the subject has been predicted to respond, or has an increased likelihood of responding, to treatment with a CRHR1 antagonist, as determined by the method described above, and wherein the CRHR1 antagonist is a compound of Formula I, as defined herein, or any one of "formulae I-VI" as disclosed at pages 2-6 and 12-48 of WO 2013/160317 (A2) (PCT/EP2013/058413).

[0112] Conditions which are treatable by a treatment with a CRHR1 antagonist are generally defined above. Specific conditions comprise, but are not limited to, behavioural disorders, psychiatric disorders, mood disorders, neurological disorders, neurodegenerative disorders, inflammatory or stress-induced immune disorders, CRH-related cardiovascular diseases or metabolic diseases. Specifically, such conditions comprise anxiety symptoms, generalized anxiety disorder, panic, phobias, obsessive-compulsive disorder, post-traumatic stress disorder, sleep disorders induced by stress, pain perception such as fibromyalgia, mood disorders such as depressive symptoms, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression, dysthymia, bipolar disorders, cyclothymia, chronic fatigue syndrome, stress-induced headache, eating disorders such as anorexia and bulimia nervosa, hemorrhagic stress, stress-induced psychotic episodes, euthyroid sick syndrome, syndrome of inappropriate antidiarrhetic hormone (ADH), obesity, infertility, head traumas, spinal cord trauma, ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia), excitotoxic neuronal damage, epilepsy, senile dementia of the Alzheimers type, multi-infarct dementia, amyotrophic lateral sclerosis, chemical dependencies and addictions (e.g., dependencies on alcohol, nicotine, cocaine, heroin, benzodiazepines, or other drugs), drug and alcohol withdrawal symptoms, hypertension, tachycardia, congestive heart failure, osteoporosis, premature birth, and hypoglycaemia, inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies, irritable bowel syndrome, Crohn's disease, spastic colon, post-operative ileus, ulcer, diarrhea, stress-induced fever, human immunodeficiency virus (HIV)

infections, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease, gastrointestinal diseases, stroke, stress induced immune dysfunctions, muscular spasms, urinary incontinence. In a preferred embodiment, the condition is selected from the groups consisting of depressive symptoms, anxiety symptoms or both depressive symptoms and anxiety symptoms.

[0113] Any CRHR1 antagonist as generally defined by Formula I herein, or any one of "formulae I-VI" as disclosed at pages 2-6 and 12-48 of WO 2013/160317 (A2) (PCT/EP2013/058413) can be used in the method of treatment. In a specific embodiment of the method of treatment, the CRHR1 antagonist is selected from the group consisting of a Type I CRHR1 antagonist, a bicyclic Type II CRHR1 antagonist, an atypical CRHR1 antagonist or a cyclohexyl amide CRHR1 antagonist. In another specific embodiment of the method of treatment, the CRHR1 antagonist is selected from the group consisting of GW876008 (Emicerfont), GSK-561679 (NBI-77860, Verucerfont), GSK586529, BMS-562,086 (Pexacerfont), NBI-30775 (R-121919), NBI-34101, CP-316,311, CP-376,395, PF-00572778, NVP-AAG561, Ono-2333MS, E2508, E2009, R317573 (JNJ19567470, CRA5626), R278995 (CRA0450), CRA-1000, CRA-1001, CP154,526, Antalarmin, DMP-695, DMP-696, DMP-904, SC-241, BMS-561388, NBI30545, PD-171729, NBI34041, NBI35965, SN003, NBI-27914, *trans*-2-chloro-N-(4-((5-fluoro-4-methyl-pyridin-2-ylamino)-methyl)-cyclohexyl)-5-(trifluoromethyl)-benzamide, or a pharmaceutically acceptable salt thereof. In one embodiment of the method of treatment, the CRHR1 antagonist is not SSR-125543.

[0114] It will be appreciated that reference to treatment is intended to include prevention as well as the partial alleviation, or full remission of symptoms.

[0115] CRHR1 antagonists may be administered as the raw chemical but the active ingredient is preferably formulated in a pharmaceutical composition suitable for administration by any convenient route, preferably in a form suitable for use in human medicine. The treatment can comprise any suitable route of administration, such as oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose) administration of the CRHR1 antagonist.

[0116] CRHR1 antagonists can be administered at any suitable efficacious dose, which one skilled in the art will readily adapt, e.g., to the specific condition to be treated. For many therapeutic indications as encompassed herein, a dose of about 1 mg to about 2000 mg per day, about 2 mg to about 1000 mg per day, about 5 mg to about 500 mg per

day, about 10 mg to about 250 mg, or about 20 to about 100 mg daily will be efficacious. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected. Thus, for parenteral administration a daily dose will typically be in the range of 1 to about 100 mg, preferably 1 to 80 mg per day. For oral administration a daily dose will typically be within the range of 1 to 300 mg e.g. 1 to 100 mg of a CRHR1 antagonist. For instance, in treating depressive symptoms and/or anxiety symptoms, daily oral doses of about 10 mg, about 20 mg, or about 100 mg of a CRHR1 antagonist can be efficacious.

Compositions, kits and arrays and uses thereof

[0117] The disclosure further provides compositions comprising polynucleotides (e.g., probes), as well as kits and arrays. Polynucleotide compositions, kits, and arrays are useful in, e.g., detecting the presence of (a) one or more polymorphism genotypes as disclosed in Table 2, (b) one or more polymorphism genotypes being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or a combination of (a) and (b). The compositions, kits and arrays are further useful for predicting the treatment response of a subject to treatment with a CRHR1 antagonist.

[0118] The compositions, kits or arrays can include at least one polynucleotide capable of specifically hybridizing to a nucleic acid comprising: (a) at least one polymorphism genotype as disclosed in Table 2; (b) at least one polymorphism genotype being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or (c) a combination of (a) and (b). In one embodiment, the at least one polynucleotide comprises less than 100,000, less than 90,000, less than 80,000, less than 70,000, less than 60,000, less than 50,000, less than 40,000, less than 30,000, less than 20,000, less than 15,000, less than 10,000, less than 5,000, less than 4,000, less than 3,000, less than 2,000, less than 1,500, less than 1,000, less than 750, less than 500, less than 200, less than 100, or less than 50 different polynucleotides in total. Specifically, the compositions, kits or arrays can include at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least 10, at least 11, at least 12, at least 15, at least 20, or at least 30, or at least 50, or at least 100, or at least 200, or 274 polynucleotides capable of specifically hybridizing to each of at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least 10, at least 11, at

least 12, at least 15, at least 20, or at least 30, or at least 50, or at least 100, or at least 200, or 274 of (a) at least one polymorphism genotype as disclosed in Table 2; (b) at least one polymorphism genotype being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or (c) a combination of (a) and (b).

[0119] A polynucleotide can include a coding sequence or non-coding sequence (e.g., exons, introns, or 5' or 3' regulatory sequences). The polynucleotide can also be single or double-stranded and of variable length. In some embodiments, the length of one strand of a polynucleotide capable of specifically hybridizing to a nucleic acid comprising: (a) at least one a polymorphism genotype as disclosed in Table 2; (b) at least one polymorphism genotype being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or (c) a combination of (a) and (b) can be about six nucleotides (e.g., about seven nucleotides, about eight nucleotides, about nine nucleotides, about 10 nucleotides, about 12 nucleotides, about 13 nucleotides, about 14 nucleotides, about 15 nucleotides, about 20 nucleotides, about 25 nucleotides, about 30 nucleotides, about 35 nucleotides, about 40 nucleotides, about 50 nucleotides, about 75 nucleotides, about 100 nucleotides, or about 150 or more nucleotides) in length. As is commonly known in the art, a longer polynucleotide often allows for higher stringency hybridization and wash conditions. The polynucleotide can be DNA, RNA, modified DNA or RNA, or a hybrid, where the nucleic acid contains any combination of deoxyribo- and ribo-nucleotides, and any combination of uracil, adenine, thymine, cytosine and guanine, as well as other bases such as inosine, xanthine, and hypoxanthine.

[0120] The polynucleotides can be attached to a solid support, e.g., a porous or non-porous material that is insoluble. The polynucleotides can be arranged in an array on the solid support, e.g., in a microarray. A solid support can be composed of a natural or synthetic material, an organic or inorganic material. The composition of the solid support on which the polynucleotide sequences are attached by either 5' or 3' terminal attachment generally depend on the method of attachment (e.g., covalent attachment). Suitable solid supports include, but are not limited to, plastics, resins, polysaccharides, silica or silica-based materials, functionalized glass, modified silicon, carbon, metals, inorganic glasses, membranes, nylon, natural fibers such as silk, wool and cotton, or polymers. The material comprising the solid support can have reactive groups such as carboxy, amino, or hydroxyl groups, which are used for attachment of the polynucleotides. Polymeric solid supports can include, e.g., polystyrene, polyethylene glycol tetraphthalate, polyvinyl acetate, polyvinyl chloride, polyvinyl pyrrolidone, polyacrylonitrile, polymethyl methacrylate,

polytetrafluoroethylene, butyl rubber, styrenebutadiene rubber, natural rubber, polyethylene, polypropylene, (poly)tetrafluoroethylene, (poly)vinylidenefluoride, polycarbonate, or polymethylpentene (see, e.g., U.S. Patent No. 5,427,779, the disclosure of which is hereby incorporated by reference in its entirety). Alternatively, polynucleotides can be attached to the solid support without the use of such functional groups.

[0121] Arrays of polynucleotides can also be conjugated to solid support particles. Many suitable solid support particles are known in the art and illustratively include, e.g., particles, such as Luminex®-type encoded particles, magnetic particles, and glass particles. Exemplary particles that can be used can have a variety of sizes and physical properties. Particles can be selected to have a variety of properties useful for particular experimental formats. For example, particles can be selected that remain suspended in a solution of desired viscosity or to readily precipitate in a solution of desired viscosity. Particles can be selected for ease of separation from sample constituents, for example, by including purification tags for separation with a suitable tag-binding material, paramagnetic properties for magnetic separation, and the like. In some embodiments, encoded particles are used. Each particle includes a unique code (such as a bar code, luminescence code, fluorescence code, a nucleic acid code, and the like). Encoding can be used to provide particles for evaluating different nucleic acids in a single biological sample. The code is embedded (for example, within the interior of the particle) or otherwise attached to the particle in a manner that is stable through hybridization and analysis. The code can be provided by any detectable means, such as by holographic encoding, by a fluorescence property, color, shape, size, weight, light emission, quantum dot emission and the like to identify particle and thus the capture probes immobilized thereto. Encoding can also be the ratio of two or more dyes in one particle that is different than the ratio present in another particle. For example, the particles may be encoded using optical, chemical, physical, or electronic tags. Examples of such coding technologies are optical bar codes fluorescent dyes, or other means. In some embodiments, the particle code is a nucleic acid, e.g., a single stranded nucleic acid.

[0122] Different encoded particles can be used to detect or measure multiple nucleic acids (e.g., polymorphism genotypes or mRNAs) in parallel, so long as the encoding can be used to identify the polynucleotide (corresponding to an analyte nucleic acid) on a particular particle, and hence the presence or amount of the analyte nucleic acid (e.g., a polymorphism genotypes or mRNA from a biological sample) being evaluated. A sample can be contacted with a plurality of such coded particles. When the particles are

evaluated, e.g., using a fluorescent scanner, the particle code is read as is the fluorescence associated with the particle from any probe used to evaluate modification of the intact substrate associated with the particles.

[0123] One exemplary platform utilizes mixtures of fluorescent dyes impregnated into polymer particles as the means to identify each member of a particle set to which a specific capture probe has been immobilized. Another exemplary platform uses holographic barcodes to identify cylindrical glass particles. For example, Chandler et al. (U.S. Patent No. 5,981,180) describes a particle-based system in which different particle types are encoded by mixtures of various proportions of two or more fluorescent dyes impregnated into polymer particles. Soini (U.S. Patent No. 5,028,545) describes a particle-based multiplexed assay system that employs time-resolved fluorescence for particle identification. Fulwyler (U.S. Patent No. 4,499,052) describes an exemplary method for using particle distinguished by color and/or size. U.S. Publication Nos. 2004-0179267, 2004-0132205, 2004-0130786, 2004-0130761, 2004-0126875, 2004-0125424, and 2004-0075907 describe exemplary particles encoded by holographic barcodes.

[0124] U.S. Patent No. 6,916,661 describes polymeric microparticles that are associated with nanoparticles that have dyes that provide a code for the particles. The polymeric microparticles can have a diameter of less than one millimeter, e.g., a size ranging from about 0.1 to about 1,000 micrometers in diameter, e.g., 3-25 µm or about 6-12 µm. The nanoparticles can have, e.g., a diameter from about 1 nanometer (nm) to about 100,000 nm in diameter, e.g., about 10 - 1,000 nm or 200 - 500 nm.

[0125] An “array”, as used herein, refers to a plurality of polynucleotides comprised in the composition or kit being immobilized at predetermined positions on a solid support such that each polynucleotide can be identified by its position.

[0126] The compositions, kits and arrays can be, but are not necessarily used in genome-wide genotyping analysis, but for efficient, low cost, and application-specific genotyping analysis, tailored to be used in the methods of predicting a treatment response to a treatment with a CRHR1 antagonist, as disclosed herein. Thus, in some embodiments of any of the compositions, kits and arrays described herein, the array of polynucleotides has less than 100,000 (e.g., less than 90,000; less than 80,000; less than 70,000; less than 60,000; less than 50,000; less than 40,000; less than 30,000; less than 20,000; less than 15,000; less than 10,000; less than 5,000; less than 4,000; less than 3,000; less than 2,000; less than 1,500; less than 1,000; less than 750; less than 500, less than 200, less than 100, or less than 50) different polynucleotides.

[0127] The kits described above can, optionally, contain instructions for detecting the presence or absence of the at least one polymorphism genotype in a sample obtained from a subject. In some embodiments, the kits can include one or more reagents for processing a biological sample. For example, a kit can include reagents for isolating mRNA or genomic DNA from a biological sample and/or reagents for amplifying isolated mRNA (e.g., reverse transcriptase, primers for reverse transcription or PCR amplification, or dNTPs) and/or genomic DNA. The kits can also, optionally, contain one or more reagents for detectably-labeling an mRNA, mRNA amplicon, genomic DNA or DNA amplicon, which reagents can include, e.g., an enzyme such as a Klenow fragment of DNA polymerase, T4 polynucleotide kinase, one or more detectably-labeled dNTPs, or detectably-labeled gamma phosphate ATP (e.g., 33P-ATP). In some embodiments, the kits can include a software package for analyzing the results of, e.g., a microarray analysis. The kits described herein can also, optionally, include instructions for administering a CRHR1 antagonist where presence or absence of one or more polymorphism genotypes detectable by the plurality of polynucleotides or the array predicts that a subject will response to a CRHR1 antagonist.

[0128] The following are examples of the practice of the invention. They are not to be construed as limiting the scope of the invention in any way.

EXAMPLES

Example 1

[0129] Based on basic science studies, the role of CRH was recognized as causal for signs and symptoms prevalent in depression, rendering blocking of CRH/CRHR1 signalling as a viable treatment option. Further clinical findings have found that CRH is elevated in a subgroup of patients with depression, where CRH causes core symptoms. Compound SSR-125543 has been developed elsewhere as a specific CRHR1 antagonist blocking the effect of CRH. A clinical trial evaluating the efficacy and tolerability of SSR-125543 in comparison to placebo and a standard antidepressant has been carried out previously without having predicted the treatment response according to the invention. However, based on additional studies (not published), it was recognized that among patients diagnosed with major depression, only a fraction of 20-30% has central CRH over-activity. Thus, a substantial fraction of non-stratified patients might not show a treatment response, in view of about 70-80% of patients treated with the CRHR1 antagonist not

having a central CRH increase. Given the pharmacological specificity, only patients with central CRH-over-activity are likely to benefit from CRHR1 antagonists, such as SSR-125543.

[0130] Here, a method of predicting a clinical treatment response (e.g., as measured by the HAM-D score) has been devised, which detects one or more polymorphism genotypes selected from the polymorphism genotypes disclosed in Table 2, using a chip containing probes specific for these polymorphism genotypes, allowing for identification of depressive patients being likely to respond to a treatment with a CRHR1 antagonist such as SSR-125543. DNA samples obtained from 300 subjects enrolled in the earlier clinical trial, as mentioned above, were extensively analyzed by polymorphism genotyping. Using a machine-learning algorithm as described herein, polymorphism genotypes predictive of a response to SSR-125543 were identified, as disclosed in Table 2. Further, 150 or more polymorphism genotypes of this set were used to further "train" the algorithm, assisted by common machine-learning algorithms as described herein, and to test the prediction. Thus, having the set of useful polymorphism genotypes as disclosed in Table 2, at hand, a prediction algorithm can be readily devised, which provides superior prediction of a clinical response with high sensitivity and specificity. As is shown in Table 3, test predictions of a clinical response with a sensitivity of about 78% and a specificity of about 73% have been achieved.

Table 3

		Observed phenotype	
		Good response	Poor response
Test prediction	Good response	**21**	13
	Poor response	6	**36**
		Sensitivity 78%	Specificity 73%

[0131] To exclude the possibility that the polymorphism genotypes disclosed herein are merely identifying patients that are good responders to any kind of drug intervention, the performance of the method among patients treated with the standard antidepressant escitalopram used as comparator in the earlier clinical trial has also been tested. The sensitivity was 50%, and specificity was 43%, and thus insensitive and

unspecific regarding prediction of response to a standard antidepressant, see Table 4. Therefore, the present method is to be considered highly specific for predicting the response to CRHR1 antagonists.

Table 4

		Observed phenotype	
		Good response	Poor response
Test prediction	Good response	**23**	17
	Poor response	23	**13**
		Sensitivity 50%	Specificity 43%

[0132] The above results were further challenged by considering a "lucky split" between the training and the testing cohort. Another 10.000 random splits were calculated which corroborated the initial result, achieving an odds ratio of 5, which indicates that chances of non-response are 5 times higher if the CRH genotyping analysis described herein predicts poor response. Transforming these findings into a time course curve where those depressed patients that where tested positive in the CRH genotyping analysis and treated with SSR-125543 were compared with patients treated by placebo resulted in a clear superiority of the investigational drug, see Figure 1. The time course curves revealed a marked difference between placebo and SSR-125543 beginning after 2 weeks of treatment, as measured using, e.g., the HAM-D scale. The difference in response between patients treated with SSR-125543 and those under placebo is significant ($p < 0.01$). In essence, subjects which are tested positive using the method of prediction described herein, based on a CRH genotyping analysis using 150 of the polymorphism genotypes disclosed in Table 2, constitute 28% of the overall patient sample and 78% patients from this sample were responders when treated with SSR-125543.

Example 2

[0133] To further evaluate the usefulness of the set of polymorphism genotypes provided in Table 2, further predictions have been tested using minimal subsets selected

as prediction variables. As few as singular polymorphism genotypes selected from Table 2, as well as subsets of two, four or eight polymorphism genotypes selected from Table 2 proved useful in the method of predicting a clinical response, e.g., as measured by the HAM-D scale.

[0134] Treatment response to an anti-depressant therapy comprising SSR-125543 was predicted based on the same patient data of the earlier clinical trial and polymorphism genotyping set as described above, using statistical tools selected from the group consisting of random forests, support vector machines, neural networks, linear discriminant analyses, clustering methods such as k-nearest neighbours and their respective derivatives, linear models and their derivatives, as well as their combinations.

[0135] Surprisingly, even this univariate, bivariate, quadrivariate or octovariate analyses using combinations of polymorphism genotypes as disclosed in Tables 2, 5-7 herein, yielded clinical response predictions of a quality significantly better (i.e. both sensitivity and specificity > 50%) than randomness, based on assessing the P-value of concordance between observed and predicted outcome in a 10-fold cross-validation procedure.

[0136] In particular, a total number of 78 singular polymorphism genotypes was identified with nominally significant P-values. Of those, 46 yielded a specificity and sensitivity of > 50% each in predicting a clinical response. One singular polymorphism yielded both a sensitivity and specificity of higher than 60% each in predicting a clinical response.

[0137] Of all tested combinations of two of the univariate significantly predicting polymorphisms, 237 exhibited both a sensitivity and specificity of at least 60% each in predicting a clinical response. Finally, a number of 46 tested combinations of two of the univariate significantly predicting polymorphism genotypes yielded a sensitivity and specificity beyond 65% each in predicting a clinical response, see Table 5.

Table 5 - Bivariate sets of polymorphism genotypes

P_ID1	P_ID2	rs_p1	p2	p-value	sensitivity	specificity
11	181	rs74888440	rs9813396	0.00027897	0.62857143	0.6626506
11	192	rs74888440	rs72693005	0.00060709	0.67142857	0.60240964
11	207	rs74888440	rs220806	0.00010088	0.68571429	0.62650602
11	218	rs74888440	rs1944887	0.00015583	0.62857143	0.6746988
11	226	rs74888440	rs532996	0.00082753	0.62857143	0.63855422
11	227	rs74888440	rs9571939	0.00082753	0.62857143	0.63855422

11	228	rs74888440	rs2173530	0.00082753	0.62857143	0.63855422
11	244	rs74888440	rs2044070	0.00352822	0.62857143	0.60240964
11	245	rs74888440	rs920640	0.00352822	0.62857143	0.60240964
112	175	rs2260882	rs7648662	2.12E-05	0.64285714	0.69879518
112	237	rs2260882	rs12917505	0.00090174	0.61428571	0.65060241
112	238	rs2260882	rs16977818	2.19E-05	0.71428571	0.62650602
112	240	rs2260882	rs10851628	0.00039921	0.65714286	0.62650602
112	243	rs2260882	rs6493965	0.00137357	0.62857143	0.62650602
112	245	rs2260882	rs920640	0.0006793	0.65714286	0.61445783
112	246	rs2260882	rs920638	0.00202984	0.64285714	0.60240964
112	250	rs2260882	rs735164	0.00383837	0.61428571	0.61445783
112	277	rs2260882	rs2044230	0.00048656	0.62857143	0.65060241
116	179	rs2257474	rs6549407	0.00352822	0.62857143	0.60240964
116	182	rs2257474	rs12489026	0.00030332	0.61428571	0.6746988
116	191	rs2257474	rs1383699	7.55E-05	0.71428571	0.60240964
116	234	rs2257474	rs8042817	0.00011443	0.67142857	0.63855422
116	235	rs2257474	rs28811003	0.00039921	0.65714286	0.62650602
121	127	rs2028629	rs79320848	0.00383837	0.61428571	0.61445783
121	184	rs2028629	rs11715827	0.00015583	0.62857143	0.6746988
121	185	rs2028629	rs58882373	0.00015583	0.62857143	0.6746988
121	191	rs2028629	rs1383699	0.00082753	0.62857143	0.63855422
121	202	rs2028629	rs4836256	2.30E-05	0.62857143	0.71084337
121	233	rs2028629	rs929610	4.11E-05	0.64285714	0.68674699
121	237	rs2028629	rs12917505	7.00E-05	0.65714286	0.6626506
121	238	rs2028629	rs16977818	7.75E-05	0.64285714	0.6746988
121	239	rs2028629	rs11071351	0.00112948	0.65714286	0.60240964
121	240	rs2028629	rs10851628	3.32E-06	0.7	0.6746988
121	241	rs2028629	rs930473	7.72E-06	0.68571429	0.6746988
121	242	rs2028629	rs1441824	0.00011443	0.67142857	0.63855422
121	243	rs2028629	rs6493965	1.53E-05	0.68571429	0.6626506
121	244	rs2028629	rs2044070	3.32E-06	0.7	0.6746988
121	245	rs2028629	rs920640	3.72E-05	0.65714286	0.6746988
121	246	rs2028629	rs920638	3.32E-06	0.7	0.6746988
123	218	rs4812040	rs1944887	0.00125068	0.64285714	0.61445783
123	235	rs4812040	rs28811003	0.00052981	0.61428571	0.6626506
127	192	rs79320848	rs72693005	0.00035634	0.67142857	0.61445783
127	207	rs79320848	rs220806	0.00025408	0.64285714	0.65060241
127	218	rs79320848	rs1944887	0.00030332	0.61428571	0.6746988
132	184	rs6026567	rs11715827	2.69E-06	0.61428571	0.75903614
132	185	rs6026567	rs58882373	1.22E-05	0.61428571	0.73493976
132	213	rs6026567	rs2935752	0.00030332	0.61428571	0.6746988
132	214	rs6026567	rs2935751	0.00030332	0.61428571	0.6746988

132	237	rs6026567	rs12917505	4.82E-05	0.61428571	0.71084337
132	238	rs6026567	rs16977818	9.16E-05	0.61428571	0.69879518
132	239	rs6026567	rs11071351	0.00242522	0.61428571	0.62650602
132	240	rs6026567	rs10851628	7.00E-05	0.65714286	0.6626506
132	241	rs6026567	rs930473	0.00030332	0.61428571	0.6746988
132	244	rs6026567	rs2044070	0.00027897	0.62857143	0.6626506
133	190	rs968519	rs1383707	0.00016904	0.61428571	0.68674699
133	238	rs968519	rs16977818	0.00052981	0.61428571	0.6626506
133	240	rs968519	rs10851628	9.16E-05	0.61428571	0.69879518
133	241	rs968519	rs930473	9.16E-05	0.61428571	0.69879518
133	243	rs968519	rs6493965	9.16E-05	0.61428571	0.69879518
133	245	rs968519	rs920640	0.00052981	0.61428571	0.6626506
141	157	rs6092704	rs2242071	0.0006793	0.65714286	0.61445783
141	181	rs6092704	rs9813396	4.11E-05	0.71428571	0.61445783
141	187	rs6092704	rs10034039	0.00012826	0.65714286	0.65060241
141	190	rs6092704	rs1383707	0.00012826	0.65714286	0.65060241
141	191	rs6092704	rs1383699	0.00202984	0.64285714	0.60240964
141	212	rs6092704	rs3133622	0.00383837	0.61428571	0.61445783
141	259	rs6092704	rs487011	0.00149683	0.61428571	0.63855422
155	207	rs7523266	rs220806	0.00090174	0.61428571	0.65060241
156	207	rs6686061	rs220806	0.00090174	0.61428571	0.65060241
157	215	rs2242071	rs4570614	0.00352822	0.62857143	0.60240964
168	192	rs809482	rs72693005	0.00352822	0.62857143	0.60240964
176	234	rs616870	rs8042817	0.00593832	0.61428571	0.60240964
179	223	rs6549407	rs876270	0.00039921	0.65714286	0.62650602
179	224	rs6549407	rs11834041	0.00020436	0.67142857	0.62650602
179	248	rs6549407	rs7165629	0.00015717	0.7	0.60240964
180	187	rs6766242	rs10034039	4.11E-05	0.71428571	0.61445783
180	220	rs6766242	rs7121326	0.00082753	0.62857143	0.63855422
180	223	rs6766242	rs876270	7.75E-05	0.64285714	0.6746988
180	224	rs6766242	rs11834041	3.72E-05	0.65714286	0.6746988
180	227	rs6766242	rs9571939	0.00593832	0.61428571	0.60240964
180	234	rs6766242	rs8042817	0.00030332	0.61428571	0.6746988
180	235	rs6766242	rs28811003	0.00090174	0.61428571	0.65060241
182	187	rs12489026	rs10034039	2.94E-05	0.68571429	0.65060241
182	188	rs12489026	rs17616338	0.00052981	0.61428571	0.6626506
182	218	rs12489026	rs1944887	0.00383837	0.61428571	0.61445783
182	224	rs12489026	rs11834041	4.82E-05	0.61428571	0.71084337
184	218	rs11715827	rs1944887	0.00082753	0.62857143	0.63855422
184	219	rs11715827	rs10894873	0.00383837	0.61428571	0.61445783
184	236	rs11715827	rs894342	4.48E-05	0.62857143	0.69879518
184	237	rs11715827	rs12917505	2.30E-05	0.62857143	0.71084337

184	238	rs11715827	rs16977818	2.30E-05	0.62857143	0.71084337
184	239	rs11715827	rs11071351	8.72E-06	0.67142857	0.68674699
184	240	rs11715827	rs10851628	1.14E-05	0.62857143	0.72289157
184	241	rs11715827	rs930473	4.82E-05	0.61428571	0.71084337
184	242	rs11715827	rs1441824	2.30E-05	0.62857143	0.71084337
184	243	rs11715827	rs6493965	9.16E-05	0.61428571	0.69879518
184	244	rs11715827	rs2044070	4.48E-05	0.62857143	0.69879518
184	245	rs11715827	rs920640	1.06E-05	0.64285714	0.71084337
184	246	rs11715827	rs920638	2.12E-05	0.64285714	0.69879518
185	219	rs58882373	rs10894873	0.00137357	0.62857143	0.62650602
185	234	rs58882373	rs8042817	0.00149683	0.61428571	0.63855422
185	236	rs58882373	rs894342	0.00015583	0.62857143	0.6746988
185	237	rs58882373	rs12917505	1.14E-05	0.62857143	0.72289157
185	238	rs58882373	rs16977818	2.30E-05	0.62857143	0.71084337
185	239	rs58882373	rs11071351	8.72E-06	0.67142857	0.68674699
185	240	rs58882373	rs10851628	1.14E-05	0.62857143	0.72289157
185	241	rs58882373	rs930473	4.82E-05	0.61428571	0.71084337
185	242	rs58882373	rs1441824	2.30E-05	0.62857143	0.71084337
185	243	rs58882373	rs6493965	4.48E-05	0.62857143	0.69879518
185	244	rs58882373	rs2044070	4.48E-05	0.62857143	0.69879518
185	245	rs58882373	rs920640	4.48E-05	0.62857143	0.69879518
185	246	rs58882373	rs920638	4.48E-05	0.62857143	0.69879518
186	236	rs12490095	rs894342	2.57E-06	0.62857143	0.74698795
187	188	rs10034039	rs17616338	8.78E-05	0.7	0.61445783
187	193	rs10034039	rs1170303	0.00090174	0.61428571	0.65060241
187	198	rs10034039	rs66624622	0.00015583	0.62857143	0.6746988
187	215	rs10034039	rs4570614	0.00052981	0.61428571	0.6626506
187	216	rs10034039	rs4758040	0.00014215	0.64285714	0.6626506
187	239	rs10034039	rs11071351	0.00030332	0.61428571	0.6746988
188	191	rs17616338	rs1383699	0.00018028	0.68571429	0.61445783
189	218	rs80049044	rs1944887	0.00018028	0.68571429	0.61445783
190	193	rs1383707	rs1170303	0.00039921	0.65714286	0.62650602
190	212	rs1383707	rs3133622	1.61E-06	0.75714286	0.62650602
190	216	rs1383707	rs4758040	0.00039921	0.65714286	0.62650602
190	234	rs1383707	rs8042817	1.53E-05	0.74285714	0.60240964
190	237	rs1383707	rs12917505	0.00027897	0.62857143	0.6626506
190	242	rs1383707	rs1441824	0.00149683	0.61428571	0.63855422
190	252	rs1383707	rs4610906	0.00090174	0.61428571	0.65060241
191	216	rs1383699	rs4758040	0.00137357	0.62857143	0.62650602
191	234	rs1383699	rs8042817	0.00015717	0.7	0.60240964
191	235	rs1383699	rs28811003	0.00031476	0.68571429	0.60240964
191	237	rs1383699	rs12917505	2.19E-05	0.71428571	0.62650602

191	238	rs1383699	rs16977818	4.03E-06	0.74285714	0.62650602
191	240	rs1383699	rs10851628	2.19E-05	0.71428571	0.62650602
191	241	rs1383699	rs930473	0.00010088	0.68571429	0.62650602
191	242	rs1383699	rs1441824	0.00112948	0.65714286	0.60240964
191	243	rs1383699	rs6493965	1.14E-05	0.71428571	0.63855422
191	244	rs1383699	rs2044070	0.0006793	0.65714286	0.61445783
191	245	rs1383699	rs920640	1.14E-05	0.71428571	0.63855422
191	246	rs1383699	rs920638	3.27E-06	0.75714286	0.61445783
191	259	rs1383699	rs487011	4.11E-05	0.71428571	0.61445783
192	252	rs72693005	rs4610906	0.00202984	0.64285714	0.60240964
192	259	rs72693005	rs487011	1.53E-05	0.74285714	0.60240964
193	218	rs1170303	rs1944887	0.00112948	0.65714286	0.60240964
193	259	rs1170303	rs487011	0.00137357	0.62857143	0.62650602
198	226	rs66624622	rs532996	0.00039921	0.65714286	0.62650602
198	227	rs66624622	rs9571939	0.00039921	0.65714286	0.62650602
198	228	rs66624622	rs2173530	0.00137357	0.62857143	0.62650602
199	259	rs72784444	rs487011	0.00149683	0.61428571	0.63855422
201	237	rs62377761	rs12917505	0.00060709	0.67142857	0.60240964
201	238	rs62377761	rs16977818	0.00137357	0.62857143	0.62650602
201	244	rs62377761	rs2044070	0.00052981	0.61428571	0.6626506
202	206	rs4836256	rs730976	0.00593832	0.61428571	0.60240964
202	218	rs4836256	rs1944887	0.00016904	0.61428571	0.68674699
202	225	rs4836256	rs67959715	0.00044281	0.64285714	0.63855422
202	236	rs4836256	rs894342	7.00E-05	0.65714286	0.6626506
202	237	rs4836256	rs12917505	1.82E-06	0.68571429	0.69879518
202	238	rs4836256	rs16977818	2.12E-05	0.64285714	0.69879518
202	239	rs4836256	rs11071351	0.00044281	0.64285714	0.63855422
202	240	rs4836256	rs10851628	4.11E-05	0.64285714	0.68674699
202	241	rs4836256	rs930473	4.27E-06	0.67142857	0.69879518
202	242	rs4836256	rs1441824	0.00012826	0.65714286	0.65060241
202	243	rs4836256	rs6493965	4.27E-06	0.67142857	0.69879518
202	244	rs4836256	rs2044070	1.73E-05	0.67142857	0.6746988
202	245	rs4836256	rs920640	8.72E-06	0.67142857	0.68674699
202	246	rs4836256	rs920638	8.72E-06	0.67142857	0.68674699
206	218	rs730976	rs1944887	0.00242522	0.61428571	0.62650602
211	235	rs3735833	rs28811003	8.47E-05	0.62857143	0.68674699
213	233	rs2935752	rs929610	0.00149683	0.61428571	0.63855422
213	236	rs2935752	rs894342	0.00011443	0.67142857	0.63855422
213	237	rs2935752	rs12917505	9.69E-06	0.65714286	0.69879518
213	238	rs2935752	rs16977818	4.73E-06	0.65714286	0.71084337
213	239	rs2935752	rs11071351	0.00014215	0.64285714	0.6626506
213	240	rs2935752	rs10851628	4.73E-06	0.65714286	0.71084337

213	241	rs2935752	rs930473	1.06E-05	0.64285714	0.71084337
213	242	rs2935752	rs1441824	6.25E-05	0.67142857	0.65060241
213	243	rs2935752	rs6493965	1.06E-05	0.64285714	0.71084337
213	244	rs2935752	rs2044070	9.69E-06	0.65714286	0.69879518
213	245	rs2935752	rs920640	9.69E-06	0.65714286	0.69879518
213	246	rs2935752	rs920638	4.48E-05	0.62857143	0.69879518
214	236	rs2935751	rs894342	0.00044281	0.64285714	0.63855422
214	237	rs2935751	rs12917505	9.69E-06	0.65714286	0.69879518
214	238	rs2935751	rs16977818	4.73E-06	0.65714286	0.71084337
214	239	rs2935751	rs11071351	0.00014215	0.64285714	0.6626506
214	240	rs2935751	rs10851628	2.30E-05	0.62857143	0.71084337
214	241	rs2935751	rs930473	1.06E-05	0.64285714	0.71084337
214	242	rs2935751	rs1441824	6.25E-05	0.67142857	0.65060241
214	243	rs2935751	rs6493965	4.82E-05	0.61428571	0.71084337
214	244	rs2935751	rs2044070	4.48E-05	0.62857143	0.69879518
214	245	rs2935751	rs920640	9.69E-06	0.65714286	0.69879518
214	246	rs2935751	rs920638	9.69E-06	0.65714286	0.69879518
215	218	rs4570614	rs1944887	0.00011443	0.67142857	0.63855422
215	237	rs4570614	rs12917505	0.00137357	0.62857143	0.62650602
215	240	rs4570614	rs10851628	0.00593832	0.61428571	0.60240964
215	246	rs4570614	rs920638	0.00149683	0.61428571	0.63855422
216	237	rs4758040	rs12917505	0.00202984	0.64285714	0.60240964
216	240	rs4758040	rs10851628	0.00112948	0.65714286	0.60240964
216	244	rs4758040	rs2044070	0.00352822	0.62857143	0.60240964
216	245	rs4758040	rs920640	0.00090174	0.61428571	0.65060241
216	246	rs4758040	rs920638	0.00052981	0.61428571	0.6626506
218	234	rs1944887	rs8042817	3.33E-05	0.67142857	0.6626506
218	259	rs1944887	rs487011	0.00593832	0.61428571	0.60240964
223	234	rs876270	rs8042817	0.00022908	0.65714286	0.63855422
223	235	rs876270	rs28811003	0.00039921	0.65714286	0.62650602
223	259	rs876270	rs487011	0.00075306	0.64285714	0.62650602
224	234	rs11834041	rs8042817	0.00011443	0.67142857	0.63855422
224	235	rs11834041	rs28811003	0.00020436	0.67142857	0.62650602
224	248	rs11834041	rs7165629	0.00039921	0.65714286	0.62650602
225	246	rs67959715	rs920638	5.82E-06	0.61428571	0.74698795
233	236	rs929610	rs894342	0.0006793	0.65714286	0.61445783
233	237	rs929610	rs12917505	7.72E-06	0.68571429	0.6746988
233	239	rs929610	rs11071351	0.00039921	0.65714286	0.62650602
233	240	rs929610	rs10851628	4.11E-05	0.64285714	0.68674699
233	243	rs929610	rs6493965	4.11E-05	0.64285714	0.68674699
233	244	rs929610	rs2044070	7.75E-05	0.64285714	0.6746988
233	245	rs929610	rs920640	1.73E-05	0.67142857	0.6746988

233	246	rs929610	rs920638	1.73E-05	0.67142857	0.6746988
234	237	rs8042817	rs12917505	0.00075306	0.64285714	0.62650602
234	240	rs8042817	rs10851628	0.00149683	0.61428571	0.63855422
237	239	rs12917505	rs11071351	6.46E-06	0.75714286	0.60240964
237	259	rs12917505	rs487011	6.73E-06	0.7	0.6626506
238	239	rs16977818	rs11071351	3.27E-06	0.75714286	0.61445783
238	259	rs16977818	rs487011	5.45E-07	0.72857143	0.6746988
239	240	rs11071351	rs10851628	3.27E-06	0.75714286	0.61445783
239	241	rs11071351	rs930473	7.95E-06	0.74285714	0.61445783
239	243	rs11071351	rs6493965	7.95E-06	0.74285714	0.61445783
239	244	rs11071351	rs2044070	3.27E-06	0.75714286	0.61445783
239	245	rs11071351	rs920640	3.27E-06	0.75714286	0.61445783
239	246	rs11071351	rs920638	3.27E-06	0.75714286	0.61445783
240	259	rs10851628	rs487011	5.45E-07	0.72857143	0.6746988
241	259	rs930473	rs487011	1.37E-06	0.71428571	0.6746988
242	259	rs1441824	rs487011	0.00018028	0.68571429	0.61445783
243	248	rs6493965	rs7165629	0.00352822	0.62857143	0.60240964
243	259	rs6493965	rs487011	1.73E-05	0.67142857	0.6746988
244	259	rs2044070	rs487011	6.73E-06	0.7	0.6626506
245	259	rs920640	rs487011	1.16E-06	0.72857143	0.6626506
246	259	rs920638	rs487011	1.16E-06	0.72857143	0.6626506

[0138] In higher order analyses, using sets of four and eight polymorphism genotypes selected from the group disclosed in Table 2, a complete enumeration becomes unpractical (over a million combinations for the sets of four and over 10^{10} for the set of eight polymorphism genotypes). Therefore, randomly sampled sets (1000 combinations each) of such cardinalities k are presented herein.

[0139] For k = 4, 72.1% of tested polymorphism genotype combinations yield a sensitivity and specificity of higher than 50% each, 20,5% of polymorphism genotype combinations yield a sensitivity and specificity of higher than 60% each, and 5,8% of polymorphism genotype combinations yield a sensitivity and specificity of higher than 65% each in predicting a clinical response. Two quadriavariate combinations even yield at least 70% in both sensitivity and specificity in predicting a clinical response, see Table 6.

Table 6 - Quadrivariate sets of polymorphism genotypes

P_ID1	P_ID2	P_ID3	P_ID4	p-value	sensitivity	specificity
233	123	121	127	8.72E-06	0.67142857	0.68674699

236	186	223	215	1.82E-06	0.68571429	0.69879518
202	215	184	233	9.40E-07	0.67142857	0.72289157
207	171	185	121	1.94E-07	0.65714286	0.75903614
240	207	141	157	8.01E-08	0.65714286	0.77108434
158	214	133	246	1.53E-05	0.68571429	0.6626506
241	219	188	127	8.72E-06	0.67142857	0.68674699
233	157	185	158	4.58E-08	0.78571429	0.65060241
188	225	223	237	7.45E-07	0.7	0.69879518
225	247	202	179	3.72E-05	0.65714286	0.6746988
157	213	219	218	7.00E-05	0.65714286	0.6626506
188	242	112	192	6.25E-05	0.67142857	0.65060241
237	226	158	216	6.25E-05	0.67142857	0.65060241
205	226	156	181	2.04E-06	0.67142857	0.71084337
191	239	226	234	0.00012826	0.65714286	0.65060241
116	243	246	158	2.24E-06	0.65714286	0.72289157
193	233	240	198	9.69E-06	0.65714286	0.69879518
202	141	204	160	7.00E-05	0.65714286	0.6626506
184	233	192	215	3.72E-05	0.65714286	0.6746988
191	188	159	243	2.94E-05	0.68571429	0.65060241
246	227	238	224	1.94E-07	0.65714286	0.75903614
202	241	224	183	3.90E-09	0.7	0.77108434
227	191	112	246	7.00E-05	0.65714286	0.6626506
252	161	192	240	4.55E-07	0.65714286	0.74698795
161	207	202	160	1.68E-07	0.75714286	0.6626506
212	243	190	116	4.95E-10	0.65714286	0.8313253
246	184	11	243	3.33E-05	0.67142857	0.6626506
184	241	259	187	7.00E-05	0.65714286	0.6626506
226	243	190	224	4.73E-06	0.65714286	0.71084337
237	157	240	160	1.53E-05	0.68571429	0.6626506
223	245	132	184	1.03E-06	0.65714286	0.73493976
188	207	182	228	1.03E-06	0.65714286	0.73493976
224	205	227	186	7.00E-05	0.65714286	0.6626506
223	176	245	206	4.73E-06	0.65714286	0.71084337
190	204	234	238	6.29E-08	0.7	0.73493976
201	192	240	187	1.73E-05	0.67142857	0.6746988
227	185	190	215	7.45E-07	0.7	0.69879518
185	241	202	186	1.93E-05	0.65714286	0.68674699
214	11	157	220	9.61E-07	0.74285714	0.65060241
242	190	192	245	2.86E-06	0.71428571	0.6626506
121	246	238	190	9.69E-06	0.65714286	0.69879518
223	157	241	190	1.82E-06	0.68571429	0.69879518
233	116	132	243	3.72E-05	0.65714286	0.6746988

218	158	250	244	9.40E-07	0.67142857	0.72289157
250	158	141	213	3.33E-05	0.67142857	0.6626506
240	215	213	158	9.69E-06	0.65714286	0.69879518
235	243	214	208	4.73E-06	0.65714286	0.71084337
202	244	234	127	1.33E-05	0.7	0.65060241
175	184	127	219	4.27E-06	0.67142857	0.69879518
190	240	212	223	1.81E-07	0.67142857	0.74698795
248	219	233	185	6.44E-07	0.71428571	0.68674699
184	234	205	244	9.69E-06	0.65714286	0.69879518
201	246	192	233	4.27E-06	0.67142857	0.69879518
251	245	191	176	1.82E-06	0.68571429	0.69879518
233	223	235	225	3.72E-05	0.65714286	0.6746988
237	220	236	192	9.69E-06	0.65714286	0.69879518
241	236	248	218	4.73E-06	0.65714286	0.71084337
252	218	219	239	6.98E-08	0.68571429	0.74698795

[0140] For k = 8, 93.3% of tested polymorphism genotype combinations yield a sensitivity and specificity of higher than 50% each, 32.6% of polymorphism genotype yield a sensitivity and specificity of higher than 60% each, 8.7% of polymorphism genotype combinations yield a sensitivity and specificity of 65% each, and, finally, 0.5% (5 combinations) of octovariate polymorphism genotype combinations yield a sensitivity and specificity at least 70% in sensitivity and specificity in predicting a clinical response, see Table 7.

Table 7 - Octovariate sets of polymorphism genotypes

P_ID1	P_ID2	P_ID3	P_ID4	P_ID5	P_ID6	P_ID7	P_ID8	p-value	sensitivity	specificity
201	198	191	248	176	213	220	239	3.85E-06	0.65714286	0.72289157
206	112	186	247	205	171	184	246	2.41E-05	0.65714286	0.68674699
188	243	227	191	240	202	242	176	3.85E-06	0.65714286	0.72289157
160	193	132	235	121	192	188	236	7.10E-07	0.67142857	0.73493976
246	112	237	220	190	185	116	186	6.78E-07	0.65714286	0.74698795
116	189	241	246	213	225	191	132	1.57E-08	0.68571429	0.77108434
132	202	236	245	184	193	192	198	4.11E-08	0.67142857	0.77108434
244	188	225	206	192	214	234	213	2.99E-07	0.68571429	0.73493976
235	214	211	156	245	190	188	237	1.66E-08	0.7	0.75903614
185	238	244	206	237	184	183	259	1.64E-06	0.65714286	0.73493976
185	168	191	193	184	160	238	141	1.93E-05	0.65714286	0.69879518
159	244	202	133	259	243	223	121	4.03E-06	0.67142857	0.71084337

211	238	235	158	228	218	214	189	4.11E-08	0.67142857	0.77108434
190	238	185	259	213	179	184	188	2.71E-07	0.65714286	0.75903614
11	157	223	188	236	185	244	201	2.41E-05	0.65714286	0.68674699
188	246	171	242	127	184	234	132	6.78E-07	0.65714286	0.74698795
240	158	112	235	259	242	226	205	1.06E-05	0.68571429	0.6746988
211	213	205	171	202	185	259	116	1.50E-07	0.72857143	0.69879518
187	121	250	116	233	243	198	220	7.46E-07	0.68571429	0.72289157
216	168	185	132	183	112	213	238	1.49E-08	0.67142857	0.78313253
157	248	236	259	171	238	239	192	4.86E-05	0.65714286	0.6746988
234	227	224	251	277	198	187	245	1.05E-07	0.65714286	0.77108434
237	223	11	215	116	218	182	233	1.49E-08	0.67142857	0.78313253
201	220	127	234	157	219	186	141	6.78E-07	0.65714286	0.74698795
218	247	193	241	192	236	224	186	2.84E-07	0.67142857	0.74698795
233	201	158	226	235	132	223	190	3.85E-06	0.65714286	0.72289157
225	186	156	241	204	214	218	212	2.71E-07	0.65714286	0.75903614
116	179	112	184	190	259	239	215	1.64E-06	0.65714286	0.73493976
121	252	186	189	241	133	141	223	1.41E-08	0.65714286	0.79518072
250	248	241	184	159	206	187	192	7.10E-07	0.67142857	0.73493976
168	277	250	238	245	218	227	184	1.57E-08	0.68571429	0.77108434
212	181	184	159	237	223	179	213	2.84E-07	0.67142857	0.74698795
241	219	175	187	156	233	157	184	2.99E-07	0.68571429	0.73493976
224	192	206	121	202	214	241	239	5.48E-09	0.68571429	0.78313253
241	192	214	141	179	227	212	121	8.76E-06	0.65714286	0.71084337
212	241	239	121	191	187	224	238	5.48E-09	0.68571429	0.78313253
245	225	236	132	160	211	244	238	2.85E-09	0.65714286	0.81927711
121	237	234	205	132	244	190	238	1.22E-07	0.7	0.73493976
121	220	241	245	219	214	248	132	8.76E-06	0.65714286	0.71084337
240	220	252	250	157	214	218	245	5.48E-09	0.68571429	0.78313253
193	211	179	132	185	246	238	240	2.85E-09	0.65714286	0.81927711
243	241	252	237	192	141	259	190	7.10E-07	0.67142857	0.73493976
227	190	213	250	191	218	214	248	4.91E-09	0.65714286	0.80722892
242	214	239	179	201	190	181	192	1.78E-11	0.7	0.8313253
224	121	259	246	207	228	204	219	3.85E-06	0.65714286	0.72289157
236	186	116	187	184	204	219	121	2.84E-07	0.67142857	0.74698795
179	11	239	184	159	202	123	185	4.33E-08	0.68571429	0.75903614
248	127	240	141	133	233	156	201	1.05E-07	0.65714286	0.77108434
185	237	188	191	247	189	216	158	2.84E-07	0.67142857	0.74698795
219	132	176	191	277	214	236	175	1.49E-08	0.67142857	0.78313253
133	241	214	220	189	191	233	211	6.78E-07	0.65714286	0.74698795
202	182	233	259	218	127	243	159	2.71E-07	0.65714286	0.75903614
189	238	216	223	214	158	190	179	2.85E-09	0.65714286	0.81927711
123	112	243	141	202	121	190	116	1.76E-08	0.71428571	0.74698795

237	193	116	185	228	202	186	132	2.71E-07	0.65714286	0.75903614
190	11	237	182	202	132	214	246	1.10E-07	0.67142857	0.75903614
214	237	224	218	250	181	155	160	3.92E-08	0.65714286	0.78313253
237	252	234	133	185	250	239	188	5.48E-09	0.68571429	0.78313253
188	228	245	185	248	234	161	224	4.03E-06	0.67142857	0.71084337
204	228	188	202	212	223	168	141	2.71E-07	0.65714286	0.75903614
206	238	186	245	191	220	155	192	6.78E-07	0.65714286	0.74698795
237	246	168	188	141	198	192	190	3.85E-06	0.65714286	0.72289157
223	252	190	160	205	212	184	233	4.03E-06	0.67142857	0.71084337
141	187	121	188	246	193	185	133	1.16E-07	0.68571429	0.74698795
218	238	228	234	184	213	132	248	1.10E-07	0.67142857	0.75903614
11	213	238	219	246	112	187	248	2.30E-05	0.67142857	0.6746988
121	190	160	213	184	239	246	189	1.10E-07	0.67142857	0.75903614
168	225	176	251	236	189	190	218	4.11E-08	0.67142857	0.77108434
235	116	187	250	168	220	238	190	6.78E-07	0.65714286	0.74698795
216	214	246	116	244	182	240	186	7.10E-07	0.67142857	0.73493976
208	188	187	218	245	238	199	157	1.64E-06	0.65714286	0.73493976
239	112	176	185	246	250	219	202	4.86E-05	0.65714286	0.6746988
250	220	233	127	224	116	226	237	1.72E-06	0.67142857	0.72289157
156	212	204	259	214	237	240	191	1.05E-07	0.65714286	0.77108434
259	204	213	228	180	218	242	193	1.72E-06	0.67142857	0.72289157
218	250	227	211	171	185	251	133	1.05E-07	0.65714286	0.77108434
176	202	185	187	277	248	233	189	1.72E-06	0.67142857	0.72289157
112	277	218	155	156	237	235	244	5.67E-10	0.67142857	0.81927711
187	252	240	116	175	184	239	242	2.84E-07	0.67142857	0.74698795
182	227	206	181	132	224	244	188	1.10E-07	0.67142857	0.75903614
239	238	214	223	242	218	186	192	1.66E-08	0.7	0.75903614
185	188	277	241	219	193	201	176	1.64E-06	0.65714286	0.73493976
116	233	199	247	183	238	214	180	4.11E-08	0.67142857	0.77108434
180	242	116	239	158	238	243	240	7.46E-07	0.68571429	0.72289157
234	237	193	235	224	179	190	233	3.92E-08	0.65714286	0.78313253

[0141] For k = 32, 99.9% of tested polymorphism genotype combinations yield a sensitivity and specificity of higher than 50% each in specificity and sensitivity, 98.9% of tested polymorphism genotype combinations yield a sensitivity and specificity of higher than 60% each, 72.8% of tested polymorphism genotype combinations yield a sensitivity and specificity of higher than 65% each, 15.6% of tested polymorphism genotype combinations yield a sensitivity and specificity of higher than 70% each in predicting a clinical response. Finally, some of the tested polymorphism genotype combinations (0.3%) even yield a sensitivity and specificity of higher than 75% each (data not shown).

[0142] As will be understood from the above explanations and data in Table 5, Table 6, and Table 7, even minimal subsets of polymorphism genotypes selected from the particularly useful set of polymorphism genotypes disclosed in Table 2 already allow for predictions of a clinical response significantly better than 50% ("coin-flip"). Therefore, while the present invention ideally aims at predicting the treatment response to a CRHR1 antagonist with sensitivity and specificity of at least 75% each, at least 80% each, at least 85% each, or even at least 90% each, methods of prediction using smaller subsets, e.g., of only one, two, four, or eight polymorphism genotypes selected from the group consisting of the polymorphism genotypes disclosed in Table 2 already provide a significant performance in predicting clinical responses. A subset of k = 32 polymorphism genotypes already comprises combinations yielding a sensitivity and specificity of at least 75% each in predicting a clinical response. The predictive performance can be further increased by including, e.g., 150 polymorphism genotypes, as has been done in Example 1, 200 polymorphism genotypes, 250 polymorphism genotypes or all polymorphism genotypes as disclosed in Table 2.

Equivalents

[0143] The foregoing exemplary embodiments are to be considered illustrative of, and not limiting to, the invention disclosed herein. It will be apparent to those skilled in the art that various modifications may be made without departing from the scope or spirit of the invention. Therefore, it will be appreciated that the scope of the present invention is primarily defined by the appended claims, and is not limited by the specific embodiments which have been presented as examples. All changes which come within the meaning and range of equivalency of the claims are intended to be encompassed.

Claims

1. A method for predicting a treatment response of a subject to a treatment with a CRHR1 antagonist, the method comprising:

providing a biological sample obtained from the subject;

detecting the presence or absence of one or more polymorphism genotypes in the biological sample, wherein the one or more polymorphism genotypes comprise:

(a) at least one polymorphism genotype selected from the group consisting of rs34169260 (A/G), rs796287 (A/C), rs56149945 (A/G), rs6190 (T/C), rs7179092 (T/C), rs7614867 (A/G), rs920640 (T/C), rs7167722 (T/C), rs920638 (T/C), rs7165629 (T/C), rs80049044 (T/A), rs16941058 (A/G), rs112015971 (A/G), rs10894873 (T/C), rs117455294 (T/G), rs1170303 (T/C), rs16940681 (C/G), rs968519 (T/C), rs28381866 (T/C), rs79320848 (T/G), rs114653646 (T/G), rs2589496 (T/C), rs10482650 (A/G), rs17614642 (A/G), rs73200317 (T/C), rs1380146 (T/A), rs735164 (T/C), rs730976 (T/G), rs55934524 (T/G), rs4570614 (A/G), rs4458044 (C/G), rs77850169 (A/G), rs35339359 (A/G), rs34800935 (T/C), rs72945439 (T/C), rs113959523 (A/G), rs116798177 (A/G), rs11247577 (T/G), rs75869266 (T/C), rs74372553 (T/C), rs11691508 (A/G), rs6493965 (A/G), rs4869476 (T/C), rs3730170 (T/C), rs2145288 (A/C), rs2935752 (A/C), rs146512400 (A/G), rs62057097 (T/C), rs115061314 (T/C), rs34113594 (T/G), rs61751173 (A/G), rs74338736 (A/C), rs10851726 (T/C), rs4610906 (T/C), rs59485211 (T/C), rs7060015 (T/G), rs75710780 (T/G), rs6520908 (T/C), rs487011 (T/G), rs1383699 (A/C), rs67516871 (A/G), rs114106519 (T/C), rs7220091 (A/G), rs12489026 (A/G), rs876270 (T/C), rs4968161 (T/C), rs62056907 (A/G), rs2235013 (T/C), rs16878812 (A/G), rs6549407 (A/G), rs28381848 (A/G), rs79723704 (A/C), rs72814052 (A/G), rs10152908 (T/C), rs172769 (A/C), rs78596668 (T/C), rs73307922 (T/C), rs3842 (A/G), rs7210584 (A/C), rs62402121 (T/C), rs55709291 (A/G), rs72747088 (A/G), rs929610 (G/C), rs6766242 (T/C), rs1468552 (G/C), rs78838114 (T/C), rs62489862 (T/C), rs894342 (A/G), rs58882373 (T/C), rs3811939 (A/G), rs6984688 (T/G), rs1018160 (T/C), rs76602912 (A/G), rs80067508 (A/G), rs74888440 (T/C), rs12481583 (T/C), rs66794218 (A/G), rs16946701 (A/G), rs75726724 (A/G), rs67959715 (T/A), rs11871392 (T/G), rs2044070 (A/G), rs77612799 (T/C), rs6743702 (T/C), rs616870 (T/C), rs79590198 (A/G), rs75715199 (A/G), rs13087555 (T/C), rs4869618 (T/C), rs117397046 (A/G), rs8042817 (A/G), rs2258097 (T/C), rs2260882 (C/G), rs532996 (A/G), rs11747040 (T/C), rs10034039 (T/G), rs116909369 (A/G), rs79134986 (A/G), rs117615688 (T/C), rs8032253 (T/C),

rs12818653 (T/A), rs4587884 (A/C), rs77122853 (T/C), rs117615061 (T/C), rs74682905 (A/G), rs2257468 (T/C), rs2032582 (T/G), rs2235015 (T/G), rs2729794 (T/C), rs77549514 (A/G), rs74790420 (A/C), rs73129579 (T/C), rs12913346 (A/C), rs117560908 (T/C), rs72747091 (A/G), rs2935751 (A/G), rs4331446 (A/G), rs7523266 (T/C), rs7648662 (T/C), rs117034065 (A/G), rs4836256 (T/C), rs80238698 (T/C), rs3730173 (T/C), rs11687884 (T/C), rs72693005 (T/C), rs2589476 (T/C), rs9813396 (T/C), rs10482667 (A/G), rs72784444 (A/G), rs75074511 (T/C), rs7951003 (A/G), rs79584784 (A/G), rs2214102 (T/C), rs28811003 (A/G), rs6100261 (A/T), rs77152456 (A/G), rs66624622 (T/G), rs140302965 (A/G), rs11653269 (T/C), rs74405057 (A/G), rs7121 (A/G), rs16977818 (A/C), rs12490095 (T/C), rs118003903 (A/G), rs62377761 (T/C), P1_M_061510_6_34_M (-/CACTTAC CTTCTTTGTGCCACAGTTTCCCTATCTAAAACACAAGGTTATCAGTTATCAACATC TCTTGGGATTGTGAGGACTAAAGTAATGCACATAAAG), rs375115639 (-/AAATTACCCTGTTAGGTTTCAATGAAACACCTTTTCTCTTGTAACAAACATCTCC TCCAAGCTAGAATTTCAAAACAG), rs1002204 (A/C), rs10062367 (A/G), rs10482642 (A/G), rs10482658 (A/G), rs1053989 (A/C), rs10851628 (T/C), rs10947562 (T/C), rs11069612 (A/G), rs11071351 (T/C), rs11091175 (A/G), rs11638450 (T/C), rs11715827 (T/G), rs11745958 (T/C), rs11834041 (A/G), rs1202180 (T/C), rs12054781 (A/G), rs12539395 (A/G), rs12720066 (T/G), rs1279754 (A/C), rs12872047 (T/C), rs12876742 (A/C), rs12917505 (A/G), rs13066950 (T/G), rs13229143 (C/G), rs1383707 (T/C), rs1441824 (T/C), rs1652311 (A/G), rs17064 (T/A), rs17100236 (A/G), rs17149699 (A/G), rs1724386 (A/G), rs17250255 (A/G), rs17327624 (T/G), rs17616338 (A/G), rs17687796 (A/G), rs17740874 (T/C), rs17763104 (T/C), rs1880748 (T/C), rs1882478 (A/G), rs1944887 (T/C), rs2028629 (A/G), rs2143404 (A/G), rs2173530 (T/C), rs220806 (T/C), rs2235047 (A/C), rs2242071 (A/G), rs2257474 (T/C), rs2295583 (A/T), rs234629 (T/C), rs234630 (A/G), rs2436401 (A/G), rs258750 (T/C), rs2589487 (T/C), rs28364018 (T/G), rs28381774 (T/C), rs28381784 (A/G), rs2963155 (A/G), rs3133622 (T/G), rs32897 (T/C), rs33388 (A/T), rs3730168 (T/C), rs3735833 (T/G), rs3777747 (A/G), rs3786066 (T/C), rs3798346 (T/C), rs3822736 (A/G), rs389035 (T/C), rs3924144 (A/G), rs4148737 (T/C), rs4148749 (G/C), rs417968 (T/C), rs4458144 (T/C), rs4515335 (T/C), rs4728699 (A/G), rs4758040 (A/G), rs4812040 (A/G), rs4912650 (T/G), rs4957891 (T/C), rs5906392 (A/G), rs6026561 (T/C), rs6026565 (T/A), rs6026567 (A/G), rs6026593 (A/G), rs6092704 (T/G), rs6100260 (A/G), rs6128461 (T/C), rs6415328 (T/C), rs6610868 (T/C), rs6686061 (A/C), rs6730350 (T/G), rs6746197 (T/C), rs6963426 (T/C), rs7121326 (T/C), rs7721799

(A/G), rs7787082 (T/C), rs7799592 (A/C), rs796245 (T/C), rs809482 (A/C), rs8125112 (T/C), rs919196 (A/G), rs920750 (T/C), rs9332385 (A/G), rs930473 (T/G), rs9324921 (A/C), rs9348979 (A/G), rs9571939 (A/C), and rs9892359 (T/C);

(b) at least one polymorphism genotype being in linkage disequilibrium with any one of the polymorphism genotypes of (a); or

(c) a combination of (a) and (b); and

predicting the treatment response from the presence or absence of the one or more polymorphism genotypes of (a), (b), or (c).

2. The method of claim 1, wherein the predicting step comprises:
(a) determining whether the subject will respond, or has an increased likelihood of responding to the treatment with a CRHR1 antagonist; and/or
(b) determining whether the subject will not respond, or has a decreased likelihood of responding to the treatment with a CRHR1 antagonist.

3. The method of claim 2, wherein the determining step comprises one or more statistical analysis method selected from the group consisting of artificial neural network learning, decision tree learning, decision tree forest learning, linear discriminant analysis, non-linear discriminant analysis, genetic expression programming, relevance vector machines, linear models, generalized linear models, generalized estimating equations, generalized linear mixed models, the elastic net, the lasso support vector machine learning, Bayesian network learning, probabilistic neural network learning, clustering, and regression analysis, optionally wherein the statistical analysis method is computer-implemented.

4. The method of any one of claims 1 to 3, wherein the one or more polymorphism genotypes comprise:
(a) at least two;
(b) at least four;
(c) at least eight;
(d) at least sixteen;
(e) at least thirty-two; or
(f) all
of the polymorphism genotypes as defined in claim 1.

5. The method of any one of claims 1 to 3, wherein the one or more polymorphism genotypes comprise:
(a) at least two polymorphism genotypes selected from the combinations of polymorphism genotypes disclosed in Table 5;
(b) at least four polymorphism genotypes selected from the combinations of polymorphism genotypes disclosed in Table 6;
(c) at least eight polymorphism genotypes selected from the combinations of polymorphism genotypes disclosed in Table 7;
(d) all of the polymorphism genotypes disclosed in Table 2.

6. The method of any one of claims 1 to 5, wherein the treatment response to treatment with the CRHR1 antagonist is a clinical response.

7. The method of any one of claims 1 to 6, wherein the subject has depressive symptoms, anxiety symptoms or both depressive symptoms and anxiety symptoms or a sleep disorder; and/or
wherein the treatment is a treatment of depressive symptoms, anxiety symptoms or both depressive symptoms and anxiety symptoms or a sleep disorder.

8. The method of claim 7, wherein the treatment response to treatment with the CRHR1 antagonist is a clinical response, and wherein the clinical response is a prevention, alteration, alleviation or complete remission of depressive symptoms and/or anxiety symptoms or a sleep disorder.

9. The method of claim 8, wherein the clinical response is a prevention, alteration, alleviation or complete remission of depressive symptoms and/or anxiety symptoms as determined using a scale selected from the group consisting of HAM-D, BDI, MADRS, GDS, ZSRDS, HAM-A and STAI.

10. The method of any one of claims 1-9, wherein the biological sample is a buccal or a blood sample.

11. The method of any one of claims 1-10, wherein detecting comprises the use of one or more polynucleotides capable of specifically hybridizing to at least one nucleic acid comprising the one or more polymorphism genotypes.

12. The method of any one of claims 1-11, wherein the subject has been administered a CRHR1 antagonist, further comprising comparing the prediction that the subject will respond to a treatment with a CRHR1 antagonist with the treatment response of the subject to administration of the CRHR1 antagonist.

13. The method of any one of claims 1-12, wherein the prediction that the subject will respond to a treatment with a CRHR1 antagonist has a sensitivity of higher than 50% and a specificity of higher than 50%.

14. The method of any one of claims 1-13, wherein the CRHR1 antagonist is selected from the group consisting of GW876008 (Emicerfont), GSK-561679 (NBI-77860, Verucerfont), GSK586529, BMS-562,086 (Pexacerfont), NBI-30775 (R-121919), NBI-34101, CP-316,311, CP-376,395, PF-00572778, NVP-AAG561, Ono-2333MS, E2508, E2009, R317573 (JNJ19567470, CRA5626, TAI-041), R278995 (CRA0450), CRA-1000, CRA-1001, CP154,526, Antalarmin, DMP-695, DMP-696, DMP-904, SC-241, BMS-561388, NBI30545, PD-171729, NBI34041, NBI35965, SN003, NBI-27914, *trans*-2-chloro-N-(4-((5-fluoro-4-methyl-pyridin-2-ylamino)-methyl)-cyclohexyl)-5-(trifluoromethyl)-benzamide, SSR-125543, or a pharmaceutically acceptable salt thereof.

15. A method of treating a condition which is treatable by a CRHR1 antagonist in a subject in need thereof, comprising administering an effective amount of a CRHR1 antagonist to the subject, wherein the subject has been predicted to respond, or has an increased likelihood of responding, to a treatment with a CRHR1 antagonist, as determined by the method according to any one of claims 1-14, and wherein the CRHR1 antagonist is:
(a) a compound of Formula (I), as defined herein; or
(b) selected from the group consisting of a Type I CRHR1 antagonist, a bicyclic Type II CRHR1 antagonist, an atypical CRHR1 antagonist, a cyclohexyl amide CRHR1 antagonist.

16. The method of claim 15, wherein the condition is selected from the group consisting of depressive symptoms, anxiety symptoms, both depressive symptoms and anxiety symptoms, and a sleep disorder.

17. The method of claims 15 or 16, wherein the CRHR1 antagonist is selected from the group consisting of GW876008 (Emicerfont), GSK-561679 (NBI-77860, Verucerfont), GSK586529, BMS-562,086 (Pexacerfont), NBI-30775 (R-121919), NBI-34101, CP-316,311, CP-376,395, PF-00572778, NVP-AAG561, Ono-2333MS, E2508, E2009, R317573 (JNJ19567470, CRA5626, TAI-041), R278995 (CRA0450), CRA-1000, CRA-1001, CP154,526, Antalarmin, DMP-695, DMP-696, DMP-904, SC-241, BMS-561388, NBI30545, PD-171729, NBI34041, NBI35965, SN003, NBI-27914, *trans*-2-chloro-N-(4-((5-fluoro-4-methyl-pyridin-2-ylamino)-methyl)-cyclohexyl)-5-(trifluoromethyl)-benzamide, or a pharmaceutically acceptable salt thereof.

18. A composition comprising at least one polynucleotide capable of specifically hybridizing to a nucleic acid comprising:

(a) at least one polymorphism genotype selected from the group consisting of rs34169260 (A/G), rs796287 (A/C), rs56149945 (A/G), rs6190 (T/C), rs7179092 (T/C), rs7614867 (A/G), rs920640 (T/C), rs7167722 (T/C), rs920638 (T/C), rs7165629 (T/C), rs80049044 (T/A), rs16941058 (A/G), rs112015971 (A/G), rs10894873 (T/C), rs117455294 (T/G), rs1170303 (T/C), rs16940681 (C/G), rs968519 (T/C), rs28381866 (T/C), rs79320848 (T/G), rs114653646 (T/G), rs2589496 (T/C), rs10482650 (A/G), rs17614642 (A/G), rs73200317 (T/C), rs1380146 (T/A), rs735164 (T/C), rs730976 (T/G), rs55934524 (T/G), rs4570614 (A/G), rs4458044 (C/G), rs77850169 (A/G), rs35339359 (A/G), rs34800935 (T/C), rs72945439 (T/C), rs113959523 (A/G), rs116798177 (A/G), rs11247577 (T/G), rs75869266 (T/C), rs74372553 (T/C), rs11691508 (A/G), rs6493965 (A/G), rs4869476 (T/C), rs3730170 (T/C), rs2145288 (A/C), rs2935752 (A/C), rs146512400 (A/G), rs62057097 (T/C), rs115061314 (T/C), rs34113594 (T/G), rs61751173 (A/G), rs74338736 (A/C), rs10851726 (T/C), rs4610906 (T/C), rs59485211 (T/C), rs7060015 (T/G), rs75710780 (T/G), rs6520908 (T/C), rs487011 (T/G), rs1383699 (A/C), rs67516871 (A/G), rs114106519 (T/C), rs7220091 (A/G), rs12489026 (A/G), rs876270 (T/C), rs4968161 (T/C), rs62056907 (A/G), rs2235013 (T/C), rs16878812 (A/G), rs6549407 (A/G), rs28381848 (A/G), rs79723704 (A/C), rs72814052 (A/G), rs10152908 (T/C), rs172769 (A/C), rs78596668 (T/C), rs73307922 (T/C), rs3842 (A/G), rs7210584 (A/C), rs62402121 (T/C), rs55709291 (A/G), rs72747088 (A/G), rs929610 (G/C), rs6766242 (T/C), rs1468552 (G/C), rs78838114 (T/C), rs62489862 (T/C), rs894342 (A/G), rs58882373 (T/C), rs3811939 (A/G), rs6984688 (T/G), rs1018160 (T/C), rs76602912 (A/G), rs80067508 (A/G), rs74888440 (T/C), rs12481583 (T/C), rs66794218 (A/G), rs16946701 (A/G), rs75726724 (A/G), rs67959715 (T/A), rs11871392 (T/G), rs2044070 (A/G),

rs77612799 (T/C), rs6743702 (T/C), rs616870 (T/C), rs79590198 (A/G), rs75715199 (A/G), rs13087555 (T/C), rs4869618 (T/C), rs117397046 (A/G), rs8042817 (A/G), rs2258097 (T/C), rs2260882 (C/G), rs532996 (A/G), rs11747040 (T/C), rs10034039 (T/G), rs116909369 (A/G), rs79134986 (A/G), rs117615688 (T/C), rs8032253 (T/C), rs12818653 (T/A), rs4587884 (A/C), rs77122853 (T/C), rs117615061 (T/C), rs74682905 (A/G), rs2257468 (T/C), rs2032582 (T/G), rs2235015 (T/G), rs2729794 (T/C), rs77549514 (A/G), rs74790420 (A/C), rs73129579 (T/C), rs12913346 (A/C), rs117560908 (T/C), rs72747091 (A/G), rs2935751 (A/G), rs4331446 (A/G), rs7523266 (T/C), rs7648662 (T/C), rs117034065 (A/G), rs4836256 (T/C), rs80238698 (T/C), rs3730173 (T/C), rs11687884 (T/C), rs72693005 (T/C), rs2589476 (T/C), rs9813396 (T/C), rs10482667 (A/G), rs72784444 (A/G), rs75074511 (T/C), rs7951003 (A/G), rs79584784 (A/G), rs2214102 (T/C), rs28811003 (A/G), rs6100261 (A/T), rs77152456 (A/G), rs66624622 (T/G), rs140302965 (A/G), rs11653269 (T/C), rs74405057 (A/G), rs7121 (A/G), rs16977818 (A/C), rs12490095 (T/C), rs118003903 (A/G), rs62377761 (T/C), P1_M_061510_6_34_M (-/CACTTAC CTTCTTTGTGCCACAGTTTCCCTATCTAAAACACAAGGTTATCAGTTATCAACATC TCTTGGGATTGTGAGGACTAAAGTAATGCACATAAAG), rs375115639 (-/AAATTACCCTGTTAGGTTTCAATGAAACACCTTTTCTCTTGTAACAAACATCTCC TCCAAGCTAGAATTTCAAAACAG), rs1002204 (A/C), rs10062367 (A/G), rs10482642 (A/G), rs10482658 (A/G), rs1053989 (A/C), rs10851628 (T/C), rs10947562 (T/C), rs11069612 (A/G), rs11071351 (T/C), rs11091175 (A/G), rs11638450 (T/C), rs11715827 (T/G), rs11745958 (T/C), rs11834041 (A/G), rs1202180 (T/C), rs12054781 (A/G), rs12539395 (A/G), rs12720066 (T/G), rs1279754 (A/C), rs12872047 (T/C), rs12876742 (A/C), rs12917505 (A/G), rs13066950 (T/G), rs13229143 (C/G), rs1383707 (T/C), rs1441824 (T/C), rs1652311 (A/G), rs17064 (T/A), rs17100236 (A/G), rs17149699 (A/G), rs1724386 (A/G), rs17250255 (A/G), rs17327624 (T/G), rs17616338 (A/G), rs17687796 (A/G), rs17740874 (T/C), rs17763104 (T/C), rs1880748 (T/C), rs1882478 (A/G), rs1944887 (T/C), rs2028629 (A/G), rs2143404 (A/G), rs2173530 (T/C), rs220806 (T/C), rs2235047 (A/C), rs2242071 (A/G), rs2257474 (T/C), rs2295583 (A/T), rs234629 (T/C), rs234630 (A/G), rs2436401 (A/G), rs258750 (T/C), rs2589487 (T/C), rs28364018 (T/G), rs28381774 (T/C), rs28381784 (A/G), rs2963155 (A/G), rs3133622 (T/G), rs32897 (T/C), rs33388 (A/T), rs3730168 (T/C), rs3735833 (T/G), rs3777747 (A/G), rs3786066 (T/C), rs3798346 (T/C), rs3822736 (A/G), rs389035 (T/C), rs3924144 (A/G), rs4148737 (T/C), rs4148749 (G/C), rs417968 (T/C), rs4458144 (T/C), rs4515335 (T/C), rs4728699 (A/G), rs4758040 (A/G), rs4812040

(A/G), rs4912650 (T/G), rs4957891 (T/C), rs5906392 (A/G), rs6026561 (T/C), rs6026565 (T/A), rs6026567 (A/G), rs6026593 (A/G), rs6092704 (T/G), rs6100260 (A/G), rs6128461 (T/C), rs6415328 (T/C), rs6610868 (T/C), rs6686061 (A/C), rs6730350 (T/G), rs6746197 (T/C), rs6963426 (T/C), rs7121326 (T/C), rs7721799 (A/G), rs7787082 (T/C), rs7799592 (A/C), rs796245 (T/C), rs809482 (A/C), rs8125112 (T/C), rs919196 (A/G), rs920750 (T/C), rs9332385 (A/G), rs930473 (T/G), rs9324921 (A/C), rs9348979 (A/G), rs9571939 (A/C), and rs9892359 (T/C),

(b) at least one polymorphism genotype being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or

(c) a combination of (a) and (b).

19. A kit comprising at least one polynucleotide capable of specifically hybridizing to a nucleic acid comprising:

(a) at least one polymorphism genotype selected from the group consisting of rs34169260 (A/G), rs796287 (A/C), rs56149945 (A/G), rs6190 (T/C), rs7179092 (T/C), rs7614867 (A/G), rs920640 (T/C), rs7167722 (T/C), rs920638 (T/C), rs7165629 (T/C), rs80049044 (T/A), rs16941058 (A/G), rs112015971 (A/G), rs10894873 (T/C), rs117455294 (T/G), rs1170303 (T/C), rs16940681 (C/G), rs968519 (T/C), rs28381866 (T/C), rs79320848 (T/G), rs114653646 (T/G), rs2589496 (T/C), rs10482650 (A/G), rs17614642 (A/G), rs73200317 (T/C), rs1380146 (T/A), rs735164 (T/C), rs730976 (T/G), rs55934524 (T/G), rs4570614 (A/G), rs4458044 (C/G), rs77850169 (A/G), rs35339359 (A/G), rs34800935 (T/C), rs72945439 (T/C), rs113959523 (A/G), rs116798177 (A/G), rs11247577 (T/G), rs75869266 (T/C), rs74372553 (T/C), rs11691508 (A/G), rs6493965 (A/G), rs4869476 (T/C), rs3730170 (T/C), rs2145288 (A/C), rs2935752 (A/C), rs146512400 (A/G), rs62057097 (T/C), rs115061314 (T/C), rs34113594 (T/G), rs61751173 (A/G), rs74338736 (A/C), rs10851726 (T/C), rs4610906 (T/C), rs59485211 (T/C), rs7060015 (T/G), rs75710780 (T/G), rs6520908 (T/C), rs487011 (T/G), rs1383699 (A/C), rs67516871 (A/G), rs114106519 (T/C), rs7220091 (A/G), rs12489026 (A/G), rs876270 (T/C), rs4968161 (T/C), rs62056907 (A/G), rs2235013 (T/C), rs16878812 (A/G), rs6549407 (A/G), rs28381848 (A/G), rs79723704 (A/C), rs72814052 (A/G), rs10152908 (T/C), rs172769 (A/C), rs78596668 (T/C), rs73307922 (T/C), rs3842 (A/G), rs7210584 (A/C), rs62402121 (T/C), rs55709291 (A/G), rs72747088 (A/G), rs929610 (G/C), rs6766242 (T/C), rs1468552 (G/C), rs78838114 (T/C), rs62489862 (T/C), rs894342 (A/G), rs58882373 (T/C), rs3811939 (A/G), rs6984688 (T/G), rs1018160 (T/C), rs76602912 (A/G), rs80067508 (A/G), rs74888440 (T/C), rs12481583 (T/C), rs66794218 (A/G), rs16946701 (A/G),

rs75726724 (A/G), rs67959715 (T/A), rs11871392 (T/G), rs2044070 (A/G), rs77612799 (T/C), rs6743702 (T/C), rs616870 (T/C), rs79590198 (A/G), rs75715199 (A/G), rs13087555 (T/C), rs4869618 (T/C), rs117397046 (A/G), rs8042817 (A/G), rs2258097 (T/C), rs2260882 (C/G), rs532996 (A/G), rs11747040 (T/C), rs10034039 (T/G), rs116909369 (A/G), rs79134986 (A/G), rs117615688 (T/C), rs8032253 (T/C), rs12818653 (T/A), rs4587884 (A/C), rs77122853 (T/C), rs117615061 (T/C), rs74682905 (A/G), rs2257468 (T/C), rs2032582 (T/G), rs2235015 (T/G), rs2729794 (T/C), rs77549514 (A/G), rs74790420 (A/C), rs73129579 (T/C), rs12913346 (A/C), rs117560908 (T/C), rs72747091 (A/G), rs2935751 (A/G), rs4331446 (A/G), rs7523266 (T/C), rs7648662 (T/C), rs117034065 (A/G), rs4836256 (T/C), rs80238698 (T/C), rs3730173 (T/C), rs11687884 (T/C), rs72693005 (T/C), rs2589476 (T/C), rs9813396 (T/C), rs10482667 (A/G), rs72784444 (A/G), rs75074511 (T/C), rs7951003 (A/G), rs79584784 (A/G), rs2214102 (T/C), rs28811003 (A/G), rs6100261 (A/T), rs77152456 (A/G), rs66624622 (T/G), rs140302965 (A/G), rs11653269 (T/C), rs74405057 (A/G), rs7121 (A/G), rs16977818 (A/C), rs12490095 (T/C), rs118003903 (A/G), rs62377761 (T/C), P1_M_061510_6_34_M (-/CACTTAC CTTCTTTGTGCCACAGTTTCCCTATCTAAAACACAAGGTTATCAGTTATCAACATC TCTTGGGATTGTGAGGACTAAAGTAATGCACATAAAG), rs375115639 (-/AAATTACCCTGTTAGGTTTCAATGAAACACCTTTTCTCTTGTAACAAACATCTCC TCCAAGCTAGAATTTCAAAACAG), rs1002204 (A/C), rs10062367 (A/G), rs10482642 (A/G), rs10482658 (A/G), rs1053989 (A/C), rs10851628 (T/C), rs10947562 (T/C), rs11069612 (A/G), rs11071351 (T/C), rs11091175 (A/G), rs11638450 (T/C), rs11715827 (T/G), rs11745958 (T/C), rs11834041 (A/G), rs1202180 (T/C), rs12054781 (A/G), rs12539395 (A/G), rs12720066 (T/G), rs1279754 (A/C), rs12872047 (T/C), rs12876742 (A/C), rs12917505 (A/G), rs13066950 (T/G), rs13229143 (C/G), rs1383707 (T/C), rs1441824 (T/C), rs1652311 (A/G), rs17064 (T/A), rs17100236 (A/G), rs17149699 (A/G), rs1724386 (A/G), rs17250255 (A/G), rs17327624 (T/G), rs17616338 (A/G), rs17687796 (A/G), rs17740874 (T/C), rs17763104 (T/C), rs1880748 (T/C), rs1882478 (A/G), rs1944887 (T/C), rs2028629 (A/G), rs2143404 (A/G), rs2173530 (T/C), rs220806 (T/C), rs2235047 (A/C), rs2242071 (A/G), rs2257474 (T/C), rs2295583 (A/T), rs234629 (T/C), rs234630 (A/G), rs2436401 (A/G), rs258750 (T/C), rs2589487 (T/C), rs28364018 (T/G), rs28381774 (T/C), rs28381784 (A/G), rs2963155 (A/G), rs3133622 (T/G), rs32897 (T/C), rs33388 (A/T), rs3730168 (T/C), rs3735833 (T/G), rs3777747 (A/G), rs3786066 (T/C), rs3798346 (T/C), rs3822736 (A/G), rs389035 (T/C), rs3924144 (A/G), rs4148737 (T/C), rs4148749 (G/C), rs417968 (T/C),

rs4458144 (T/C), rs4515335 (T/C), rs4728699 (A/G), rs4758040 (A/G), rs4812040 (A/G), rs4912650 (T/G), rs4957891 (T/C), rs5906392 (A/G), rs6026561 (T/C), rs6026565 (T/A), rs6026567 (A/G), rs6026593 (A/G), rs6092704 (T/G), rs6100260 (A/G), rs6128461 (T/C), rs6415328 (T/C), rs6610868 (T/C), rs6686061 (A/C), rs6730350 (T/G), rs6746197 (T/C), rs6963426 (T/C), rs7121326 (T/C), rs7721799 (A/G), rs7787082 (T/C), rs7799592 (A/C), rs796245 (T/C), rs809482 (A/C), rs8125112 (T/C), rs919196 (A/G), rs920750 (T/C), rs9332385 (A/G), rs930473 (T/G), rs9324921 (A/C), rs9348979 (A/G), rs9571939 (A/C), and rs9892359 (T/C),

(b) at least one polymorphism genotype being in linkage disequilibrium with any one of the polymorphism genotypes of (a), or

(c) a combination of (a) and (b);

and

one or more additional reagents for detecting the presence or absence of the one or more polymorphism genotypes;

optionally comprising instructions for detecting the presence or absence of the at least one polymorphism genotype in a sample obtained from a subject.

20. The composition of claim 18, or the kit of claim 19, wherein the at least one polynucleotide comprises:

(a) at least two polynucleotides capable of specifically hybridizing to nucleic acids comprising each of at least two of said polymorphism genotypes;

(b) at least four polynucleotides capable of specifically hybridizing to nucleic acids comprising each of at least four of said polymorphism genotypes;

(c) at least eight polynucleotides capable of specifically hybridizing to nucleic acids comprising each of at least eight of said polymorphism genotypes;

(d) at least 16 polynucleotides capable of specifically hybridizing to nucleic acids comprising each of at least 16 of said polymorphism genotypes;

(e) at least 32 polynucleotides capable of specifically hybridizing to nucleic acids comprising each of at least 32 of said polymorphism genotypes; or

(f) 274 polynucleotides capable of specifically hybridizing to nucleic acids comprising each of said polymorphism genotypes.

21. The composition of claims 18 or 20, or the kit of claims 19 or 20, wherein the at least one polymorphism genotype comprises:

(a) at least two polynucleotides capable of specifically hybridizing to nucleic acids comprising each of at least two polymorphism genotypes selected from the combinations of polymorphism genotypes disclosed in Table 5;
(b) at least four polynucleotides capable of specifically hybridizing to nucleic acids comprising each of at least four polymorphism genotypes selected from the combinations of polymorphism genotypes disclosed in Table 6;
(c) at least eight polynucleotides capable of specifically hybridizing to nucleic acids comprising each of at least eight polymorphism genotypes selected from the combinations of polymorphism genotypes disclosed in Table 7; or
(d) 274 polynucleotides capable of specifically hybridizing to nucleic acids comprising each of the polymorphism genotypes disclosed in Table 2.

22. The composition of any one of claims 18-21, or the kit of any one of claims 19-21, wherein the at least one polynucleotide is bound to a solid support.

23. The composition or kit of claim 22, wherein the at least one polynucleotide is bound to the solid support in the form of an array.

24. The kit of any one of claims 19-23, further comprising one or more reagents for isolating a nucleic acid from a sample.

25. The kit of any one of claims 19-24, further comprising a means for amplifying a nucleic acid.

26. Use of a composition as defined in any one of claims 18-23, or a kit as defined in any one of claims 19-25, for predicting the treatment response of a subject to a treatment with a CRHR1 antagonist, wherein the composition or kit is used to detect the presence or absence of one or more polymorphism genotypes within a sample obtained from a subject.

27. A method for detecting a polymorphism genotype associated with a treatment response of a subject to treatment with a CRHR1 antagonist, the method comprising:

providing a biological sample obtained from the subject, and

detecting the presence or absence of one or more polymorphism genotypes in the biological sample, wherein the one or more polymorphism genotypes comprise:
(a) at least one polymorphism genotype selected from the group consisting of

rs34169260 (A/G), rs796287 (A/C), rs56149945 (A/G), rs6190 (T/C), rs7179092 (T/C), rs7614867 (A/G), rs920640 (T/C), rs7167722 (T/C), rs920638 (T/C), rs7165629 (T/C), rs80049044 (T/A), rs16941058 (A/G), rs112015971 (A/G), rs10894873 (T/C), rs117455294 (T/G), rs1170303 (T/C), rs16940681 (C/G), rs968519 (T/C), rs28381866 (T/C), rs79320848 (T/G), rs114653646 (T/G), rs2589496 (T/C), rs10482650 (A/G), rs17614642 (A/G), rs73200317 (T/C), rs1380146 (T/A), rs735164 (T/C), rs730976 (T/G), rs55934524 (T/G), rs4570614 (A/G), rs4458044 (C/G), rs77850169 (A/G), rs35339359 (A/G), rs34800935 (T/C), rs72945439 (T/C), rs113959523 (A/G), rs116798177 (A/G), rs11247577 (T/G), rs75869266 (T/C), rs74372553 (T/C), rs11691508 (A/G), rs6493965 (A/G), rs4869476 (T/C), rs3730170 (T/C), rs2145288 (A/C), rs2935752 (A/C), rs146512400 (A/G), rs62057097 (T/C), rs115061314 (T/C), rs34113594 (T/G), rs61751173 (A/G), rs74338736 (A/C), rs10851726 (T/C), rs4610906 (T/C), rs59485211 (T/C), rs7060015 (T/G), rs75710780 (T/G), rs6520908 (T/C), rs487011 (T/G), rs1383699 (A/C), rs67516871 (A/G), rs114106519 (T/C), rs7220091 (A/G), rs12489026 (A/G), rs876270 (T/C), rs4968161 (T/C), rs62056907 (A/G), rs2235013 (T/C), rs16878812 (A/G), rs6549407 (A/G), rs28381848 (A/G), rs79723704 (A/C), rs72814052 (A/G), rs10152908 (T/C), rs172769 (A/C), rs78596668 (T/C), rs73307922 (T/C), rs3842 (A/G), rs7210584 (A/C), rs62402121 (T/C), rs55709291 (A/G), rs72747088 (A/G), rs929610 (G/C), rs6766242 (T/C), rs1468552 (G/C), rs78838114 (T/C), rs62489862 (T/C), rs894342 (A/G), rs58882373 (T/C), rs3811939 (A/G), rs6984688 (T/G), rs1018160 (T/C), rs76602912 (A/G), rs80067508 (A/G), rs74888440 (T/C), rs12481583 (T/C), rs66794218 (A/G), rs16946701 (A/G), rs75726724 (A/G), rs67959715 (T/A), rs11871392 (T/G), rs2044070 (A/G), rs77612799 (T/C), rs6743702 (T/C), rs616870 (T/C), rs79590198 (A/G), rs75715199 (A/G), rs13087555 (T/C), rs4869618 (T/C), rs117397046 (A/G), rs8042817 (A/G), rs2258097 (T/C), rs2260882 (C/G), rs532996 (A/G), rs11747040 (T/C), rs10034039 (T/G), rs116909369 (A/G), rs79134986 (A/G), rs117615688 (T/C), rs8032253 (T/C), rs12818653 (T/A), rs4587884 (A/C), rs77122853 (T/C), rs117615061 (T/C), rs74682905 (A/G), rs2257468 (T/C), rs2032582 (T/G), rs2235015 (T/G), rs2729794 (T/C), rs77549514 (A/G), rs74790420 (A/C), rs73129579 (T/C), rs12913346 (A/C), rs117560908 (T/C), rs72747091 (A/G), rs2935751 (A/G), rs4331446 (A/G), rs7523266 (T/C), rs7648662 (T/C), rs117034065 (A/G), rs4836256 (T/C), rs80238698 (T/C), rs3730173 (T/C), rs11687884 (T/C), rs72693005 (T/C), rs2589476 (T/C), rs9813396 (T/C), rs10482667 (A/G), rs72784444 (A/G), rs75074511 (T/C), rs7951003 (A/G), rs79584784 (A/G), rs2214102 (T/C), rs28811003 (A/G), rs6100261 (A/T), rs77152456 (A/G), rs66624622 (T/G), rs140302965 (A/G), rs11653269 (T/C),

rs74405057 (A/G), rs7121 (A/G), rs16977818 (A/C), rs12490095 (T/C), rs118003903 (A/G), rs62377761 (T/C), P1_M_061510_6_34_M (-/CACTTACCTTCTTTGTGCCACAGTTTCCCTATCTAAAACACAAGGTTATCAGTTATC AACATCTCTTGGGATTGTGAGGACTAAAGTAATGCACATAAAG), rs375115639 (-/AAATTACCCTGTTAGGTTTCAATGAAACACCTTTTCTCTTGTAACAAACATCTCCTCCAAGCTAGAATTTCAAAACAG), rs1002204 (A/C), rs10062367 (A/G), rs10482642 (A/G), rs10482658 (A/G), rs1053989 (A/C), rs10851628 (T/C), rs10947562 (T/C), rs11069612 (A/G), rs11071351 (T/C), rs11091175 (A/G), rs11638450 (T/C), rs11715827 (T/G), rs11745958 (T/C), rs11834041 (A/G), rs1202180 (T/C), rs12054781 (A/G), rs12539395 (A/G), rs12720066 (T/G), rs1279754 (A/C), rs12872047 (T/C), rs12876742 (A/C), rs12917505 (A/G), rs13066950 (T/G), rs13229143 (C/G), rs1383707 (T/C), rs1441824 (T/C), rs1652311 (A/G), rs17064 (T/A), rs17100236 (A/G), rs17149699 (A/G), rs1724386 (A/G), rs17250255 (A/G), rs17327624 (T/G), rs17616338 (A/G), rs17687796 (A/G), rs17740874 (T/C), rs17763104 (T/C), rs1880748 (T/C), rs1882478 (A/G), rs1944887 (T/C), rs2028629 (A/G), rs2143404 (A/G), rs2173530 (T/C), rs220806 (T/C), rs2235047 (A/C), rs2242071 (A/G), rs2257474 (T/C), rs2295583 (A/T), rs234629 (T/C), rs234630 (A/G), rs2436401 (A/G), rs258750 (T/C), rs2589487 (T/C), rs28364018 (T/G), rs28381774 (T/C), rs28381784 (A/G), rs2963155 (A/G), rs3133622 (T/G), rs32897 (T/C), rs33388 (A/T), rs3730168 (T/C), rs3735833 (T/G), rs3777747 (A/G), rs3786066 (T/C), rs3798346 (T/C), rs3822736 (A/G), rs389035 (T/C), rs3924144 (A/G), rs4148737 (T/C), rs4148749 (G/C), rs417968 (T/C), rs4458144 (T/C), rs4515335 (T/C), rs4728699 (A/G), rs4758040 (A/G), rs4812040 (A/G), rs4912650 (T/G), rs4957891 (T/C), rs5906392 (A/G), rs6026561 (T/C), rs6026565 (T/A), rs6026567 (A/G), rs6026593 (A/G), rs6092704 (T/G), rs6100260 (A/G), rs6128461 (T/C), rs6415328 (T/C), rs6610868 (T/C), rs6686061 (A/C), rs6730350 (T/G), rs6746197 (T/C), rs6963426 (T/C), rs7121326 (T/C), rs7721799 (A/G), rs7787082 (T/C), rs7799592 (A/C), rs796245 (T/C), rs809482 (A/C), rs8125112 (T/C), rs919196 (A/G), rs920750 (T/C), rs9332385 (A/G), rs930473 (T/G), rs9324921 (A/C), rs9348979 (A/G), rs9571939 (A/C), and rs9892359 (T/C); (b) at least one polymorphism genotype being in linkage disequilibrium with any one of the polymorphism genotypes of (a); or (c) a combination of (a) and (b).

28. The method of claim 27, wherein the method further comprises predicting the treatment response from the presence or absence of the polymorphism genotypes of (a), (b), or (c).

29. The method of claims 27 or 28, wherein detecting a polymorphism genotype associated with a treatment response comprises:
(a) determining whether the subject will respond, or has an increased likelihood of responding to the treatment with a CRHR1 antagonist; and/or
(b) determining whether the subject will not respond, or has a decreased likelihood of responding to the treatment with a CRHR1 antagonist.

30. The method of claim 29, wherein the determining step comprises one or more statistical analysis method selected from the group consisting of artificial neural network learning, decision tree learning, decision tree forest learning, linear discriminant analysis, non-linear discriminant analysis, genetic expression programming, relevance vector machines, linear models, generalized linear models, generalized estimating equations, generalized linear mixed models, the elastic net, the lasso support vector machine learning, Bayesian network learning, probabilistic neural network learning, clustering, and regression analysis, optionally wherein the statistical analysis method is computer-implemented.

31. The method of any one of claims 27 to 30, wherein the one or more polymorphism genotypes comprise:
(a) at least two;
(b) at least four;
(c) at least eight;
(d) at least sixteen;
(e) at least thirty-two; or
(f) all
of the polymorphism genotypes as defined in claim 1.

32. The method of any one of claims 27 to 30, wherein the one or more polymorphism genotypes comprise:
(a) at least two polymorphism genotypes selected from the combinations of polymorphism genotypes disclosed in Table 5;
(b) at least four polymorphism genotypes selected from the combinations of polymorphism genotypes disclosed in Table 6;
(c) at least eight polymorphism genotypes selected from the combinations of polymorphism genotypes disclosed in Table 7;

(d) all of the polymorphism genotypes disclosed in Table 2.

33. The method of any one of claims 27 to 32, wherein the treatment response to treatment with the CRHR1 antagonist is a clinical response.

34. The method of any one of claims 27 to 33, wherein the subject has depressive symptoms, anxiety symptoms or both depressive symptoms and anxiety symptoms or a sleep disorder; and/or

wherein the treatment is a treatment of depressive symptoms, anxiety symptoms or both depressive symptoms and anxiety symptoms or a sleep disorder.

35. The method of claim 34, wherein the treatment response to treatment with the CRHR1 antagonist is a clinical response, and wherein the clinical response is a prevention, alteration, alleviation or complete remission of depressive symptoms and/or anxiety symptoms or a sleep disorder.

36. The method of claim 35, wherein the clinical response is a prevention, alteration, alleviation or complete remission of depressive symptoms and/or anxiety symptoms as determined using a scale selected from the group consisting of HAM-D, BDI, MADRS, GDS, ZSRDS, HAM-A and STAI.

37. The method of any one of claims 27 to 36, wherein the biological sample is a buccal or a blood sample.

38. The method of any one of claims 27 to 37, wherein detecting comprises the use of one or more polynucleotides capable of specifically hybridizing to at least one nucleic acid comprising the one or more polymorphism genotypes.

39. The method of any one of claims 27 to 38, wherein the subject has been administered a CRHR1 antagonist, further comprising comparing the prediction that the subject will respond to a treatment with a CRHR1 antagonist with the treatment response of the subject to administration of the CRHR1 antagonist.

40. The method of any one of claims 27 to 39, wherein the prediction that the subject will respond to a treatment with a CRHR1 antagonist has a sensitivity of higher than 50% and a specificity of higher than 50%.

41. The method of any one of claims 27 to 40, wherein the CRHR1 antagonist is selected from the group consisting of GW876008 (Emicerfont), GSK-561679 (NBI-77860, Verucerfont), GSK586529, BMS-562,086 (Pexacerfont), NBI-30775 (R-121919), NBI-34101, CP-316,311, CP-376,395, PF-00572778, NVP-AAG561, Ono-2333MS, E2508, E2009, R317573 (JNJ19567470, CRA5626, TAI-041), R278995 (CRA0450), CRA-1000, CRA-1001, CP154,526, Antalarmin, DMP-695, DMP-696, DMP-904, SC-241, BMS-561388, NBI30545, PD-171729, NBI34041, NBI35965, SN003, NBI-27914, *trans*-2-chloro-N-(4-((5-fluoro-4-methyl-pyridin-2-ylamino)-methyl)-cyclohexyl)-5-(trifluoromethyl)-benzamide, SSR-125543, or a pharmaceutically acceptable salt thereof.

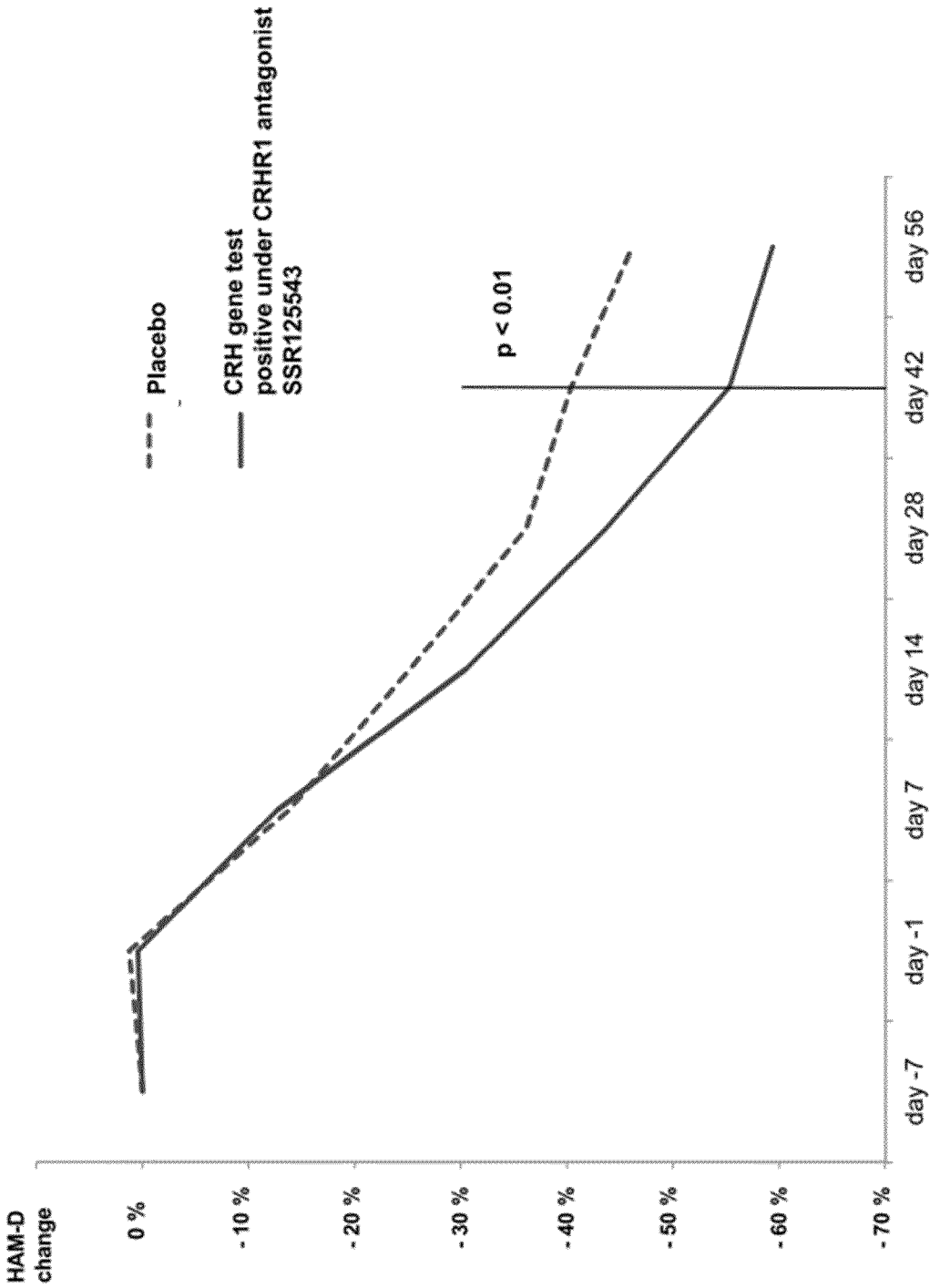

HAM-D change
0 %
- 10 %
- 20 %
- 30 %
- 40 %
- 50 %
- 60 %
- 70 %
day -7
day -1
day 7
day 14
day 28
day 42
day 56
p < 0.01
Placebo
CRH gene test positive under CRHR1 antagonist SSR125543

Figure 1