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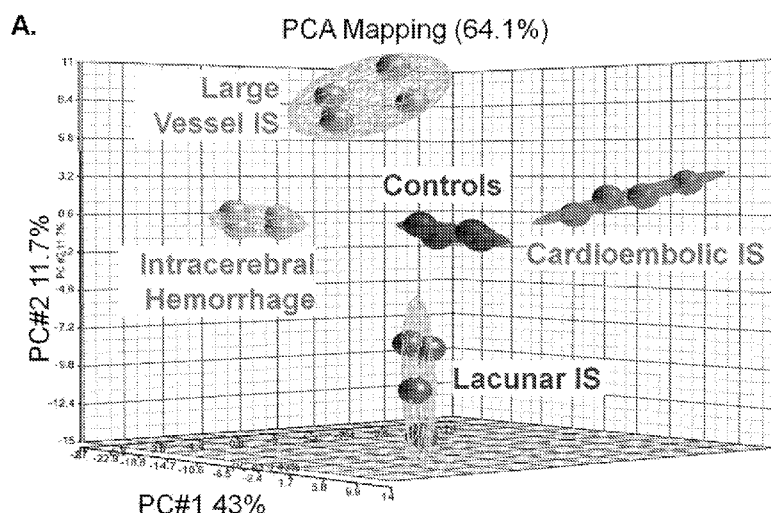


Fig. 2

(57) Abstract: Provided are compositions and methods for differentiating and diagnosing ischemic stroke and subgroups thereof (e.g., cardioembolic stroke, large vessel stroke, atherothrombotic stroke, lacunar stroke) from intracerebral hemorrhage.

METHODS OF DISTINGUISHING ISCHEMIC STROKE FROM INTRACEREBRAL HEMORRHAGE

CROSS-REFERENCE TO RELATED APPLICATIONS

- 5 **[0001]** This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 62/159,502, filed on May 11, 2015, which is hereby incorporated herein by reference.

STATEMENT OF GOVERNMENTAL SUPPORT

- 10 **[0002]** This invention was made with Government support under Grant Nos. NS075035, NS079153 and AG042292, all awarded by the National Institutes of Health. The government has certain rights in this invention.

FIELD

- 15 **[0003]** Provided are compositions and methods for differentiating and diagnosing ischemic stroke and subgroups thereof (*e.g.*, cardioembolic stroke, large vessel stroke, atherothrombotic stroke, lacunar stroke) from intracerebral hemorrhage.

BACKGROUND

- 20 **[0004]** Clinicians diagnose stroke based on patient history, neurological exams and brain imaging. This can be difficult and distinguishing ischemic stroke (IS) from hemorrhage can be challenging when imaging is unavailable in the acute setting.

- 25 **[0005]** Blood transcriptomes have provided insights into the immune response following human stroke and show promise as diagnostic biomarkers [1-6]. However, these studies have investigated only a proportion of the protein coding transcriptome, since they have used 3'-biased microarrays to measure blood mRNA expression [1-6]. Though these studies provided proof-of-principle, the vast complexity of the stroke transcriptome which is comprised of alternatively spliced isoforms remains unstudied in stroke. The importance of alternative splicing (AS) in stroke is supported by increasing evidence implicating AS in the pathogenesis of many diseases [7, 8].

- 30 **[0006]** AS is the process whereby exons from a single gene are included or excluded in the final mRNA transcript (Figure 1). A single gene produces several AS isoforms with

specific functions in different cells, tissues, developmental stages and disease states. Thus, the ~20,000 known genes code for >250,000 different mRNAs and proteins. Differential alternative splicing (DAS) is AS that differs between groups. We investigated whether DAS would vary for different IS causes (cardioembolic, large vessel and lacunar) compared to intracerebral hemorrhage (ICH) and controls. Therefore, we used RNA sequencing (RNA-Seq) to measure DAS in whole blood samples of humans with ICH and with different causes of IS and compared these to controls. RNA-Seq is a new technology that allows for estimation of expression of each splice variant (Figure 1), a significant advance over previously used technologies in stroke. To date, there have been no RNA-Seq studies for AS markers of stroke etiology, or for distinguishing between ischemic stroke and ICH either in humans or in animal models.

SUMMARY

[0007] In one aspect, provided are methods for diagnosing cardioembolic ischemic stroke (CE IS) or a predisposition for experiencing CE IS. In some embodiments, the methods comprise determining a level of exon or splice variant usage or expression of a plurality of biomarkers in a biological sample from a patient, wherein an increase of the level of exon usage or expression compared to a control indicates that the patient has suffered or is at risk of experiencing CE IS, wherein the plurality of exons or splice variants of the biomarkers is selected from the biomarkers set forth in Table 1A, thereby diagnosing CE IS or a predisposition for experiencing CE IS.

[0008] In a further aspect, provided are methods for diagnosing large vessel ischemic stroke (LV IS) or a predisposition for experiencing LV IS. In some embodiments, the methods comprise determining a level of exon or splice variant usage or expression of a plurality of biomarkers in a biological sample from a patient, wherein an increase of the level of exon usage or expression compared to a control indicates that the patient has suffered or is at risk of experiencing LV IS, wherein the plurality of exons or splice variants of the biomarkers is selected from the biomarkers set forth in Table 1B, thereby diagnosing LV IS or a predisposition for experiencing LV IS.

[0009] In a further aspect, provided are methods for diagnosing lacunar ischemic stroke (L IS) or a predisposition for experiencing L IS. In some embodiments, the methods comprise determining a level of exon or splice variant usage or expression of a plurality of biomarkers in a biological sample from a patient, wherein an increase of the level of exon

usage or expression compared to a control indicates that the patient has suffered or is at risk of experiencing L IS, wherein the plurality of exons or splice variants of the biomarkers is selected from the biomarkers set forth in Table 1C, thereby diagnosing L IS or a predisposition for experiencing L IS.

5 **[0010]** In a further aspect, provided are methods for diagnosing intracerebral hemorrhage (ICH) or a predisposition for experiencing ICH. In some embodiments, the methods comprise determining a level of exon usage or expression of a plurality of biomarkers in a biological sample from a patient, wherein an increase of the level of exon or splice variant usage or expression compared to a control indicates that the patient has
10 suffered or is at risk of experiencing ICH, wherein the plurality of exons or splice variants of the biomarkers is selected from the biomarkers set forth in Table 1D, thereby diagnosing ICH or a predisposition for experiencing ICH.

[0011] In a further aspect, provided are methods of differentiating between ischemic stroke (IS) from intracerebral hemorrhage (ICH). In some embodiments, the methods
15 comprise determining a level of exon or splice variant usage or expression of a plurality of biomarkers set forth in Table 1A, a plurality of biomarkers set forth in Table 1B, a plurality of biomarkers set forth in Table 1C, and a plurality of biomarkers set forth in Table 1D, in a biological sample from a patient, wherein detecting:

 a) an increase of the level of exon or splice variant usage or expression of a
20 plurality of exons of the biomarkers set forth in Table 1A compared to a control indicates that the patient has suffered or is at risk of experiencing cardioembolic ischemic stroke (CE IS);

 b) an increase of the level of exon or splice variant usage or expression of a
25 plurality of exons of the biomarkers set forth in Table 1B compared to a control indicates that the patient has suffered or is at risk of experiencing large vessel ischemic stroke (LV IS);

 c) an increase of the level of exon or splice variant usage or expression of a
plurality of exons of the biomarkers set forth in Table 1C compared to a control indicates that the patient has suffered or is at risk of experiencing lacunar ischemic stroke (L IS); and

30 d) an increase of the level of exon or splice variant usage or expression of a plurality of exons of the biomarkers set forth in Table 1D compared to a control indicates that the patient has suffered or is at risk of experiencing ICH; thereby differentiating between ischemic stroke (IS) from ICH.

[0012] With respect to embodiments of the methods, in some embodiments, the determining step is performed at 3 or more hours after a suspected ischemic stroke or ICH. In some embodiments, the determining step is performed at 3 or fewer hours after a suspected ischemic stroke or ICH. In some embodiments, the determining step is performed at 24 or fewer hours after a suspected ischemic stroke or ICH. In some embodiments, the determining step is performed at least 24 hours after a suspected ischemic stroke or ICH. In some embodiments, the level of expression of the biomarker is determined at the transcriptional level. In varying embodiments, the level of expression is determined by detecting hybridization of a nucleic acid probe to gene transcripts of the biomarkers in the biological sample. In varying embodiments, the hybridization step is performed on a nucleic acid microarray chip. In varying embodiments, the hybridization step is performed in a microfluidics assay plate. In varying embodiments, the level of expression is determined by direct RNA sequencing of gene transcripts of the biomarkers. In varying embodiments, the level of expression is determined by amplification of gene transcripts of the biomarkers. In varying embodiments, the amplification reaction is a polymerase chain reaction (PCR). In varying embodiments, the amplification reaction comprises quantitative reverse transcription polymerase chain reaction (qRT-PCR). In varying embodiments, the amplification reaction comprises reverse transcription (RT) followed by a ligase detection reaction (LDR) with single-pair fluorescence resonance energy transfer (spFRET) (RT-LDR/spFRET). In varying embodiments, the level of expression of the biomarker isoform is determined at the protein level. In varying embodiments, the level of expression of at least 15 biomarkers, *e.g.*, at least 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 biomarkers, or all listed biomarkers in the identified Table (*e.g.*, Table 1A, Table 1B, Table 1C, Table 1D and/or Table 1E), are determined. In varying embodiments, the methods further comprise the step of obtaining a biological sample. In varying embodiments, the biological sample is blood, serum or plasma. In varying embodiments, the increased level of exon usage of a biomarker is at least about 1.2-fold in comparison to a control. In varying embodiments, the control is the expression level of the same biomarker in an individual with no history of stroke, heart attack, or peripheral vascular disease. In varying embodiments, the control is a threshold level of expression representative of a population of individuals with no history of stroke, heart attack, peripheral vascular disease. In varying embodiments, the individual or the population of individuals has at least one vascular risk factor. In varying embodiments, the control is an individual or population of individuals who have increased expression of one or more biomarkers set forth in Table 1E.

In varying embodiments, the methods further comprise the step of providing a diagnosis for ischemic stroke/ICH to the patient based on the determination and identification of the level of expression of the set of ischemic stroke/ICH biomarkers. In varying embodiments, the methods further comprise the step of providing an appropriate treatment or prevention regime for ischemic stroke/ICH to the patient. In varying embodiments, the subject has experienced or is suspected of having experienced ischemic stroke or ICH. In varying embodiments, if the patient has experienced or has a predisposition to experience ischemic stroke or ICH, further comprising the step of determining the cause or risk of the ischemic stroke or ICH

[0013] In a further aspect, provided are solid supports. In varying embodiments, the solid supports comprise a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers set forth in Table 1A. In varying embodiments, the solid supports comprise a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers set forth in Table 1B. In varying embodiments, the solid supports comprise a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers set forth in Table 1C. In varying embodiments, the solid supports comprise a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers set forth in Table 1D. In varying embodiments, the solid supports comprise a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers set forth in Table 1A, Table 1B, Table 1C and/or Table 1D. In varying embodiments, the solid support is a microarray. In varying embodiments, the microarray is suitable or configured for use in a microfluidic device. In varying embodiments, the solid supports further comprise a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers set forth in Table 1E. In varying embodiments, the solid supports further comprise a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers for diagnosing one or more of cardioembolic stroke, atherothrombotic stroke, carotid stenosis, atrial fibrillation, lacunar stroke, transient ischemic attack, transient neurological events, and hemorrhagic transformation. In varying embodiments, plurality refers to at least 15 biomarkers, e.g., at least 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 biomarkers, or all listed biomarkers in the identified Table (e.g., Table 1A, Table 1B, Table 1C, Table 1D and/or Table 1E).

[0014] In another aspect, provided are reaction mixtures for amplifying one or more exons of a plurality (e.g., 2, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 biomarkers, or all listed biomarkers in the identified Table, e.g., Table 1A, Table 1B,

Table 1C, Table 1D and/or Table 1E) of biomarkers listed in Tables 1A-E. In varying embodiments, the reaction mixture comprises one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1A. In varying embodiments, the reaction mixture comprises one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1B. In varying embodiments, the reaction mixture comprises one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1C. In varying embodiments, the reaction mixture comprises one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1D. In varying embodiments, the reaction mixture comprises one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1A, Table 1B, Table 1C and Table 1D. In varying embodiments, the reaction mixture further comprises one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1E. Further provided is a kit comprising the reaction mixtures, as described above and herein.

[0015] In a related aspect, provided are kits. In varying embodiments, the kits comprise one or more solid supports, as described herein. In varying embodiments, the kits comprise one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1A. In varying embodiments, the kits comprise one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1B. In varying embodiments, the kits comprise one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1C. In varying embodiments, the kits comprise one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1D. In varying embodiments, the kits comprise one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1A, Table 1B, Table 1C and Table 1D. In varying embodiments, the kits further comprising a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1E.

DEFINITIONS

[0016] Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the

art to which this invention belongs. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry and nucleic acid chemistry and hybridization described below are those well-known and commonly employed in the art. Standard techniques are used for nucleic acid and peptide synthesis.

5 Generally, enzymatic reactions and purification steps are performed according to the manufacturer's specifications. The techniques and procedures are generally performed according to conventional methods in the art and various general references (*see generally*, Green and Sambrook, MOLECULAR CLONING: A LABORATORY MANUAL, 4th ed. (2012) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. and Ausubel, *et*
10 *al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, 1987-2015, Wiley Interscience; Wiley Online Library at <http://onlinelibrary.wiley.com/book/10.1002/0471142727/homepage/archive.htm>), which are provided throughout this document. The nomenclature used herein and the laboratory procedures in analytical chemistry and organic synthesis described below are those well-
15 known and commonly employed in the art. Standard techniques, or modifications thereof, are used for chemical syntheses and chemical analyses.

[0017] "Ischemia" or "ischemic event" as used herein refers to diseases and disorders characterized by inadequate blood supply (*i.e.*, circulation) to a local area due to blockage of the blood vessels to the area. Ischemia includes for example, strokes and
20 transient ischemic attacks. Strokes include, *e.g.*, ischemic stroke (including, but not limited to, cardioembolic strokes, atheroembolic or atherothrombotic strokes, *i.e.*, strokes caused by atherosclerosis in the carotid, aorta, heart, and brain, small vessel strokes (*i.e.*, lacunar strokes), strokes caused by diseases of the vessel wall, *i.e.*, vasculitis, strokes caused by infection, strokes caused by hematological disorders, strokes caused by migraines, and
25 strokes caused by medications such as hormone therapy).

[0018] The term "transient ischemic attack," "TIA," or "mini-stroke" interchangeably refer to a change in the blood supply to a particular area of the brain, resulting in brief neurologic dysfunction that persists, by definition, for less than 24 hours. By definition, a TIA resolves within 24 hours, but most TIA symptoms resolve within a few
30 minutes. If symptoms persist longer, then it is categorized as a stroke. Symptoms include temporary loss of vision (typically amaurosis fugax); difficulty speaking (aphasia); weakness on one side of the body (hemiparesis); numbness or tingling (paresthesia), usually on one side of the body, and dizziness, lack of coordination or poor balance. The symptoms

of a TIA usually last a few seconds to a few minutes and most symptoms disappear within 60 minutes.

[0019] Transient neurological attacks (TNA) or transient neurological events (TNE) interchangeably refer to events involving neurological symptoms typically lasting only a few minutes or hours and no more than 24 hours. TIAs are considered focal TNAs; other events -- including quickly resolving amnesia, confusion, or dizziness and fainting -- are considered nonfocal TNAs.

[0020] The term “small deep infarct” or “small deep infarction” or “SDI” interchangeably refer to focal infarction of the brain due to an uncertain cause, including but not limited to, cardioembolic, atheroembolic, atherosclerotic disease of the parent artery or disease of the perforating artery.

[0021] The term “lacunar stroke” or “lacune” interchangeably refer to focal infarction of the brain due to perforating branch occlusion from microatheroma or lipohyalinosis. Implicit in this definition of lacunar stroke is that the: 1) infarction is not due to cardioembolic source; 2) infarction is not due to atherosclerotic disease of parent arteries; 3) infarction occurs in regions of the brain supplied by penetrating arteries, *e.g.*, basal ganglia, thalamus, internal capsule, corona radiata or pons; 4) lacunar stroke is oftentimes associated with the presence of hypertension, diabetes or other vascular risk factors; and 5) infarcts tend to be smaller, generally less than 50mm in diameter. When the cause of stroke is uncertain or likely other than perforating artery disease, then the more general term—small deep infarct—is appropriate. *See, e.g.*, Caplan, *Stroke* (2003) 34(3):653-9; Norrving, *Pract Neurol* (2008) 8:222–228; Lastilla, *Clin Exp Hypertens*. (2006) 28(3-4):205-15; and Arboix and Martí-Vilalta, *Expert Rev Neurother.* (2009) 9(2):179-96.

[0022] The term “intracerebral hemorrhage” and “ICH” interchangeably refer to a type of stroke caused by bleeding within the brain tissue itself. Intracerebral hemorrhage occurs when a diseased blood vessel within the brain bursts, allowing blood to leak inside the brain.

[0023] An “ischemic stroke/ICH reference expression profile” refers to the pattern of expression of a set of gene exons or splice variants or isoforms (*e.g.*, a plurality of the exons /splice variants or isoforms of the biomarkers set forth in Tables 1A, 1B, 1C, 1D and/or 1E differentially expressed (*i.e.*, overexpressed or underexpressed) in an individual who has suffered or is at risk of experiencing ischemia (*e.g.*, transient cerebral ischemia,

transient ischemic attacks (TIA), cerebral ischemia, cardioembolic stroke, large vessel stroke, atherothrombotic stroke, lacunar stroke), intracerebral hemorrhage (ICH) relative to the expression in a control (*e.g.*, the expression level in an individual free of an ischemic stroke/ICH event or the expression level of a stably expressed endogenous reference

5 biomarker). A gene exon/splice variant or isoform from Tables 1A, 1B, 1C, 1D and/or 1E that is expressed at a level that is at least about 1.2-fold, *e.g.*, at least about 1.3-, 1.4-, 1.5-, 1.6-, 1.7-, 1.8-, 1.9-, 2.0-fold, higher than the level in a control is a gene exon/splice variant or isoform overexpressed in ischemic stroke/ICH and a gene exon/splice variant or isoform from Tables 1A, 1B, 1C, 1D and/or 1E that is expressed at a level that is at least about 1.2-
10 fold, *e.g.*, at least about 1.3-, 1.4-, 1.5-, 1.6-, 1.7-, 1.8-, 1.9-, 2.0-fold, lower than the level in a control is a gene isoform underexpressed in ischemic stroke/ICH. Alternately, gene exons/splice variants or isoforms that are expressed at a level that is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% higher than the level in a control is a gene exon/splice variant or isoform overexpressed in ischemic stroke/ICH and a gene
15 exon/splice variant or isoform that is expressed at a level that is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% lower than the level in a control is a gene exon/splice variant or isoform underexpressed in ischemic stroke/ICH.

[0024] A “plurality” refers to two or more, for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100,
20 150, 200, 250, 300, 500, 1000, 2000, 5000, or more (*e.g.*, genes). In some embodiments, a plurality refers to concurrent determination of expression levels about 15-85, 20-60 or 40-50 genes, for example, about 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 150, 200, 250, 300, 500, 1000, 2000, 5000, or more, genes. In some embodiments, “plurality” refers to all genes listed in one or more or all tables, *e.g.*, all genes listed in
25 Tables 1A, 1B, 1C, 1D and/or 1E.

[0025] As used herein, the terms “treating” and “treatment” refer to delaying the onset of, retarding or reversing the progress of, reducing the severity of, or alleviating or preventing either the disease or condition to which the term applies, or one or more symptoms of such disease or condition.

30 **[0026]** The term “mitigating” refers to reduction or elimination of one or more symptoms of that pathology or disease, and/or a reduction in the rate or delay of onset or severity of one or more symptoms of that pathology or disease, and/or the prevention of that pathology or disease. In certain embodiments, the reduction or elimination of one or more

symptoms of pathology or disease can include, but is not limited to, reduction or elimination of one or more markers that are characteristic of the pathology or disease.

[0027] The terms “subject,” “individual,” and “patient” interchangeably refer to a mammal, preferably a human or a non-human primate, but also domesticated mammals (e.g., canine or feline), laboratory mammals (e.g., mouse, rat, rabbit, hamster, guinea pig) and agricultural mammals (e.g., equine, bovine, porcine, ovine). In various embodiments, the subject can be a human (e.g., adult male, adult female, adolescent male, adolescent female, male child, female child) under the care of a physician or other healthworker in a hospital, psychiatric care facility, as an outpatient, or other clinical context. In certain embodiments the subject may not be under the care or prescription of a physician or other healthworker.

[0028] “Sample” or “biological sample” includes sections of tissues such as biopsy and autopsy samples, and frozen sections taken for histologic purposes. Such samples include blood, sputum, tissue, lysed cells, brain biopsy, cultured cells, e.g., primary cultures, explants, and transformed cells, stool, urine, etc. A biological sample is typically obtained from a eukaryotic organism, most preferably a mammal such as a primate, e.g., chimpanzee or human; cow; dog; cat; a rodent, e.g., guinea pig, rat, mouse; rabbit; or a bird; reptile; or fish.

[0029] “Array” as used herein refers to a solid support comprising attached nucleic acid or peptide probes. Arrays typically comprise a plurality of different nucleic acid or peptide probes that are coupled to a surface of a substrate in different, known locations. These arrays, also described as “microarrays” or colloquially “chips” have been generally described in the art, for example, U.S. Patent Nos. 5,143,854, 5,445,934, 5,744,305, 5,677,195, 6,040,193, 5,424,186 and Fodor *et al.*, *Science*, 251:767-777 (1991). These arrays may generally be produced using mechanical synthesis methods or light directed synthesis methods which incorporate a combination of photolithographic methods and solid phase synthesis methods. Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, e.g., U.S. Patent No. 5,384,261. Arrays may comprise a planar surface or may be nucleic acids or peptides on beads, gels, polymeric surfaces, fibers such as fiber optics, glass or any other appropriate substrate as described in, e.g., U.S. Patent No. 5,770,358, 5,789,162, 5,708,153, 6,040,193 and 5,800,992. Arrays may be packaged in such a manner as to allow for diagnostics or other manipulation of an all-inclusive device, as described in, e.g., U.S. Patent Nos. 5,856,174 and 5,922,591.

[0030] The term “gene” means the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding region (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons).

5 [0031] The terms “nucleic acid” and “polynucleotide” are used interchangeably herein to refer to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. The term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the
10 reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs).

[0032] Unless otherwise indicated, a particular nucleic acid sequence also
15 encompasses conservatively modified variants thereof (*e.g.*, degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer *et al.*, *Nucleic Acid Res.* 19:5081 (1991); Ohtsuka *et al.*, *J.*
20 *Biol. Chem.* 260:2605-2608 (1985); Rossolini *et al.*, *Mol. Cell. Probes* 8:91-98 (1994)). The term nucleic acid is used interchangeably with gene, cDNA, mRNA, oligonucleotide, and polynucleotide.

[0033] The phrase “stringent hybridization conditions” refers to conditions under which a probe will hybridize to its target subsequence, typically in a complex mixture of
25 nucleic acid, but to no other sequences. Stringent hybridization conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, *Techniques in Biochemistry and Molecular Biology--Hybridization with Nucleic Probes*, “Overview of principles of hybridization and the strategy of nucleic acid
30 assays” (1993). Generally, stringent hybridization conditions are selected to be about 5-10°C lower than the thermal melting point for the specific sequence at a defined ionic strength Ph . The T_m is the temperature (under defined ionic strength, Ph , and nucleic concentration) at which 50% of the probes complementary to the target hybridize to the

target sequence at equilibrium (as the target sequences are present in excess, at T_m , 50% of the probes are occupied at equilibrium). Stringent hybridization conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion concentration (or other salts) at Ph 7.0 to 8.3 and the temperature is at least about 30°C for short probes (*e.g.*, 10 to 50 nucleotides) and at least about 60°C for long probes (*e.g.*, greater than 50 nucleotides). Stringent hybridization conditions may also be achieved with the addition of destabilizing agents such as formamide. For selective or specific hybridization, a positive signal is at least two times background, optionally 10 times background hybridization. Exemplary stringent hybridization conditions can be as following: 50% formamide, 5x SSC, and 1% SDS, incubating at 42°C, or, 5x SSC, 1% SDS, incubating at 65°C, with wash in 0.2x SSC, and 0.1% SDS at 65°C.

[0034] Nucleic acids that do not hybridize to each other under stringent hybridization conditions are still substantially identical if the polypeptides which they encode are substantially identical. This occurs, for example, when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code. In such cases, the nucleic acids typically hybridize under moderately stringent hybridization conditions. Exemplary “moderately stringent hybridization conditions” include a hybridization in a buffer of 40% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 1X SSC at 45°C. A positive hybridization is at least twice background. Those of ordinary skill will readily recognize that alternative hybridization and wash conditions can be utilized to provide conditions of similar stringency.

[0035] The terms “isolated,” “purified,” or “biologically pure” refer to material that is substantially or essentially free from components that normally accompany it as found in its native state. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high performance liquid chromatography. A protein that is the predominant species present in a preparation is substantially purified. The term “purified” denotes that a nucleic acid or protein gives rise to essentially one band in an electrophoretic gel. Particularly, it means that the nucleic acid or protein is at least 85% pure, more preferably at least 95% pure, and most preferably at least 99% pure.

[0036] The term “heterologous” when used with reference to portions of a nucleic acid indicates that the nucleic acid comprises two or more subsequences that are not found in the same relationship to each other in nature. For instance, the nucleic acid is typically

recombinantly produced, having two or more sequences from unrelated genes arranged to make a new functional nucleic acid, *e.g.*, a promoter from one source and a coding region from another source. Similarly, a heterologous protein indicates that the protein comprises two or more subsequences that are not found in the same relationship to each other in nature
5 (*e.g.*, a fusion protein).

[0037] An “expression vector” is a nucleic acid construct, generated recombinantly or synthetically, with a series of specified nucleic acid elements that permit transcription of a particular nucleic acid in a host cell. The expression vector can be part of a plasmid, virus, or nucleic acid fragment. Typically, the expression vector includes a nucleic acid to
10 be transcribed operably linked to a promoter.

[0038] The terms “polypeptide,” “peptide” and “protein” are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid
15 polymers and non-naturally occurring amino acid polymer.

[0039] The term “amino acid” refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.*,
20 hydroxyproline, α -carboxyglutamate, and O-phosphoserine. “Amino acid analogs” refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, *i.e.*, an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but
25 retain the same basic chemical structure as a naturally occurring amino acid. “Amino acid mimetics” refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

[0040] Amino acids may be referred to herein by either their commonly known
30 three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0041] “Conservatively modified variants” applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are “silent variations,” which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence.

[0042] As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a “conservatively modified variant” where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention.

[0043] The following eight groups each contain amino acids that are conservative substitutions for one another:

- 1) Alanine (A), Glycine (G);
- 2) Aspartic acid (D), Glutamic acid (E);
- 3) Asparagine (N), Glutamine (Q);
- 4) Arginine (R), Lysine (K);
- 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V);
- 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W);
- 7) Serine (S), Threonine (T); and

8) Cysteine (C), Methionine (M)
(*see, e.g., Creighton, Proteins* (1984)).

[0044] The terms “identical” or percent “identity,” in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (*i.e.*, 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, or 95% identity over a specified region of a ischemic stroke/ICH-associated gene (*e.g.*, a gene set forth in Tables 1A-E), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Such sequences are then said to be “substantially identical.” This definition also refers to the complement of a test sequence. Preferably, the identity exists over a region that is at least about 25 amino acids or nucleotides in length, or more preferably over a region that is 50-100 amino acids or nucleotides in length.

[0045] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters. For sequence comparison of nucleic acids and proteins to TIA-associated nucleic acids and proteins, the BLAST and BLAST 2.0 algorithms and the default parameters discussed below are used.

[0046] A “comparison window”, as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson & Lipman, *Proc.*

Nat'l. Acad. Sci. USA 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (see, *e.g.*, Current Protocols in Molecular Biology (Ausubel
5 *et al.*, eds. 1995 supplement)).

[0047] A preferred example of algorithm that is suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.*, *Nuc. Acids Res.* 25:3389-3402 (1977) and Altschul *et al.*, *J. Mol. Biol.* 215:403-410 (1990), respectively. BLAST and BLAST 2.0 are used,
10 with the parameters described herein, to determine percent sequence identity for the nucleic acids and proteins of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which
15 either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be
20 increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum
25 achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a word length (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands.
30 For amino acid sequences, the BLASTP program uses as defaults a word length of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff & Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915 (1989)) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

[0048] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, *e.g.*, Karlin & Altschul, *Proc. Nat'l. Acad. Sci. USA* 90:5873-5787 (1993)). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

[0049] An indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

[0050] The phrase “selectively (or specifically) hybridizes to” refers to the binding, duplexing, or hybridizing of a molecule only to a particular nucleotide sequence under stringent hybridization conditions when that sequence is present in a complex mixture (*e.g.*, total cellular or library DNA or RNA).

BRIEF DESCRIPTION OF THE DRAWINGS

[0051] Figure 1 illustrates a schematic of alternative splicing. The 3' and 5' untranslated regions in mRNA are not depicted.

[0052] Figures 2A-B illustrates Principal Component Analysis (PCA) (Figure 2A) and Unsupervised Hierarchical Clustering (Figure 2B) of 308 exons (292 genes) with differential exon- usage among Intracerebral Hemorrhage, Ischemic Strokes (Cardioembolic, Large Vessel, and Lacunar) and Control. Dendrograms in Figure 2B are not displayed.

[0053] Figure 3 illustrates Unsupervised Hierarchical Clustering of 308 exons (292 genes) with differential exon- usage among Intracerebral Hemorrhage, Ischemic Strokes (Cardioembolic, Large Vessel, and Lacunar) and Control. Dendrograms are not displayed. This is the same figure as Figure 2B, with the addition of information on age, time since
5 event, diabetes, hypertension and hyperlipidemia.

DETAILED DESCRIPTION

1. Introduction

[0054] Provided are exon or splice variant biomarkers, and methods and tools for using such biomarkers, that can distinguish in a subject suspected of having an ischemic
10 event between no stroke, ischemic stroke (*e.g.*, cardioembolic stroke, large vessel stroke and lacunar stroke) and intracerebral hemorrhage.

2. Subjects Who Can Benefit From The Present Methods

[0055] Individuals who will benefit from the present methods may be exhibiting symptoms of or suspected of having experienced a neurological event, ischemic or non-
15 ischemic. In some embodiments, the subject has experienced or is suspected of having experienced an ischemic stroke or ICH. For example, the subject may have suffered, be currently experiencing or suspected of experiencing a small deep infarct (SDI), a transient ischemic attack (TIA), intracerebral hemorrhage (ICH), an ischemic stroke, a myocardial infarction, peripheral vascular disease, or venous thromboembolism. The subject may have
20 or have been diagnosed with cerebral vascular disease or have one or more vascular risk factors (*e.g.*, hypertension, diabetes mellitus, hyperlipidemia, or tobacco smoking).

[0056] In some embodiments, the subject has not experienced and/or is not at risk of having an intracerebral hemorrhage. In some embodiments, the subject has not experienced and/or is not at risk of having an intracerebral hemorrhage or hemorrhagic stroke. In some
25 embodiments, the subject has been diagnosed as having not experienced and/or not at risk of having an intracerebral hemorrhage or hemorrhagic stroke.

[0057] In some embodiments, the levels of expression of the panel of biomarkers is determined within 3 hours of a suspected ischemic stroke or ICH. In some embodiments, the levels of expression of the panel of biomarkers are determined at 3 or more hours after a
30 suspected ischemic stroke or ICH. In some embodiments, the levels of expression of the panel of biomarkers are determined within 6, 12, 18, 24, 36, 48 hours of a suspected ischemic stroke or ICH.

[0058] In some cases, the subject is asymptomatic, but may have a risk or predisposition to experiencing ischemic stroke/ICH, *e.g.*, based on genetics, a related disease condition, environment or lifestyle. For example, in some embodiments, the patient suffers from a chronic inflammatory condition, *e.g.*, has an autoimmune disease (*e.g.*,
5 rheumatoid arthritis, Crohn's disease inflammatory bowel disease), atherosclerosis, hypertension, or diabetes. In some embodiments, the patient has high LDL-cholesterol levels or suffers from a cardiovascular disease (*e.g.*, atherosclerosis, coronary artery disease). In some embodiments, the patient has an endocrine system disorder, a neurodegenerative disorder, a connective tissue disorder, or a skeletal and muscular
10 disorder. Exemplary disorders associated with, related to, or causative of TIA are discussed in co-pending Application No. 13/182,630 and PCT/US2011/044023, which are hereby incorporated herein by reference in their entirety for all purposes. In some embodiments, the subject has an ABCD score that is 4 or greater (*see, e.g.*, Josephson, *et al.*, *Stroke*. (2008) 39(11):3096-8; Rothwell *et al.*, *Lancet* (2005) 366(9479):29-36; and Johnston, *et al.*,
15 *Lancet*. (2007) 369(9558):283-92).

[0059] In varying embodiments, the subject may be experiencing or suspected of experiencing a small deep infarct (SDI) or a lacunar stroke. Patients presenting with clinical symptoms of lacunar infarcts or diagnosed as having lacunar syndrome will also benefit from the present diagnostic gene expression profiling. Clinical symptoms of lacunar
20 infarcts include

- pure motor hemiparesis
- pure sensory stroke
- sensorimotor stroke
- dysarthria-clumsy hand syndrome
- 25 • ataxic hemiparesis

[0060] Face, arm and leg involvement are characteristic of the first three listed symptoms. A component of ataxia is also present in the last two. Patients with a lacunar syndrome typically have no aphasia, no visuospatial disturbance, no visual field defect, generally no clear disturbance of brainstem function such as pupil abnormalities and eye
30 movement disturbances, and no decreased level of consciousness (as a direct effect rather than as a complication of the stroke) at any time after the stroke. *See, Norrving, Pract Neurol* (2008) 8:222-228.

3. Biomarkers Indicative of the Occurrence or Risk of Ischemic stroke/ICH

[0061] Biomarkers useful for the prediction, diagnosis or confirmation of the occurrence of ischemic stroke (*e.g.*, a cardioembolic stroke, a large vessel stroke, a lacunar stroke) from an intracerebral hemorrhage (ICH) are listed in Tables 1A-1E. Determination of the gene exon/splice variant or isoform expression levels of a plurality of the biomarkers of Tables 1A-1E can be performed for the prediction, diagnosis or confirmation of the occurrence of ischemic stroke (*e.g.*, a cardioembolic stroke, a large vessel stroke, a lacunar stroke) versus an intracerebral hemorrhage in conjunction with other biomarkers known in the art for the prediction, diagnosis or confirmation of the occurrence of ischemic stroke, in conjunction with other methods known in the art for the diagnosis of ischemic stroke, in conjunction with biomarkers described herein and known in the art useful for determining the cause of ischemic stroke and/or in conjunction with methods known in the art for determining the cause of ischemic stroke. Such biomarkers are described in co-pending and co-owned U.S. Patent Publications Nos. 2015/0018234 (“BIOMARKERS FOR DIAGNOSING ISCHEMIA”); 2012/0316076 (“BIOMARKERS FOR THE DIAGNOSIS OF LACUNAR STROKE”); 2012/0065087 (“BIOMARKERS FOR DIAGNOSIS OF STROKE AND ITS CAUSES”); 2012/0015904 (“BIOMARKERS FOR DIAGNOSIS OF TRANSIENT ISCHEMIC ATTACKS”); and 2010/0197518 (“METHODS FOR DIAGNOSING ISCHEMIA”), each of which is hereby incorporated herein by reference in its entirety for all purposes.

[0062] Determination of the expression levels of a plurality of the biomarkers of Tables 1A, 1B, 1C, 1D and/or 1E can be performed for the prediction, diagnosis or confirmation of the occurrence of ischemic stroke/ICH can also be performed independently, *e.g.*, to diagnose whether ischemic stroke and/or ICH has occurred, to distinguish between ischemic stroke and ICH, or to determine the risk that a patient may suffer an ischemic stroke and/or ICH.

[0063] As appropriate, the expression levels of at least about 3, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100 or more biomarkers (*e.g.*, gene exons/splice variants or isoforms) from Tables 1A, 1B, 1C, 1D and/or 1E are determined. In some embodiments, the expression levels of a plurality of biomarkers in Tables 1A, 1B, 1C, 1D and/or 1E are determined. In some embodiments, the expression levels of all listed biomarkers in Tables 1A, 1B, 1C, 1D and/or 1E are determined.

[0064] In some embodiments, the level of expression of biomarkers indicative of the occurrence of ischemic stroke/ICH is determined within 72 hours, for example, within 60, 48, 36, 24, 12, 6 or 3 hours of a suspected ischemic stroke or ICH.

[0065] In various embodiments, an increased expression level of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or all, ischemic stroke-associated biomarkers of Table 1A indicates that the subject has or is likely to have experienced, is or is likely to be experiencing cardioembolic ischemic stroke:

Table 1A: Exon Usage Upregulated in Cardioembolic Ischemic Stroke (CE IS)	
Marker ID	Gene Symbol
chr17.73000302-73002235>CDR2L	CDR2L
chr8.104406853-104407321>shuskeebu	shuskeebu
chr3.48456585-48456758>PLXNB1	PLXNB1
chr1.86861716-86861980>ODF2L	ODF2L
chr19.58427747-58427961>ZNF417andZNF814	ZNF417 and ZNF814
chr19.58427747-58427962>ZNF417andZNF814	ZNF417 and ZNF814
chr22.19115606-19115964>skatee	Skate
chr10.49253461-49254185>BMS1P7	BMS1P7
chr14.70242552-70243107>SLC10A1	SLC10A1
chr7.142630429-142630907>TRPV5	TRPV5
chr10.38299602-38299713>ZNF33A	ZNF33A
chr10.38299604-38299713>ZNF33A	ZNF33A
chr2.119988299-119988612>STEAP3	STEAP3
chr2.179463448-179463833>CCDC141andTTN	CCDC141 and TTN
chr2.25258142-25260100>LOC729723	LOC729723
chr17.34856670-34856801>MYO19	MYO19
chr7.158334118-158334470>PTPRN2	PTPRN2
chr3.188326949-188327341>LPP	LPP
chr19.18959976-18960257>UPF1	UPF1
chr6.37225553-37225751>TBC1D22B	TBC1D22B
chr20.43995515-43996066>SYS1-DBNDD2	SYS1-DBNDD2
chr3.49448633-49449168>myforbo	myforbo
chr4.15570247-15570815>klawgu	klawgu

[0066] In various embodiments, an increased expression level of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or all, ischemic stroke-associated biomarkers of Table 1B indicates that the subject has or is likely to have experienced, is or is likely to be experiencing large vessel or atherothrombotic stroke:

Table 1B: Exon Usage Upregulated in Large Vessel Ischemic Stroke (LV IS)	
Marker ID	Gene Symbol
chr6.37225553-37225751>TBC1D22B	TBC1D22B
chr20.43995515-43996066>SYS1-DBNDD2	SYS1-DBNDD2
chr3.49448633-49449168>myforbo	Myforbo
chr4.15570247-15570815>klawgu	Klawgu
chr14.53248502-53248631>GNPNAT1	GNPNAT1
chr22.29141852-29141991>HSCB	HSCB
chr16.72146312-72146551>DHX38	DHX38
chr5.176715528-176715928>NSD1	NSD1
chr6.100023529-100023949>RPS3P5	RPS3P5
chr13.103506107-103506224>BIVMandERCC5	BIVM and ERCC5
chr7.2282560-2282685>NUDT1	NUDT1
chr12.54645834-54646013>CBX5	CBX5
chr20.33056659-33057238>vytaw	Vytaw
chr5.162902464-162902680>HMMR	HMMR
chr11.62389338-62389650>B3GAT3	B3GAT3
chr15.101847418-101849510>PCSK6	PCSK6
chr5.61688639-61688819>DIMIT1L	DIMIT1L
chr12.56334947-56335111>DGKA	DGKA
chr10.46918169-46918364>FAM35B and RHEBP1	FAM35B and RHEBP1
chr2.20756227-20757430>dawgorbu	Dawgorbu
chrX.152226503-152227130>PNMA3	PNMA3
chr22.18613610-18614500>PEX26 and TUBA8	PEX26 and TUBA8
chr6.111619174-111619775>slyjey	Slyjey
chr17.43002077-43003869>KIF18B	KIF18B
chr8.90798887-90799403>RIPK2	RIPK2
chr1.214836934-214837428>CENPF	CENPF
chr3.8606070-8609807>LMCD1	LMCD1
chr20.52560545-52561537>BCAS1	BCAS1
chr2.173420100-173420449>PDK1	PDK1
chr15.81584265-81585380>IL16	IL16
chr9.131486273-131486411>ZDHHC12	ZDHHC12
chr16.4475881-4476095>DNAJA3	DNAJA3

[0067] In various embodiments, an increased expression level of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, or all, ischemic stroke-associated biomarkers of Table 1C indicates that the subject has or is likely to have experienced, is or is likely to be experiencing lacunar stroke:

Table 1C: Exon Usage Upregulated in Lacunar IS	
Marker ID	Gene Symbol
chr11.119039480-119040013>NLRX1	NLRX1
chr15.52970203-52970321>KIAA1370	KIAA1370
chr11.62475067-62475389>GNG3	GNG3
chr12.94914730-94915696>LOC400061	LOC400061
chr16.15013757-15013942>zoner	Zoner
chr2.29258330-29258512>FAM179A	FAM179A
chr18.33077683-33077897>INO80C	INO80C
chr2.160143094-160143319>WDSUB1	WDSUB1
chr22.44514918-44515022>PARVB	PARVB
chr5.156821041-156822689>ADAM19	ADAM19
chr6.146285293-146285561>SHPRH	SHPRH
chr6.146285293-146285527>SHPRH	SHPRH
chr22.24316496-24316681>GSTTP1andDDT	GSTTP1 and DDT
chr12.2966630-2968831>FOXMI	FOXMI
chr7.99674926-99675058>ZNF3	ZNF3
chr6.30610545-30612434>C6orf134	C6orf134
chr19.35173682-35173956>ZNF302	ZNF302
chr21.47706315-47706714>C21orf57	C21orf57
chr12.111065735-111066031>TCTN1	TCTN1
chrX.40495835-40495966>CXorf38	CXorf38
chr9.46687439-46688199>KGFLP1	KGFLP1
chr2.101627502-101628004>TBC1D8	TBC1D8
chr1.160580214-160580590>SLAMF1	SLAMF1
chr8.10340434-10340743>LOC346702	LOC346702
chr6.168370462-168372590>MLLT4	MLLT4
chr1.155691308-155691473>DAP3	DAP3
chr12.123262038-123262232>CCDC62	CCDC62
chr14.96795821-96795973>ATG2B	ATG2B
chr20.32079185-32079984>spawvor	spawvor
chr6.163984476-163984753>QKI	QKI
chr1.246729640-246730093>CNST	CNST

[0068] In various embodiments, an increased expression level of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 50, 75, 100, 125, 150, 175, 200, or all, ICH-associated biomarkers of Table 1D indicates that the subject has or is likely to have experienced, is or is likely to be

5 experiencing intracerebral hemorrhage:

Table 1D: Exon Usage Upregulated in Intracerebral Hemorrhage (ICH)	
Marker ID	Gene Symbol
chr19.44128266-44128396>CADM4	CADM4
chr5.139929370-139930498>APBB3andSRA1	APBB3 and SRA1
chr1.85127881-85128060>SSX2IP	SSX2IP
chr22.31733654-31734033>sneypoy	sneypoy
chr17.40280569-40280820>RAB5C	RAB5C
chr3.23929058-23929282>UBE2E1	UBE2E1
chr7.149598-152549>kehera	kehera
chr3.122283274-122283462>DTX3L	DTX3L
chr14.76107075-76107405>FLVCR2andTTLL5andC14orf179	FLVCR2 and TTLL5 and C14orf179
chr1.235956803-235956914>LYST	LYST
chr2.198175302-198175505>ANKRD44	ANKRD44
chr22.20093700-20093802>DGCR8	DGCR8
chr1.112991564-112991796>CTTNBP2NL	CTTNBP2NL
chr1.19470474-19470587>UBR4	UBR4
chr5.134343647-134343831>PCBD2andCATSPER3	PCBD2 and CATSPER3
chr19.49314066-49314180>BCAT2	BCAT2
chr2.118864235-118864481>INSIG2	INSIG2
chr18.48443613-48443880>ME2	ME2
chr22.45254869-45255778>PRR5-ARHGAP8	PRR5-ARHGAP8
chr1.27431807-27432580>SLC9A1	SLC9A1
chr8.133984843-133984988>TG	TG
chr6.41751200-41751978>PRICKLE4andTOMM6	PRICKLE4 and TOMM6
chr17.57728564-57728679>CLTC	CLTC
chr3.150280329-150280449>EIF2A	EIF2A
chr2.242282407-242282510>SEPT2	SEPT2
chr21.40619627-40619760>BRWD1	BRWD1
chr1.26799700-26800020>HMG2	HMG2
chr5.140895496-140896577>DIAPH1	DIAPH1
chr5.140895875-140896577>DIAPH1	DIAPH1
chr1.180049625-180049798>CEP350	CEP350
chr1.180049652-180049798>CEP350	CEP350
chr5.70531277-70532283>goychyby	goychyby
chr13.100543572-100543868>CLYBL	CLYBL
chr19.36515246-36515536>CLIP3	CLIP3
chr6.144289727-144290117>PLAGL1andHYMAI	PLAGL1 and HYMAI
chr21.47608408-47608857>klorley	klorley
chr9.17135038-17135425>CNTLN	CNTLN

Table 1D: Exon Usage Upregulated in Intracerebral Hemorrhage (ICH)	
Marker ID	Gene Symbol
chr1.114499947-114500542>wawleybo	wawleybo
chr17.18486655-18486839>CCDC144B	CCDC144B
chr4.40800804-40800923>NSUN7	NSUN7
chr3.39162488-39162682>TTC21A	TTC21A
chr1.161196029-161196396>TOMM40L	TOMM40L
chr7.45083306-45083699>CCM2	CCM2
chr19.13009896-13010201>SYCE2	SYCE2
chr3.20019802-20020398>RAB5A	RAB5A
chr6.122792844-122793052>SERINC1	SERINC1
chr2.231663444-231663881>CAB39	CAB39
chr1.145790974-145791172>GPR89A	GPR89A
chr4.175223190-175223339>KIAA1712	KIAA1712
chr2.182339687-182340017>ITGA4	ITGA4
chr16.18799866-18800442>ARL6IP1andRPS15A	ARL6IP1 and RPS15A
chr6.3021094-3022354>teyvybo	teyvybo
chr16.22277711-22277847>EEF2K	EEF2K
chr11.7479027-7479176>veemee	veemee
chrX.77303661-77305894>ATP7A	ATP7A
chr1.78207302-78207435>USP33	USP33
chrX.76776266-76776396>ATRX	ATRX
chr12.6761437-6761586>ING4	ING4
chr17.77079383-77079674>ENGASE	ENGASE
chr11.111889680-111893376>DIXDC1	DIXDC1
chr11.111889680-111893312>DIXDC1	DIXDC1
chr4.157731989-157732171>PDGFC	PDGFC
chr20.18449588-18449707>POLR3F	POLR3F
chr11.47738539-47739066>FNBP4	FNBP4
chr16.30593851-30595168>syrar	syrar
chr13.41593364-41593570>ELF1	ELF1
chr22.51221467-51221716>RABL2B	RABL2B
chr9.33264164-33264495>CHMP5	CHMP5
chr1.154928545-154928782>SHC1andPYGO2andPBXIP1	SHC1 and PYGO2 and PBXIP1
chr19.1953385-1953507>C19orf34	C19orf34
chr2.113175261-113175493>RGP8	RGP8
chr1.145509166-145509614>RBM8A.1	RBM8A.1
chr1.89271574-89271702>PKN2	PKN2
chr10.99433338-99433904>DHGPSLandPI4K2A	DHGPSL and PI4K2A
chr7.74166365-74166899>GTF2I	GTF2I
chr18.54318248-54318826>TXNL1	TXNL1
chr12.58345541-58345680>XRCC6BP1	XRCC6BP1
chr7.76870183-76870366>CCDC146	CCDC146
chr3.52385978-52386121>DNAH1	DNAH1
chr12.96258857-96259168>SNRPF	SNRPF
chr1.63269390-63269535>ATG4C	ATG4C

Table 1D: Exon Usage Upregulated in Intracerebral Hemorrhage (ICH)	
Marker ID	Gene Symbol
chr2.172848099-172848601>HAT1	HAT1
chr18.67508480-67516325>DOK6	DOK6
chr8.30948350-30948460>WRN	WRN
chr2.208446079-208446886>FAM119A	FAM119A
chr7.5938415-5938552>CCZ1	CCZ1
chr19.44619641-44619997>ZNF225	ZNF225
chr1.243652316-243652444>SDCCAG8	SDCCAG8
chr4.122723829-122723985>EXOSC9	EXOSC9
chr4.122723829-122723950>EXOSC9	EXOSC9
chr1.46805848-46806593>NSUN4andFAAH	NSUN4 and FAAH
chr10.51592090-51592621>LOC100287554	LOC100287554
chrX.138864706-138864889>ATP11C	ATP11C
chr14.50246313-50246526>KLHDC2	KLHDC2
chr7.22980878-22987336>FAM126A	FAM126A
chr1.150778337-150778494>CTSK	CTSK
chr12.48094974-48095389>RPAP3	RPAP3
chr15.38619054-38620018>koyzawbu	koyzawbu
chr11.836251-836527>CD151	CD151
chr17.27581220-27581515>CRYBA1	CRYBA1
chr14.105236090-105236709>AKT1	AKT1
chr10.69828759-69829526>HERC4	HERC4
chr22.50320903-50321183>CRELD2	CRELD2
chr12.10561988-10562185>KLRC4andKLRK1	KLRC4 and KLRK1
chr8.104455023-104455430>DCAF13	DCAF13
chr12.40441853-40442014>SLC2A13	SLC2A13
chrX.16870674-16871151>RBBP7	RBBP7
chr12.54789679-54790162>ITGA5	ITGA5
chr1.150939858-150940192>LASS2	LASS2
chr13.113864293-113864814>PCID2	PCID2
chr15.80191177-80191469>ST20andMTHFS	ST20 and MTHFS
chr5.145493406-145493876>LARS	LARS
chr16.3493611-3493839>ZNF174andNAT15andCLUAP1	ZNF174 and NAT15 and CLUAP1
chr6.79664949-79665571>PHIPandTRNAF13P	PHIP and TRNAF13P
chr17.62745780-62746128>LOC146880	LOC146880
chr17.61473104-61473291>TANC2	TANC2
chr15.59102429-59102589>FAM63B	FAM63B
chr10.11272033-11272458>CELF2	CELF2
chr20.34487292-34487563>PHF20	PHF20
chr8.74858684-74859057>TCEB1	TCEB1
chr2.17953901-17954053>GEN1	GEN1
chr14.88431849-88431975>GALC	GALC
chr19.1877203-1877426>FAM108A1	FAM108A1
chr17.18087711-18088069>jeeroy	jeeroy
chr1.168262382-168262518>SFT2D2andTBX19	SFT2D2 and TBX19

Table 1D: Exon Usage Upregulated in Intracerebral Hemorrhage (ICH)	
Marker ID	Gene Symbol
chr6.158088239-158089559>fyjaw	fyjaw
chr15.30711214-30711350>rukaru	rukaru
chr8.24256387-24256555>ADAMDEC1	ADAMDEC1
chr15.57545460-57545668>stoyguby	stoyguby
chr10.75230828-75230969>PPP3CB	PPP3CB
chr20.43808628-43808777>rotora	rotora
chr1.46467098-46468409>MAST2	MAST2
chr7.2635311-2636064>dochuby	dochuby
chr19.11411543-11411914>tojaw	tojaw
chrX.153744234-153744568>FAM3A	FAM3A
chr2.73957016-73957158>TPRKB	TPRKB
chr2.234112772-234113221>INPP5D	INPP5D
chr6.41036580-41036694>C6orf130andUNC5CL	C6orf130 and UNC5CL
chr15.75165540-75165690>SCAMP2	SCAMP2
chrX.74282163-74282419>ABCB7	ABCB7
chr2.88336462-88336572>KRCC1	KRCC1
chrX.2839944-2840067>ARSD	ARSD
chr11.89933252-89935721>CHORDC1	CHORDC1
chr8.62438536-62438673>ASPH	ASPH
chr3.69028819-69028940>C3orf64	C3orf64
chr5.35053745-35054336>fugey	Fugey
chr9.35737655-35737938>GBA2	GBA2
chr15.94774950-94775236>MCTP2	MCTP2
chr3.52561845-52561949>NT5DC2	NT5DC2
chr1.85039599-85040105>CTBSandGNG5	CTBS and GNG5
chr10.99195666-99196310>EXOSC1	EXOSC1
chr20.23401942-23402099>NAPB	NAPB
chr17.36351796-36351998>TBC1D3	TBC1D3
chrX.118985730-118985838>UPF3B	UPF3B
chr15.66811217-66811418>ZWILCH	ZWILCH
chr15.66811217-66811469>ZWILCH	ZWILCH
chr11.125490667-125490903>STT3AandCHEK1	STT3A and CHEK1
chr3.15778540-15778742>ANKRD28	ANKRD28
chr19.9720432-9722014>ZNF562andZNF561	ZNF562 and ZNF561
chr3.167452594-167452719>PDCD10	PDCD10
chr1.10509776-10510381>APITD1andCORT	APITD1 and CORT
chr6.34360041-34360262>RPS10andNUDT3	RPS10 and NUDT3
chr19.52207575-52207735>NCRNA00085	NCRNA00085
chr11.62105383-62105786>saroro	Saroro
chr1.17056-17744>WASH7P	WASH7P
chr1.45987501-45987611>PRDX1	PRDX1
chr1.243419358-243419544>SDCCAG8	SDCCAG8
chr2.111302237-111302385>RGPD6	RGPD6
chr2.110584278-110584426>RGPD5	RGPD5

Table 1D: Exon Usage Upregulated in Intracerebral Hemorrhage (ICH)	
Marker ID	Gene Symbol
chr6.109248281-109249438>ARMC2	ARMC2
chr14.96997812-96999042>PAPOLA	PAPOLA
chr19.58423428-58423556>ZNF417andZNF814	ZNF417 and ZNF814
chr19.58423428-58423559>ZNF417andZNF814	ZNF417 and ZNF814
chrX.149924161-149924398>MTMR1	MTMR1
chr19.5208248-5208404>PTPRS	PTPRS
chr14.20872770-20872933>TEP1	TEP1
chr20.416929-419487>TBC1D20	TBC1D20
chr15.59943710-59944527>GTF2A2	GTF2A2
chrX.15862547-15863641>AP1S2	AP1S2
chr15.64017491-64017714>HERC1	HERC1
chr5.77656415-77656554>SCAMP1	SCAMP1
chr19.47646729-47646864>SAE1	SAE1
chr19.47646751-47646864>SAE1	SAE1
chr3.81552424-81552867>chordybo	chordybo
chr1.201780731-201780887>NAV1	NAV1
chr11.61129205-61129722>CYBASC3	CYBASC3
chr11.6523983-6524158>FXC1andDNHD1	FXC1 and DNHD1
chr19.8441789-8441953>lyta	Lyta
chr6.153291674-153292551>FBXO5	FBXO5
chr6.153291660-153292551>FBXO5	FBXO5
chr6.153291654-153292551>FBXO5	FBXO5
chr7.29549802-29552167>klerky	Klerky
chr22.41175013-41175131>SLC25A17	SLC25A17
chr4.76874494-76874940>sporsmorby	sporsmorby
chr5.39274505-39274632>FYB	FYB
chr10.32324818-32324924>KIF5B	KIF5B
chr14.52957557-52957725>TXNDC16	TXNDC16
chr14.88452833-88452948>GALC	GALC
chr20.30720816-30720931>TM9SF4	TM9SF4
chr19.54610118-54610268>NDUFA3	NDUFA3
chr10.92500578-92502287>HTR7	HTR7
chr3.25637911-25639425>RARB	RARB
chr5.14381239-14381363>TRIO	TRIO
chr2.243168539-243168821>samemo	samemo
chr3.137963865-137964525>vusmyby	vusmyby
chr3.137963930-137964525>ARMC8	ARMC8
chr3.137963930-137964526>ARMC8	ARMC8
chr14.100743755-100744115>YY1	YY1

[0069] In varying embodiments, the increased expression level of the gene exon or isoform is at least about 1.2-, *e.g.*, at least about 1.3-, 1.4-, 1.5-, 1.6-, 1.7-, 1.8-, 1.9-, 2.0-fold higher than the expression level in a control.

[0070] The overexpression or the underexpression of the biomarkers are determined with reference to a control level of expression. The control level of expression can be determined using any method known in the art. For example, the control level of expression can be from a population of individuals known to not have or be at risk for ischemic stroke or ICH or can be determined with reference to a panel of stably expressed reference biomarkers. Also, threshold levels of expression can be determined based on levels of expression in predetermined populations (*e.g.*, known to not have or be at risk for an ischemic stroke or ICH versus known to have or be at risk for ischemic stroke/ICH). Overexpression or underexpression of a plurality of biomarkers from Tables 1A, 1B, 1C and/or 1D that is at least about 1.2-fold, *e.g.*, at least about 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2.0-fold, or more, in comparison to the expression levels of a plurality of stably expressed endogenous reference biomarkers, *e.g.*, as described herein or known in the art, is correlative with or indicates that the subject has experienced or is at risk of experiencing an ischemic stroke/ICH. Overexpression or underexpression of a plurality of biomarkers from Tables 1A, 1B, 1C and/or 1D that is at least about 1.2-fold, *e.g.*, 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2.0-fold, or more, in comparison to the expression level of the same biomarker in an individual or a population of individuals who have not experienced a vascular event is correlative with or indicates that the subject has experienced or is at risk of experiencing an ischemic stroke/ICH.

[0071] Biomarkers useful for the determination and diagnosis of the cause of stroke are described, *e.g.*, in co-owned and co-pending U.S. Patent Publications Nos. 2015/0018234 (“BIOMARKERS FOR DIAGNOSING ISCHEMIA”); 2012/0316076 (“BIOMARKERS FOR THE DIAGNOSIS OF LACUNAR STROKE”); 2012/0065087 (“BIOMARKERS FOR DIAGNOSIS OF STROKE AND ITS CAUSES”); 2012/0015904 (“BIOMARKERS FOR DIAGNOSIS OF TRANSIENT ISCHEMIC ATTACKS”); and 2010/0197518 (“METHODS FOR DIAGNOSING ISCHEMIA”), each of which is hereby incorporated herein by reference in its entirety for all purposes. In addition to evaluating the expression levels of a plurality of ischemic stroke/ICH biomarkers of differential gene exon/splice variant/isoform usages, the expression levels of a plurality of biomarkers can be measured to determine whether a suspected or predicted ischemic stroke is cardioembolic, atherosclerotic or lacunar. Furthermore, the expression levels of a plurality of biomarkers can be measured to determine if the cause of stroke is due to carotid stenosis, atrial fibrillation, lacunar stroke or transient ischemic attacks. Classification of stroke subtypes is

known in the art and reviewed in, e.g., in Amarenco, *et al.*, *Cerebrovasc Dis* (2009) 27:493-501. Accordingly, in some embodiments, the expression levels of at least about 3, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 85, 100, 200, 500, 1000 or more, ischemic stroke-associated biomarkers are independently determined. In some embodiments, the expression levels of
 5 all ischemic stroke-associated biomarkers in a panel are determined.

[0072] In various embodiments, the expression levels of a plurality of ischemic stroke-associated exon/splice variant biomarkers are co-determined together with the expression levels of a plurality of genes useful in the determination of whether a patient has experienced or has a predisposition to experience cardioembolic stroke (*a.k.a.*, cardiac
 10 embolism, cardioembolism emboligenic heart disease). A cardioembolic stroke occurs when a thrombus (clot) dislodges from the heart, travels through the cardiovascular system and lodges in the brain, first cutting off the blood supply and then often causing a hemorrhagic bleed. In some embodiments an increased expression level of one or more ischemic stroke-associated biomarkers selected from the group consisting of **IRF6**

(NM_006147), **ZNF254** (NM_203282), **GRM5** (NM_000842 /// NM_001143831), **EXT2**
 15 (NM_000401 /// NM_207122), **AP3S2** (NM_005829 /// NR_023361), **PIK3C2B**
 (NM_002646), **ARHGEF5** (NM_005435), **COL13A1** (NM_001130103 /// NM_005203 ///
 NM_080798 /// NM_080799 /// NM_080800 /// NM_080801 /// NM_080802 ///
 NM_080803 /// NM_080804 /// NM_080805 /// NM_080806 /// NM_080807 ///
 20 NM_080808 /// NM_080809 /// NM_080810 /// NM_080811 /// NM_080812 ///
 NM_080813 /// NM_080814 /// NM_080815), **PTPN20A** /// **PTPN20B** (NM_001042357
 /// NM_001042358 /// NM_001042359 /// NM_001042360 /// NM_001042361 ///
 NM_001042362 /// NM_001042363 /// NM_001042364 /// NM_001042365 ///
 NM_001042387 /// NM_001042389 /// NM_001042390 /// NM_001042391 ///
 25 NM_001042392 /// NM_001042393 /// NM_001042394 /// NM_001042395 ///
 NM_001042396 /// NM_001042397 /// NM_015605), **LHFP** (NM_005780), **BANK1**
 (NM_001083907 /// NM_001127507 /// NM_017935), **HLA-DOA** (NM_002119), **EBF1**
 (NM_024007), **TMEM19** (NM_018279), **LHFP** (NM_005780), **FCRL1** (NM_001159397
 /// NM_001159398 /// NM_052938), **OOEP** (NM_001080507) and **LRRC37A3**

(NM_199340) is correlative with or indicates that the patient has experienced or is at risk
 30 for cardioembolic stroke. In some embodiments, a decreased expression level of one or more ischemic stroke-associated biomarkers selected from the group consisting of
LOC284751 (NM_001025463), **CD46** (NM_002389 /// NM_153826 /// NM_172350 ///

NM_172351 /// NM_172352 /// NM_172353 /// NM_172354 /// NM_172355 ///
 NM_172356 /// NM_172357 /// NM_172358 /// NM_172359 /// NM_172360 ///
 NM_172361), **ENPP2** (NM_001040092 /// NM_001130863 /// NM_006209), **C19orf28**
 (NM_001042680 /// NM_021731 /// NM_174983), **TSKS** (NM_021733), **CHURC1**
 5 (NM_145165), **ADAMTSL4** (NM_019032 /// NM_025008), **FLJ40125** (NM_001080401),
CLEC18A (NM_001136214 /// NM_182619), **ARHGEF12** (NM_015313), **C16orf68**
 (NM_024109), **TFDP1** (NM_007111 /// NR_026580) and **GSTK1** (NM_001143679 ///
 NM_001143680 /// NM_001143681 /// NM_015917) is correlative with or indicates that the
 patient has experienced or is at risk for cardioembolic stroke.

- 10 **[0073]** In various embodiments, the expression levels of a plurality of ischemic
 stroke-associated exon/splice variant biomarkers are co-determined together with the
 expression levels of a plurality of genes useful in the determination of whether a patient has
 experienced or has a predisposition to experience carotid stenosis. Carotid stenosis is a
 narrowing or constriction of the inner surface (lumen) of the carotid artery, usually caused
 15 by atherosclerosis. An inflammatory buildup of plaque can narrow the carotid artery and
 can be a source of embolization. Emboli break off from the plaque and travel through the
 circulation to blood vessels in the brain, causing ischemia that can either be temporary (e.g.,
 a transient ischemic attack), or permanent resulting in a thromboembolic stroke (a.k.a.,
 atherothrombosis, large-artery atherosclerosis, atherosclerosis with stenosis). In some
 20 embodiments, an increased expression level of one or more ischemic stroke-associated
 biomarkers selected from the group consisting of **NT5E** (NM_002526), **CLASP2**
 (NM_015097), **GRM5** (NM_000842 /// NM_001143831), **PROCR** (NM_006404),
ARHGEF5 (NM_005435), **AKR1C3** (NM_003739), **COL13A1** (NM_001130103 ///
 NM_005203 /// NM_080798 /// NM_080799 /// NM_080800 /// NM_080801 ///
 25 NM_080802 /// NM_080803 /// NM_080804 /// NM_080805 /// NM_080806 ///
 NM_080807 /// NM_080808 /// NM_080809 /// NM_080810 /// NM_080811 ///
 NM_080812 /// NM_080813 /// NM_080814 /// NM_080815), **LHFP** (NM_005780),
RNF7 (NM_014245 /// NM_183237), **CYTH3** (NM_004227), **EBF1** (NM_024007),
RANBP10 (NM_020850), **PRSS35** (NM_153362), **C12orf42** (NM_001099336 ///
 30 NM_198521) and **LOC100127980** (XM_001720119 /// XM_001722650) is correlative with
 or indicates that the patient has experienced or is at risk for carotid stenosis. In some
 embodiments, a decreased expression level of one or more ischemic stroke-associated
 biomarkers selected from the group consisting of **FLJ31945** (XM_001714983 ///

XM_001716811 /// XM_001718431), **LOC284751** (NM_001025463), **LOC100271832** (NR_027097), **MTBP** (NM_022045), **ICAM4** (NM_001039132 /// NM_001544 /// NM_022377), **SHOX2** (NM_001163678 /// NM_003030 /// NM_006884), **DOPEY2** (NM_005128), **CMBL** (NM_138809), **LOC146880** (NR_026899 /// NR_027487),
 5 **SLC20A1** (NM_005415), **SLC6A19** (NM_001003841), **ARHGEF12** (NM_015313), **C16orf68** (NM_024109), **GIPC2** (NM_017655) and **LOC100144603** (NR_021492) is correlative with or indicates that the patient has experienced or is at risk for carotid stenosis.

[0074] In various embodiments, the expression levels of a plurality of ischemic stroke-associated exon/splice variant biomarkers are co-determined together with the
 10 expression levels of a plurality of genes useful in the determination of whether a patient has experienced or has a predisposition to experience atrial fibrillation. Atrial fibrillation (AF or A-fib) is the most common cardiac arrhythmia and involves the two upper chambers (atria) of the heart fibrillating (i.e., quivering) instead of a coordinated contraction. In some instances, cardioembolic stroke can occur as a result of atrial fibrillation. Cardioembolic
 15 stroke can be a downstream result of atrial fibrillation in that stagnant blood in the fibrillating atrium can form a thrombus that then embolises to the cerebral circulation, blocking arterial blood flow and causing ischaemic injury. In some embodiments, an increased expression level of one or more ischemic stroke-associated biomarkers selected from the group consisting of **SMC1A** (NM_006306), **SNORA68** (NR_000012), **GRLF1**
 20 (NM_004491), **SDC4** (NM_002999), **HIPK2** (NM_001113239 /// NM_022740 /// XM_001716827 /// XM_925800), **LOC100129034** (NR_027406 /// XR_079577), **CMTM1** (NM_052999 /// NM_181268 /// NM_181269 /// NM_181270 /// NM_181271 /// NM_181272 /// NM_181283 /// NM_181296) and **TTC7A** (NM_020458) is correlative with or indicates that the patient has experienced or is at risk for atrial fibrillation. In some
 25 embodiments, a decreased expression level of one or more ischemic stroke-associated biomarkers selected from the group consisting of **LRRC43** (NM_001098519 /// NM_152759), **MIF** /// **SLC2A11** (NM_001024938 /// NM_001024939 /// NM_002415 /// NM_030807), **PER3** (NM_016831), **PPIE** (NM_006112 /// NM_203456 /// NM_203457), **COL13A1** (NM_001130103 /// NM_005203 /// NM_080798 /// NM_080799 ///
 30 NM_080800 /// NM_080801 /// NM_080802 /// NM_080803 /// NM_080804 /// NM_080805 /// NM_080806 /// NM_080807 /// NM_080808 /// NM_080809 /// NM_080810 /// NM_080811 /// NM_080812 /// NM_080813 /// NM_080814 /// NM_080815), **DUSP16** (NM_030640), **BRUNOL6** (NM_052840), **GPR176**

(NM_007223), **C6orf164** (NR_026784) and **MAP3K7IP1** (NM_006116 /// NM_153497) is correlative with or indicates that the patient has experienced or is at risk for atrial fibrillation.

[0075] In various embodiments, the expression levels of a plurality of ischemic

5 stroke-associated exon/splice variant biomarkers are co-determined together with the expression levels of a plurality of genes useful in the determination of whether a patient has experienced or has a predisposition to experience transient ischemic attacks (TIA). A transient ischemic attack is a change in the blood supply to a particular area of the brain, resulting in brief neurologic dysfunction that persists, by definition, for less than 24 hours.

10 If symptoms persist longer, then it is categorized as a stroke. In some embodiments, an increased expression level of one or more TIA-associated biomarkers selected from the group consisting of **GABRB2** (NM_000813 /// NM_021911), **ELAVL3** (NM_001420 /// NM_032281), **COL1A1** (NM_000088), **SHOX2** (NM_003030 /// NM_006884), **TWIST1** (NM_000474), **DPPA4** (NM_018189), **DKFZP434P211** (NR_003714), **WIT1**

15 (NM_015855 /// NR_023920), **SOX9** (NM_000346), **DLX6** (NM_005222), **ANXA3** (NM_005139), **EPHA3** (NM_005233 /// NM_182644), **SOX11** (NM_003108), **SLC26A8** (NM_052961 /// NM_138718), **CCRL1** (NM_016557 /// NM_178445), **FREM2** (NM_207361), **STOX2** (NM_020225), **ZNF479** (NM_033273 /// XM_001714591 /// XM_001719979), **LOC338862** (NR_038878.1), **ASTN2** (NM_014010 /// NM_198186 ///

20 NM_198187 /// NM_198188), **FOLH1** (NM_001014986 /// NM_004476), **SNX31** (NM_152628), **KREMEN1** (NM_001039570 /// NM_001039571), **ALS2CR11** (NM_152525), **FIGN** (NM_018086), **RORB** (NM_006914), **LOC732096** (XM_001720784 /// XM_001725388 /// XR_016064), **GYPA** (NM_002099), **ALPL** (NM_000478 /// NM_001127501), **LHX2** (NM_004789), **GALNT5** (NM_014568),

25 **SRD5A2L2** (NM_001010874), **GALNT14** (NM_024572), **OVOL2** (NM_021220), **BMPRI1B** (NM_001203), **UNC5B** (NM_170744), **ODZ2** (NM_001080428 /// NM_001122679), **RASAL2** (NM_004841 /// NM_170692), **SHOX** (NM_000451 /// NM_006883), **C19orf59** (NM_174918), **ZNF114** (NM_153608), **SRGAP1** (NM_020762), **ELAVL2** (NM_004432), **NCRNA00032** (XM_376821 /// XM_938938), **LOC440345**

30 (XR_015786), **FLJ30375** (XM_001724993 /// XM_001725199 /// XM_001725628), **TFPI** (NM_001032281 /// NM_006287), **PTGR1** (NM_012212), **ROBO1** (NM_002941 /// NM_133631), **NR2F2** (NM_021005), **GRM5** (NM_000842 /// NM_001143831), **LUM** (NM_002345), **FLJ39051** (NR_033839.1), **COL1A2** (NM_000089), **CASP5**

(NM_001136109 /// NM_001136110 /// NM_001136111 /// NM_001136112 /// NM_004347 //), **OPCML** (NM_001012393 /// NM_002545), **TTC6** (NM_001007795), **TFAP2B** (NM_003221), **CRISP2** (NM_001142407 /// NM_001142408 /// NM_001142417 /// NM_001142435 /// NM_003296), **SOX11** (NM_003108), **ANKRD30B**

5 (XM_001716904 /// XM_001717561 /// XM_001717810), **SCN2A** (NM_001040142 /// NM_001040143 /// NM_021007), **MYNN** (NM_018657), **FOXA2** (NM_021784 /// NM_153675), **DKFZP434B061** (XR_015528 /// XR_040812), **LOC645323** (NR_015436 /// NR_024383 /// NR_024384 /// XR_041118 /// XR_041119 /// XR_041120), **SNIP** (NM_025248), **LOC374491** (NR_002815), **ADAM30** (NM_021794), **SIX3** (NM_005413),

10 **FLJ36144** (XR_040632 /// XR_040633 /// XR_040634), **CARD8** (NM_014959), **RP1-127L4.6** (NM_001010859), **FAM149A** (NM_001006655 /// NM_015398), **B3GAT2** (NM_080742), **SPOCK3** (NM_001040159 /// NM_016950), **ITGBL1** (NM_004791), **IQGAP3** (NM_178229), **C7orf45** (NM_145268), **ZNF608** (NM_020747), **LOC375010** (XR_041271), **LRP2** (NM_004525), **TGFB2** (NM_001135599 /// NM_003238), **SHOX2**

15 (NM_003030 /// NM_006884), **HOXC4** /// **HOXC6** (NM_004503 /// NM_014620 /// NM_153633 /// NM_153693), **ELTD1** (NM_022159), **FAM182B** /// **RP13-401N8.2** (XM_001132551 /// XM_001133521 /// XM_001718365 /// XM_933752), **LIFR** (NM_001127671 /// NM_002310), **FOLH1** (NM_001014986 /// NM_004476), **EHF** (NM_012153), **NDST3** (NM_004784), **BRUNOL5** (NM_021938), **LOC728460**

20 (XM_001128581 /// XM_001129498 /// XM_001723364), **PDE1A** (NM_001003683 /// NM_005019), **POU2AF1** (NM_006235), **FAT1** (NM_005245), **PCDH11X** /// **PCDH11Y** (NM_014522 /// NM_032967 /// NM_032968 /// NM_032969 /// NM_032971 /// NM_032972), **FLJ37786** (XR_041472 /// XR_041473), **SLC22A4** (NM_003059), **DHRS13** (NM_144683), **MEG3** (NR_002766 /// NR_003530 /// NR_003531), **PIWIL1**

25 (NM_004764), **LOC203274** (AL117607.1 /// BC080605.1), **LOC100133920** /// **LOC286297** (NR_024443 /// XM_001714612 /// XM_372109 /// XM_933054 /// XM_933058), **DMRT1** (NM_021951), **ADM** (NM_001124), **VWA3B** (NM_144992), **GAFA3** (XM_001715321 /// XM_001722922 /// XM_001723636), **HESX1** (NM_003865), **ADAMDEC1** (NM_014479), **CAV1** (NM_001753), **LAMB4** (NM_007356), **TPTE**

30 (NM_199259 /// NM_199260 /// NM_199261), **PPP1R1C** (NM_001080545), **HPSE** (NM_001098540 /// NM_006665), **AIM2** (NM_004833), **RUNDC3B** (NM_001134405 /// NM_001134406 /// NM_138290), **CARD16** (NM_001017534 /// NM_052889), **FAM124A** (NM_145019), **MGC39584** (XR_017735 /// XR_017787 /// XR_041937), **OSM** (NM_020530), **RFX2** (NM_000635 /// NM_134433), **MYBPC1** (NM_002465 ///

NM_206819 /// NM_206820 /// NM_206821), **LTBR** (NM_002342), **C18orf2**
 (NM_031416 /// NR_023925 /// NR_023926 /// NR_023927 /// NR_023928), **SNRPN**
 (NM_003097 /// NM_022805 /// NM_022806 /// NM_022807 /// NM_022808 ///
 NR_001289), **FLJ36031** (NM_175884), **IL1B** (NM_000576), **TRPM1** (NM_002420),
 5 **OSTCL** (NM_145303), **MAPK14** (NM_001315 /// NM_139012 /// NM_139013 ///
 NM_139014), **KCNJ15** /// **LOC100131955** (NM_002243 /// NM_170736 /// NM_170737
 /// XM_001713900 /// XM_001715532 /// XM_0), **FIGN** (NM_018086), **HNT**
 (NM_001048209 /// NM_016522), **S100A12** (NM_005621), **CHIT1** (NM_003465),
C7orf53 (NM_001134468 /// NM_182597), **FAM13A1** (NM_001015045 /// NM_014883),
 10 **GNAO1** (NM_020988 /// NM_138736), **MAPK14** (NM_001315 /// NM_139012 ///
 NM_139013 /// NM_139014), **FAM55D** (NM_001077639 /// NM_017678), **PRKD2**
 (NM_001079880 /// NM_001079881 /// NM_001079882 /// NM_016457), **LIMK2**
 (NM_001031801 /// NM_005569 /// NM_016733), **C18orf54** (NM_173529), **IGFBP5**
 (NM_000599), **EVII** (NM_001105077 /// NM_001105078 /// NM_005241), **PLSCR1**
 15 (NM_021105), **FOXC1** (NM_001453), **LOC646627** (NM_001085474), **ZNF462**
 (NM_021224), **CNTLN** (NM_001114395 /// NM_017738), **ZNF438** (NM_001143766 ///
 NM_001143767 /// NM_001143768 /// NM_001143769 /// NM_001143770), **DEFB105A**
 /// **DEFB105B** (NM_001040703 /// NM_152250), **LOC340017** (NR_026992.1), **C1orf67**
 (NM_144989), **ACSL1** (NM_001995), **ADH1B** (NM_000668), **SLC2A14** /// **SLC2A3**
 20 (NM_006931 /// NM_153449), **IL1B** (NM_000576), **ST3GAL4** (NM_006278 ///
 XM_001714343 /// XM_001726541 /// XM_001726562), **UBE2J1** (NM_016021),
PNPLA3 (NM_025225) and **PAPPA** (NM_002581) is correlative with or indicates that the
 patient has experienced or is at risk for TIA. In some embodiments, a decreased expression
 level of one or more TIA-associated biomarkers selected from the group consisting of
 25 **NBPF10** /// **RP11-94I2.2** (NM_001039703 /// NM_183372 /// XM_001722184), **SFXN1**
 (NM_022754), **SPIN3** (NM_001010862), **UNC84A** (NM_001130965 /// NM_025154),
OLFM2 (NM_058164), **PPM1K** (NM_152542), **P2RY10** (NM_014499 /// NM_198333),
ZNF512B (NM_020713), **MORF4L2** (NM_001142418 /// NM_001142419 ///
 NM_001142420 /// NM_001142421 /// NM_001142422), **GIGYF2** (NM_001103146 ///
 30 NM_001103147 /// NM_001103148 /// NM_015575), **ERAP2** (NM_001130140 ///
 NM_022350), **SLFN13** (NM_144682), **LOC401431** (XR_040272 /// XR_040273 ///
 XR_040274 /// XR_040275), **MED6** (NM_005466), **BAIAP2L1** /// **LOC100128461**
 (NM_018842 /// XM_001722656 /// XM_001724217 /// XM_001724858), **LNPEP**
 (NM_005575 /// NM_175920), **MBNL1** (NM_021038 /// NM_207292 /// NM_207293 ///

NM_207294 /// NM_207295 /// NM_207296), **NOS3** (NM_000603), **MCF2L**
 (NM_001112732 /// NM_024979), **KIAA1659** (XM_001723799 /// XM_001725435 ///
 XM_001726785), **SCAMP5** (NM_138967), **LOC648921** (XM_001715629 ///
 XM_001720571 /// XR_018520), **ANAPC5** (NM_001137559 /// NM_016237), **SPON1**
 5 (NM_006108), **FUS** (NM_004960), **GPR22** (NM_005295), **GAL3ST4** (NM_024637),
METTL3 (NM_019852), **LOC100131096** (XM_001720907 /// XM_001726205 ///
 XM_001726705), **FAAH2** (NM_174912), **SMURF2** (NM_022739), **SNRPN** (NM_003097
 /// NM_022805 /// NM_022806 /// NM_022807 /// NM_022808 /// NR_001289), **FBLN7**
 (NM_001128165 /// NM_153214), **GLS** (NM_014905), **G3BP1** (NM_005754 ///
 10 NM_198395), **RCAN3** (NM_013441), **EPHX2** (NM_001979), **DIP2C** (NM_014974),
CCDC141 (NM_173648), **CLTC** (NM_004859), **FOSB** (NM_001114171 ///
 NM_006732), **CACNA1I** (NM_001003406 /// NM_021096), **UNQ6228** (XM_001725293
 /// XM_001725359 /// XM_001726164), **ATG9B** (NM_173681), **AK5** (NM_012093 ///
 NM_174858), **RBM14** (NM_006328), **MAN1C1** (NM_020379), **HELLS** (NM_018063),
 15 **EDAR** (NM_022336), **SLC3A1** (NM_000341), **ZNF519** (NM_145287), **LOC100130070**
 /// **LOC100130775** /// **LOC100131787** /// **LOC100131905** /// **LOC100132291** ///
LOC100132488 /// **RPS27** (NM_001030 /// XM_001721002 /// XM_001722161 ///
 XM_001722965 /// XM_001723889 //), **ZC3H12B** (NM_001010888), **IQGAP2**
 (NM_006633), **SOX8** (NM_014587), **WHDC1L2** (XM_926785), **TNPO1** (NM_002270 ///
 20 NM_153188), **TNFRSF21** (NM_014452), **TSHZ2** (NM_173485), **DMRTC1** ///
DMRTC1B (NM_001080851 /// NM_033053), **GSTM1** (NM_000561 /// NM_146421),
GSTM2 (NM_000848 /// NM_001142368), **PNMA6A** (NM_032882), **CAND1**
 (NM_018448), **CCND3** (NM_001136017 /// NM_001136125 /// NM_001136126 ///
 NM_001760), **GSTM1** (NM_000561 /// NM_146421), and **GUSBL2** (NR_003660 ///
 25 XR_042150 /// XR_042151) is correlative with or indicates that the patient has experienced
 or is at risk for TIA. Further biomarkers of interest are published in Zhan, *et al.*, *Neurology*.
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[0076] In various embodiments, the expression levels of a plurality of ischemic
 stroke-associated exon/splice variant biomarkers are co-determined together with the
 30 expression levels of a plurality of genes useful in the determination of whether a patient has
 experienced or has a predisposition to experience a transient neurological event (TNE). In
 some embodiments, an increased expression level of one or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9,
 10, 11, 12, 13, 14, 15 or all) ischemic stroke-associated biomarkers selected from the group

consisting of UBE2J1, ELAVL3, FCGR2B, BLVRA, JMJD6, DDAH2, PTRH2, CARD16, CAV1, ZNF608, NDUFB3, SLC22A4, PCMT1, CACNA1A, CASP1 and LOC100129105 indicates that the patient has suffered or is at risk of experiencing a transient neurological event (TNE). In some embodiments, an increased expression level of one or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40 or all) ischemic stroke-associated biomarkers selected from the group consisting of AIM2, C14orf101, DNAH17, UBE2J1, LOC203274, PGS1, ZEB2, DDAH2, CARD16, SPATA4, ANXA3, WIT1, FCGR2B, CACNA1A, FKBP15, N4BP2L2, HNRNPH2, ELAVL3, ZNF608, TLR10, BLVRA, SLC22A4, RAB27A, LTBR, CARD16 /// CASP1, IGFBP5, CASP5, LTB, NDUFB3, SHOX2, CAV1, CNIH4, FLJ39051, CASP1, PTRH2, LOC100129105, PCMT1, CYTH4, JMJD6, DRAM1, FCGR1B indicates that the patient has suffered or is at risk of experiencing a transient neurological event (TNE). In some embodiments, an increased expression level of one or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30 or all) ischemic stroke-associated biomarkers selected from the group consisting of CARD16, IRF7, TLR6, NMU, C13orf16, TAPBP, BTC, ZBP1, HSPA6, TWIST1, PLSCR1, SAMD9L, OSTCL, C9orf66, GYPA, ADM, ANKRD22, SHOX, ZNF354A, SRGAP1, GRM5, BAGE, XRCC4, SLC37A3, OVOL2, LIFR, RASAL2, hCG_1749898, IQGAP3, HS3ST3A1, NPR3, SIX3 and HCN1 indicates that the patient has suffered or is at risk of experiencing a transient neurological event (TNE). In some embodiments, an increased expression level of one or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40 or all) ischemic stroke-associated biomarkers selected from the group consisting of UBE2J1, CARD16, LOC203274, ZNF608, CARD16 /// CASP1, PTRH2, ANXA3, FCGR2B, C14orf101, LOC100129105, DDAH2, RAB27A, AIM2, CASP5, HNRNPH2, RAB27A, SHOX2, CNIH4, TLR10, ZEB2, NDUFB3, CYTH4, BLVRA, FLJ39051, SLC22A4, DNAH17, SPATA4, CACNA1A, CASP1, PGS1, LTBR, FCGR1B, IGFBP5, LTB, N4BP2L2, DRAM1, WIT1, ELAVL3, FKBP15, JMJD6, CAV1 and PCMT1 indicates that the patient has suffered or is at risk of experiencing a transient neurological event (TNE). Conversely, in some embodiments, a decreased expression level of one or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or all) ischemic stroke-associated biomarkers selected from the group consisting of UBE2J1, ELAVL3, FCGR2B, BLVRA, JMJD6, DDAH2, PTRH2, CARD16, CAV1, ZNF608, NDUFB3, SLC22A4, PCMT1, CACNA1A, CASP1 and LOC100129105 indicates that the patient has not suffered or is not at risk of experiencing a transient neurological event (TNE). In some embodiments, a decreased expression level of one or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,

12, 13, 14, 15, 20, 25, 30, 35, 40 or all) ischemic stroke-associated biomarkers selected from the group consisting of AIM2, C14orf101, DNAH17, UBE2J1, LOC203274, PGS1, ZEB2, DDAH2, CARD16, SPATA4, ANXA3, WIT1, FCGR2B, CACNA1A, FKBP15, N4BP2L2, HNRNPH2, ELAVL3, ZNF608, TLR10, BLVRA, SLC22A4, RAB27A, LTBR, CARD16
 5 /// CASP1, IGFBP5, CASP5, LTB, NDUFB3, SHOX2, CAV1, CNIH4, FLJ39051, CASP1, PTRH2, LOC100129105, PCMT1, CYTH4, JMJD6, DRAM1, FCGR1B indicates that the patient has not suffered or is not at risk of experiencing a transient neurological event (TNE). In some embodiments, a decreased expression level of one or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30 or all) ischemic stroke-associated biomarkers
 10 selected from the group consisting of CARD16, IRF7, TLR6, NMU, C13orf16, TAPBP, BTC, ZBP1, HSPA6, TWIST1, PLSCR1, SAMD9L, OSTCL, C9orf66, GYPA, ADM, ANKRD22, SHOX, ZNF354A, SRGAP1, GRM5, BAGE, XRCC4, SLC37A3, OVOL2, LIFR, RASAL2, hCG_1749898, IQGAP3, HS3ST3A1, NPR3, SIX3 and HCN1 indicates that the patient has not suffered or is not at risk of experiencing a transient neurological
 15 event (TNE). In some embodiments, a decreased expression level of one or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40 or all) ischemic stroke-associated biomarkers selected from the group consisting of UBE2J1, CARD16, LOC203274, ZNF608, CARD16 /// CASP1, UBE2J1, PTRH2, ANXA3, FCGR2B, C14orf101, LOC100129105, DDAH2, RAB27A, AIM2, CASP5, HNRNPH2, RAB27A, SHOX2,
 20 CNIH4, TLR10, ZEB2, NDUFB3, CYTH4, BLVRA, FLJ39051, SLC22A4, DNAH17, SPATA4, CACNA1A, CASP1, PGS1, LTBR, FCGR1B, IGFBP5, LTB, N4BP2L2, DRAM1, WIT1, ELAVL3, FKBP15, JMJD6, CAV1 and PCMT1 indicates that the patient has not suffered or is not at risk of experiencing a transient neurological event (TNE).

[0077] In various embodiments, the expression levels of a plurality of ischemic stroke-associated exon/splice variant biomarkers are co-determined together with the expression levels of a plurality of genes useful in the determination of whether a patient has experienced or has a predisposition to experience lacunar stroke. In some embodiments, an increase of the expression level of one or more biomarkers selected from the group consisting of **RASEF** (NM_152573), **CALM1** (NM_006888), **TTC12** (NM_017868),
 25 **CCL3** /// **CCL3L1** /// **CCL3L3** (NM_001001437 /// NM_002983 /// NM_021006), **CCDC78** (NM_001031737), **PRSS23** (NM_007173), **LAIR2** (NM_002288 /// NM_021270), **C18orf49** (AK000229.1 /// BC047606.1), **UTS2** (NM_006786 /// NM_021995), **LGR6** (NM_001017403 /// NM_001017404 /// NM_021636), **PROCR**

(NM_006404), **LAG3** (NM_002286), **OASL** (NM_003733 /// NM_198213),
LOC100132181 (XM_001722051.1), **HLA-DRB4** (NM_021983 /// XM_002346251),
CCL2 (NM_002982), **ALS2CR11** (NM_152525), **SCAND2** (NR_003654 /// NR_004859),
GBP4 (NM_052941), **RUNX3** (NM_001031680 /// NM_004350), **TSEN54** (NM_207346),
5 **UBA7** (NM_003335), **FAM179A** (NM_199280), **TGFBR3** (NM_003243), **CCDC114**
(NM_144577), **AKAP9** (NM_005751 /// NM_147185), **BNC2** (NM_017637), **BZRAP1**
(NM_004758 /// NM_024418), **CCL4** (NM_002984), **CHST2** (NM_004267), **CSF1**
(NM_000757 /// NM_172210 /// NM_172211 /// NM_172212), **ERBB2** (NM_001005862
/// NM_004448), **GBR56** (NM_001145770 /// NM_001145771 /// NM_001145772 ///
10 NM_001145773 /// NM_001145774), **GRAMD3** (NM_001146319 /// NM_001146320 ///
NM_001146321 /// NM_001146322 /// NM_023927), **GRHL2** (NM_024915), **GRK4**
(NM_001004056 /// NM_001004057 /// NM_182982), **ITIH4** (NM_002218), **KIAA1618**
(NM_020954), **LOC147646** (XM_001134195 /// XM_001134326 /// XM_001726058),
LOC150622 (NR_026832), **LOC161527** (NM_002675 /// NM_033238 /// NM_033239 ///
15 NM_033240 /// NM_033244 /// NM_033246), **PLEKHF1** (NM_024310), **PRKD2**
(NM_001079880 /// NM_001079881 /// NM_001079882 /// NM_016457), **RGNEF**
(NM_001080479), **SESN2** (NM_031459), **SLAMF7** (NM_021181), **SPON2**
(NM_001128325 /// NM_012445), **STAT1** (NM_007315 /// NM_139266), **SYNGR1**
(NM_004711 /// NM_145731 /// NM_145738), **TRX21** (NM_013351), **TMEM67**
20 (NM_001142301 /// NM_153704 /// NR_024522), **TUBE1** (NM_016262), and **ZNF827**
(NM_178835), and/or a decrease of the expression level of one or more biomarkers selected
from the group consisting of **HLA-DQA1** (NM_002122), **FLJ13773** (AK023835.1), **QKI**
(NM_006775 /// NM_206853 /// NM_206854 /// NM_206855), **MPZL3** (NM_198275),
FAM70B (NM_182614), **LOC254128** (NR_037856.1 /// NR_037857.1 /// NR_037858.1),
25 **IL8** (NM_000584), **CHML** (NM_001821), **STX7** (NM_003569), **VAPA** (NM_003574 ///
NM_194434), **UGCG** (NM_003358), **PDXDC1** (NM_015027), **LRRC8B**
(NM_001134476 /// NM_015350), **STK4** (NM_006282), **GTF2H2** (NM_001515), **AGFG1**
(NM_001135187 /// NM_001135188 /// NM_001135189 /// NM_004504), **BTG1**
(NM_001731), **CFDP1** (NM_006324), **CNPY2** (NM_014255), **FAM105A** (NM_019018),
30 **GATM** (NM_001482), **GTF2H2B** (NM_001042490 /// NM_001098728 ///
NM_001098729 /// NM_001515), **IGHG1** (NG_001019.5 /// NC_000014.8), **IL18RAP**
(NM_003853), **N4BP2** (NM_018177), **PHACTR1** (NM_030948), **RTKN2** (NM_145307),
SLC16A1 (NM_003051), **SOCS1** (NM_003745), **SPAG17** (NM_206996),
ST6GALNAC1 (NM_018414), **STK17B** (NM_004226), **STT3B** (NM_178862), **STX16**

(NM_001001433 /// NM_001134772 /// NM_001134773 /// NM_003763), **TBC1D12** (NM_015188), **TRIM4** (NM_033017 /// NM_033091), **UACA** (NM_001008224 /// NM_018003), and **WHAMML2** (NR_026589) is correlative with or indicates that the patient has experienced or is at risk for experiencing lacunar stroke.

5 **[0078]** In various embodiments, the expression levels of a plurality of exon/splice variant biomarkers are co-determined together with the expression levels of a plurality of genes useful in the determination of whether a patient has experienced or has a predisposition to experience a hemorrhagic transformation. In varying embodiments, detecting an increase of the expression level of one or more biomarkers (e.g., 1, 2, 3, 4, 5 or
10 6 biomarkers) selected from the group consisting of MARCH7, SMAD4, AREG and INPP5D, and/or a decrease of the expression level of one or more biomarkers selected from the group consisting of TNFSF15 and MCFD22, compared to the control level of expression indicates that the patient suffers from or is at risk of experiencing hemorrhagic transformation of ischemic stroke. In some embodiments the methods further comprise
15 determining a level of expression of a plurality of biomarkers (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or all biomarkers) selected from the group consisting of MARCH7, SMAD4, AREG, INPP5D, IRAK3, PELI1, CPD, PRKDC, GAFA3, AMACR, MKLN1, IQCK, TSC22D2, TAF8, POLH, SYTL3, EXOC6, RIF1, RNF144B, ATXN1L, TSPYL1, RAPGEF2, MTPAP, ABHD12B, LRRC18, LOC151438,
20 NCRNA00081, TNFSF15 and MCFD22, wherein an increase of the expression level of one or more biomarkers selected from the group consisting of MARCH7, SMAD4, AREG, INPP5D, IRAK3, PELI1, CPD, PRKDC, GAFA3, AMACR, MKLN1, TSC22D2, TAF8, SYTL3, EXOC6, RIF1, RNF144B, RAPGEF2, ABHD12B, LRRC18, LOC151438 and NCRNA00081, and/or a decrease of the expression level of one or more biomarkers
25 selected from the group consisting of TNFSF15 MCFD22, IQCK, POLH, ATXN1L, TSPYL1 and MTPAP compared to a control level of expression indicates that the patient suffers from or is at risk of experiencing hemorrhagic transformation of ischemic stroke, thereby diagnosing the occurrence of hemorrhagic transformation of ischemic stroke or the predisposition for experiencing hemorrhagic transformation of ischemic stroke.

30 **4. Comparison to a Control Level of Expression**

[0079] The expression of the ischemic stroke/ICH-associated biomarkers are compared to a control level of expression. As appropriate, the control level of expression can be the expression level of the same ischemic stroke/ICH-associated biomarker in an otherwise

healthy individual (*e.g.*, in an individual who has not experienced and/or is not at risk of experiencing ischemic stroke/ICH). In some embodiments, the control level of expression is the expression level of a plurality of stably expressed endogenous reference biomarkers, as described herein or known in the art. In some embodiments, the control level of expression is a predetermined threshold level of expression of the same ischemic stroke/ICH-associated biomarker, *e.g.*, based on the expression level of the biomarker in a population of otherwise healthy individuals. In some embodiments, the expression level of the ischemic stroke/ICH-associated biomarker and the ischemic stroke/ICH-associated biomarker in an otherwise healthy individual are normalized to (*i.e.*, divided by), *e.g.*, the expression levels of a plurality of stably expressed endogenous reference biomarkers.

[0080] In varying embodiments, a subject may experience a vascular event that may be incorrectly diagnosed as ischemic stroke/ICH. In assessing a patient with a possible ischemic stroke or intracerebral hemorrhage, sometimes patients will have events that seem like ischemic stroke/ICH but are not - for example, a simple faint. Such patients will have a biomarker profile that is negative for stroke. To determine and distinguish subjects who have not experienced an ischemic stroke/ICH from subjects who have experienced an ischemic stroke or an intracerebral hemorrhage, provided herein are exon or splice variant biomarkers that identify subjects who have not experienced ischemic stroke or an intracerebral hemorrhage as distinguished from subjects who likely have experienced an ischemic stroke and intracerebral hemorrhage. These exon or splice variant biomarkers facilitate determining and distinguishing those patients who did not have an ischemic stroke or an intracerebral hemorrhage, even if presenting with one or more symptoms that might be diagnosed as ischemic stroke/ICH.

[0081] Accordingly, in varying embodiments, an increased expression level in comparison to a control of one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or all), ischemic stroke/ICH-associated biomarkers of Table 1E indicates that the subject has not or is unlikely to have experienced, ischemic stroke/ICH. High levels of expression of the exon or splice variant biomarkers, *e.g.*, as compared to historical controls, indicate that the subject has not or is unlikely to have experienced, ischemic stroke/ICH. Low levels of expression of these control exon or splice variant biomarkers, *e.g.*, as compared to historical controls, indicate that the subject has or is likely to have experienced ischemic stroke/ICH.

Table 1E: Exon Usage Upregulated in Subjects Who Have Not Experienced ischemic Stroke/ICH	
Marker ID	Gene Symbol
chr20.32880178-32880361>AHCY	AHCY
chr2.242611606-242612018>ATG4B	ATG4B
chr9.96866557-96866669>PTPDC1	PTPDC1
chr17.42982993-42984758>GFAP	GFAP
chr22.41252435-41253038>ST13	ST13
chr1.53416427-53416560>SCP2	SCP2
chr6.32806430-32806549>TAP2andHLA-DOB	TAP2 and HLA-DOB
chr14.19683027-19683436>DUXAP10	DUXAP10
chr9.95018962-95019084>IARS	IARS
chr19.39138368-39138549>ACTN4	ACTN4
chr9.140473077-140473342>WDR85	WDR85
chrX.48367956-48368346>PORCN	PORCN
chr2.101606718-101606910>NPAS2	NPAS2
chr7.101475858-101476867>snorkar	snorkar
chr19.45543176-45543571>SFRS16	SFRS16
chr18.28642978-28643441>DSC2	DSC2
chr22.36892014-36892257>FOXRED2andTXN2	FOXRED2 and TXN2
chr18.43417478-43417852>SIGLEC15	SIGLEC15

[0082] In some embodiments, the overexpression or underexpression of a ischemic stroke/ICH-associated biomarker is determined with reference to the expression of the same ischemic stroke/ICH-associated biomarker in an otherwise healthy individual. For example, a healthy or normal control individual has not experienced and/or is not at risk of experiencing ischemic stroke/ICH. The healthy or normal control individual generally has not experienced a vascular event (*e.g.*, cardioembolic stroke, large vessel stroke, lacunar stroke, TIA, ischemic stroke, myocardial infarction, peripheral vascular disease, venous thromboembolism or intracerebral hemorrhage). The healthy or normal control individual generally does not have one or more vascular risk factors (*e.g.*, hypertension, diabetes mellitus, hyperlipidemia, or tobacco smoking). As appropriate, the expression levels of the target ischemic stroke/ICH-associated biomarker in the healthy or normal control individual can be normalized (*i.e.*, divided by) the expression levels of a plurality of stably expressed endogenous reference biomarkers.

[0083] In some embodiments, the overexpression or underexpression of a ischemic stroke/ICH-associated biomarker is determined with reference to one or more stably expressed endogenous reference biomarkers. Internal control biomarkers or endogenous

reference biomarkers are expressed at the same or nearly the same expression levels in the blood of patients who have experienced ischemic stroke/ICH as compared to control patients. Target biomarkers are expressed at higher or lower levels in the blood, serum and/or plasma of patients who have experienced or are at risk of experiencing ischemic stroke/ICH. The expression levels of the target biomarker to the reference biomarker are normalized by dividing the expression level of the target biomarker to the expression levels of a plurality of stably expressed endogenous reference biomarkers. The normalized expression level of a target biomarker can be used to predict the occurrence or lack thereof of ischemic stroke/ICH, and/or the cause of the ischemic stroke/ICH.

[0084] In some embodiments, the expression level of the ischemic stroke/ICH-associated biomarker (*e.g.*, from Tables 1A-1D and biomarkers associated with cardioembolic stroke, atherothrombotic stroke, lacunar stroke, transient ischemic attack (TIA), hemorrhagic transformation described herein) from a patient suspected of having or experiencing an ischemic and from a control patient are normalized with respect to the expression levels of a plurality of stably expressed endogenous reference biomarkers. The expression levels of the normalized expression of the ischemic stroke/ICH-associated biomarkers are compared to the expression levels of the normalized expression of the same ischemic stroke/ICH-associated biomarker in a control patient. The determined fold change in expression = normalized expression of target biomarker in the ischemic stroke/ICH patient/ normalized expression of target biomarker in control patient. In varying embodiments, ischemic stroke/ICH-associated biomarker of interest (*e.g.*, whole gene or exon/slice variant/isoform) is divided by the geometric average of the stably expressed endogenous reference biomarkers. If the normalized values are similar to historical controls (*e.g.*, within two standard deviations), then the samples from such patients are diagnosed as indicating that the individual has not experienced and/or is not at risk of experiencing an ischemic stroke or intracerebral hemorrhage. If the expression levels of these exons are higher or lower than expected from historical controls (*e.g.*, greater than two standard deviations), then the samples from such patients are diagnosed as indicating that the individual has experienced and/or is at risk of experiencing an ischemic stroke or intracerebral hemorrhage. In varying embodiments, software may be employed involving Support Vector Machine (SVM) or PAM signature determination and determining which side of the hyperplane subjects falls into for classification as having an ischemic stroke or an ICH. Overexpression or underexpression of the normalized ischemic stroke/ICH-

associated biomarker in the ischemic stroke/ICH patient by at least about 1.2-fold, *e.g.*, at least about 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2.0-fold, or more, in comparison to the expression levels of the normalized ischemic stroke/ICH-associated biomarker in a healthy control patient indicates that the patient has experienced or is at risk of experiencing an ischemic stroke/ICH.

[0085] The biomarkers of Table 1E can also be normalized in comparison to internal control biomarkers or stably expressed endogenous reference biomarkers, as described above. The control exon biomarkers in Table 1E (upregulated in subjects who have not experienced ischemic stroke/ICH) can be divided by the geometric average of the endogenous control exons. If the normalized expression levels of the biomarkers listed in Table 1E are similar to historical controls (*e.g.*, within two standard deviations), then the samples from these patients are diagnosed as controls who have not experienced or are unlikely to experience ischemic stroke or intracerebral hemorrhage. That is, the biomarkers of Table 1E are expressed at higher levels in controls compared to patients with ischemic stroke or intracerebral hemorrhage. If the expression levels of these exons are lower than expected from historical controls (greater than two standard deviations), then the samples from these patients are diagnosed as controls who have experienced or are likely to experience ischemic stroke or intracerebral hemorrhage. Additional biomarkers (*e.g.*, from Tables 1A-1D and biomarkers associated with cardioembolic stroke, atherothrombotic stroke, lacunar stroke, transient ischemic attack (TIA), hemorrhagic transformation described herein) can then be used to distinguish whether the patient had an ischemic stroke or an intracerebral hemorrhage. The biomarkers of Table 1E are expressed at higher levels in subjects who have not experienced ischemic stroke/ICH compared to ischemic stroke and hemorrhage patients. They are thus lower in ischemic stroke and hemorrhage patients compared to controls. The expression of the biomarkers of Table 1E can be normalized to or divided by the expression of stably expressed endogenous reference biomarkers, described herein. If low levels of expression of the biomarkers of Table 1E compared to a normalized control are detected, this indicates the subject has experienced or is at risk to experience ischemic stroke or intracerebral hemorrhage. If higher levels of expression of the biomarkers of Table 1E compared to a normalized control are detected this indicates the subject has not experienced or is not at risk to experience ischemic stroke or intracerebral hemorrhage.

[0086] In some embodiments, the control level of expression is a predetermined threshold level. The threshold level can correspond to the level of expression of the same ischemic stroke/ICH-associated biomarker in an otherwise healthy individual or a population of otherwise healthy individuals, optionally normalized to the expression levels of a plurality of stably expressed endogenous reference biomarkers. After expression levels and normalized expression levels of the ischemic stroke/ICH-associated biomarkers are determined in a representative number of otherwise healthy individuals and individuals predisposed to experiencing ischemic stroke/ICH, normal and ischemic stroke/ICH-predisposed expression levels of the ischemic stroke/ICH-associated biomarkers can be maintained in a database, allowing for determination of threshold expression levels indicative of the presence or absence of risk to experience ischemic stroke/ICH or the occurrence of ischemic stroke/ICH. If the predetermined threshold level of expression is with respect to a population of normal control patients, then overexpression or underexpression of the ischemic stroke/ICH-associated biomarker (usually normalized) in the patient by at least about 1.2-fold, *e.g.*, at least about 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2.0-fold, or more, in comparison to the threshold level indicates that the patient has experienced or is at risk of experiencing ischemic stroke/ICH. If the predetermined threshold level of expression is with respect to a population of patients known to have experienced an ischemic stroke/ICH or known to be at risk for experiencing ischemic stroke/ICH, then an expression level in the patient suspected of experiencing ischemic stroke/ICH that is approximately equal to the threshold level (or overexpressed or underexpressed greater than the threshold level of expression), indicates that the patient has experienced or is at risk of experiencing an ischemic stroke/ICH.

[0087] With respect to the stably expressed endogenous reference biomarkers used for comparison, preferably, the endogenous reference biomarkers are stably expressed in blood. Exemplary endogenous reference biomarkers that find use are published, *e.g.*, in Stamova, *et al.*, *BMC Medical Genomics* (2009) 2:49. Additional endogenous reference biomarkers include without limitation, *e.g.*, GAPDH, ACTB, B2M, HMBS, PPIB, USP7, MAPRE2, CSNK1G2, SAFB2, PRKAR2A, PI4KB, CRTCL1, HADHA, MAP1LC3B, KAT5, CDC2L1 /// CDC2L2, GTSE1, CDC2L1 /// CDC2L2, TCF25, CHP, LRRC40, hCG_2003956 /// LYPLA2 /// LYPLA2P1, DAXX, UBE2NL, EIF1, KCMF1, PRKRIP1, CHMP4A, TMEM184C, TNF2, PODNL1, FBXO42, LOC441258, RRP1, C10orf104, ZDHHC5, C9orf23, LRRC45, NACC1, LOC100133445 /// LOC115110, PEX16. In some

embodiments, the expression levels of a plurality of stably expressed endogenous reference biomarkers are determined as a control. In some embodiments, the expression levels of at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or more, stably expressed endogenous reference biomarkers described herein or known in the art, are determined as a control.

5 [0088] In some embodiments, the expression levels of the stably expressed endogenous reference biomarkers GAPDH, ACTB, B2M, HMBS and PPIB are determined as a control. In some embodiments, the expression levels of 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, or more, endogenous reference biomarkers selected from the group consisting of USP7, MAPRE2, CSNK1G2, SAFB2, PRKAR2A, PI4KB, CRTCL1, HADHA, MAP1LC3B, 10 KAT5, CDC2L1 /// CDC2L2, GTSE1, CDC2L1 /// CDC2L2, TCF25, CHP, LRRC40, hCG_2003956 /// LYPLA2 /// LYPLA2P1, DAXX, UBE2NL, EIF1, KCMF1, PRKRIP1, CHMP4A, TMEM184C, TNF2, PODNL1, FBXO42, LOC441258, RRP1, C10orf104, ZDHHC5, C9orf23, LRRC45, NACC1, LOC100133445 /// LOC115110, PEX16 are determined as a control.

15 5. Methods of Detecting Biomarkers Associated with Ischemic stroke/ICH

[0089] Gene expression may be measured using any method known in the art. One of skill in the art will appreciate that the means of measuring gene expression is not a critical aspect of the invention. The expression levels of the biomarkers can be detected at the transcriptional or translational (*i.e.*, protein) level.

20 [0090] In some embodiments, the expression levels of the biomarkers are detected at the transcriptional level. A variety of methods of specific DNA and RNA measurement using nucleic acid hybridization techniques are known to those of skill in the art (*see*, Green and Sambrook, *supra* and Ausubel, *supra*) and may be used to detect the expression of the biomarkers set forth in Tables 1A-1E. Some methods involve an electrophoretic separation 25 (e.g., Southern blot for detecting DNA, and Northern blot for detecting RNA), but measurement of DNA and RNA can also be carried out in the absence of electrophoretic separation (e.g., by dot blot). Southern blot of genomic DNA (e.g., from a human) can be used for screening for restriction fragment length polymorphism (RFLP) to detect the presence of a genetic disorder affecting a polypeptide of the invention. All forms of RNA 30 can be detected, including, e.g., message RNA (mRNA), microRNA (miRNA), ribosomal RNA (rRNA) and transfer RNA (tRNA).

[0091] The selection of a nucleic acid hybridization format is not critical. A variety of nucleic acid hybridization formats are known to those skilled in the art. For example, common formats include sandwich assays and competition or displacement assays.

Hybridization techniques are generally described in Hames and Higgins Nucleic Acid Hybridization, A Practical Approach, IRL Press (1985); Gall and Pardue, Proc. Natl. Acad. Sci. U.S.A., 63:378-383 (1969); and John et al. Nature, 223:582-587 (1969).

[0092] Detection of a hybridization complex may require the binding of a signal-generating complex to a duplex of target and probe polynucleotides or nucleic acids.

Typically, such binding occurs through ligand and anti-ligand interactions as between a ligand-conjugated probe and an anti-ligand conjugated with a signal. The binding of the signal generation complex is also readily amenable to accelerations by exposure to ultrasonic energy.

[0093] The label may also allow indirect detection of the hybridization complex.

For example, where the label is a hapten or antigen, the sample can be detected by using antibodies. In these systems, a signal is generated by attaching fluorescent or enzyme molecules to the antibodies or in some cases, by attachment to a radioactive label (see, e.g., Tijssen, "Practice and Theory of Enzyme Immunoassays," Laboratory Techniques in Biochemistry and Molecular Biology, Burdon and van Knippenberg Eds., Elsevier (1985), pp. 9-20).

[0094] The probes can be labeled either directly, *e.g.*, with isotopes, chromophores, lumiphores, chromogens, or indirectly, such as with biotin, to which a streptavidin complex may later bind. Thus, the detectable labels used in the assays of the present invention can be primary labels (where the label comprises an element that is detected directly or that produces a directly detectable element) or secondary labels (where the detected label binds to a primary label, *e.g.*, as is common in immunological labeling). Typically, labeled signal nucleic acids are used to detect hybridization. Complementary nucleic acids or signal nucleic acids may be labeled by any one of several methods typically used to detect the presence of hybridized polynucleotides. The most common method of detection is the use of autoradiography with ^3H , ^{125}I , ^{35}S , ^{14}C , or ^{32}P -labeled probes or the like.

[0095] Other labels include, *e.g.*, ligands that bind to labeled antibodies, fluorophores, chemiluminescent agents, enzymes, and antibodies which can serve as specific binding pair members for a labeled ligand. An introduction to labels, labeling procedures and detection of labels is found in Polak and Van Noorden Introduction to

Immunocytochemistry, 2nd ed., Springer Verlag, NY (1997); and in Haugland Handbook of Fluorescent Probes and Research Chemicals, a combined handbook and catalogue Published by Molecular Probes, Inc. (1996).

[0096] In general, a detector which monitors a particular probe or probe

5 combination is used to detect the detection reagent label. Typical detectors include spectrophotometers, phototubes and photodiodes, microscopes, scintillation counters, cameras, film and the like, as well as combinations thereof. Examples of suitable detectors are widely available from a variety of commercial sources known to persons of skill in the art. Commonly, an optical image of a substrate comprising bound labeling moieties is
10 digitized for subsequent computer analysis.

[0097] Most typically, the amount of RNA is measured by quantifying the amount of label fixed to the solid support by binding of the detection reagent. Typically, the presence of a modulator during incubation will increase or decrease the amount of label fixed to the solid support relative to a control incubation which does not comprise the

15 modulator, or as compared to a baseline established for a particular reaction type. Means of detecting and quantifying labels are well known to those of skill in the art.

[0098] In preferred embodiments, the target nucleic acid or the probe is immobilized on a solid support. Solid supports suitable for use in the assays of the invention are known to those of skill in the art. As used herein, a solid support is a matrix of material in a
20 substantially fixed arrangement.

[0099] For example, in one embodiment of the invention, microarrays are used to detect the pattern of gene expression. Microarrays provide one method for the simultaneous measurement of the expression levels of large numbers of genes. Each array has a reproducible pattern of a plurality of nucleic acids (e.g., a plurality of oligonucleotide
25 probes that hybridize to a plurality of the biomarkers set forth in Tables 1A-1E) attached to a solid support. In one embodiment, the array contains a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers listed in Table 1A. In one embodiment, the array contains a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers listed in Table 1B. In one embodiment, the array contains a plurality of
30 oligonucleotide probes that hybridize to a plurality of the biomarkers listed in Table 1C. In one embodiment, the array contains a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers listed in Table 1D. In one embodiment, the array contains a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers listed in

Table 1E. In one embodiment, the array further contains a plurality of oligonucleotide probes that hybridize to a plurality of genes useful for diagnosing ischemic stroke, cardioembolic stroke, carotid stenosis, atrial fibrillation, transient ischemic attacks, lacunar stroke, and/or hemorrhagic transformation, as described herein and/or known in the art. In various embodiments, the array further contains a plurality of stably expressed endogenous reference biomarkers. Labeled RNA or DNA is hybridized to complementary probes on the array and then detected by laser scanning. Hybridization intensities for each probe on the array are determined and converted to a quantitative read-out of relative gene expression levels in ischemic stroke/ICH (e.g., correlative with or associative of ischemic stroke/ICH, or allowing the differentiation of a transient neurological event as ischemic or non-ischemic).

[0100] In some embodiments, a sample is obtained from a subject, total mRNA is isolated from the sample and is converted to labeled cRNA and then hybridized to an array. Relative transcript levels are calculated by reference to appropriate controls present on the array and in the sample. See Mahadevappa and Warrington, Nat. Biotechnol. 17, 1134-1136 (1999).

[0101] A variety of automated solid-phase assay techniques are also appropriate. For instance, very large scale immobilized polymer arrays (VLSIPS™), available from Affymetrix, Inc. (Santa Clara, CA) can be used to detect changes in expression levels of a plurality of genes involved in the same regulatory pathways simultaneously. See, Tijssen, supra., Fodor et al. (1991) Science, 251: 767- 777; Sheldon et al. (1993) Clinical Chemistry 39(4): 718-719, and Kozal et al. (1996) Nature Medicine 2(7): 753-759. Integrated microfluidic systems and other point-of-care diagnostic devices available in the art also find use. See, e.g., Liu and Mathies, Trends Biotechnol. (2009) 27(10):572-81 and Tothill, Semin Cell Dev Biol (2009) 20(1):55-62. Microfluidics systems for use in detecting levels of expression of a plurality of nucleic acids are commercially available, e.g., from NanoString Technologies (on the internet at nanostring.com), Applied Biosystems (Life Technologies) (appliedbiosystems.com) and Fluidigm (fluidigm.com).

[0102] Detection can be accomplished, for example, by using a labeled detection moiety that binds specifically to duplex nucleic acids (e.g., an antibody that is specific for RNA-DNA duplexes). One preferred example uses an antibody that recognizes DNA-RNA heteroduplexes in which the antibody is linked to an enzyme (typically by recombinant or covalent chemical bonding). The antibody is detected when the enzyme reacts with its

substrate, producing a detectable product. Coutlee et al. (1989) *Analytical Biochemistry* 181:153-162; Bogulavski (1986) et al. *J. Immunol. Methods* 89:123-130; Prooijen-Knegt (1982) *Exp. Cell Res.* 141:397-407; Rudkin (1976) *Nature* 265:472-473, Stollar (1970) *Proc. Nat'l Acad. Sci. USA* 65:993-1000; Ballard (1982) *Mol. Immunol.* 19:793-799; 5 Pisetsky and Caster (1982) *Mol. Immunol.* 19:645-650; Viscidi et al. (1988) *J. Clin. Microbial.* 41:199-209; and Kiney et al. (1989) *J. Clin. Microbiol.* 27:6-12 describe antibodies to RNA duplexes, including homo and heteroduplexes. Kits comprising antibodies specific for DNA:RNA hybrids are available, e.g., from Digene Diagnostics, Inc. (Beltsville, MD).

10 **[0103]** In addition to available antibodies, one of skill in the art can easily make antibodies specific for nucleic acid duplexes using existing techniques, or modify those antibodies that are commercially or publicly available. In addition to the art referenced above, general methods for producing polyclonal and monoclonal antibodies are known to those of skill in the art (see, e.g., Paul (3rd ed.) *Fundamental Immunology* Raven Press, 15 Ltd., NY (1993); Coligan, et al., *Current Protocols in Immunology*, Wiley Interscience (1991-2008); Harlow and Lane, *Antibodies: A Laboratory Manual* Cold Spring Harbor Press, NY (1988); Harlow and Lane, *Using Antibodies*, Cold Spring Harbor Press, NY (1999); Stites et al. (eds.) *Basic and Clinical Immunology* (4th ed.) Lange Medical Publications, Los Altos, CA, and references cited therein; Goding *Monoclonal Antibodies: Principles and Practice* (2d ed.) Academic Press, New York, NY, (1986); and Kohler and 20 Milstein *Nature* 256: 495-497 (1975)). Other suitable techniques for antibody preparation include selection of libraries of recombinant antibodies in phage or similar vectors (see, Huse et al. *Science* 246:1275-1281 (1989); and Ward et al. *Nature* 341:544-546 (1989)). Specific monoclonal and polyclonal antibodies and antisera will usually bind with a 25 dissociation constant (K_D) of at least about 0.1 μ M, preferably at least about 0.01 μ M or better, and most typically and preferably, 0.001 μ M or better.

[0104] The nucleic acids used in this invention can be either positive or negative probes. Positive probes bind to their targets and the presence of duplex formation is evidence of the presence of the target. Negative probes fail to bind to the suspect target and 30 the absence of duplex formation is evidence of the presence of the target. For example, the use of a wild type specific nucleic acid probe or PCR primers may serve as a negative probe in an assay sample where only the nucleotide sequence of interest is present.

[0105] The sensitivity of the hybridization assays may be enhanced through use of a nucleic acid amplification system that multiplies the target nucleic acid being detected.

Examples of such systems include the polymerase chain reaction (PCR) system, in particular RT-PCR or real time PCR, and the ligase chain reaction (LCR) system. Other methods recently described in the art are the nucleic acid sequence based amplification (NASBA, Cangene, Mississauga, Ontario) and Q Beta Replicase systems. These systems can be used to directly identify mutants where the PCR or LCR primers are designed to be extended or ligated only when a selected sequence is present. Alternatively, the selected sequences can be generally amplified using, for example, nonspecific PCR primers and the amplified target region later probed for a specific sequence indicative of a mutation. High throughput multiplex nucleic acid sequencing or “deep sequencing” to detect captured expressed biomarker genes also finds use. High throughput sequencing techniques are known in the art (e.g., 454 Sequencing on the internet at 454.com). In varying embodiments, next generation sequencing, deep sequencing or ultra deep sequencing methodologies are applied. Deep sequencing data analysis is described, *e.g.*, in “Deep Sequencing Data Analysis (Methods in Molecular Biology),” Noam Shomron (Editor), Humana Press; 2013 edition. Next generation sequencing is described, *e.g.*, in “Next-Generation DNA Sequencing Informatics,” Stuart M. Brown (Editor), Cold Spring Harbor Laboratory Press; 1st edition (2013); “Next-generation Sequencing: Current Technologies and Applications,” Jianping Xu (Editor), Caister Academic Press (2014); Wilhelm, *et al.*, *Nature*. (2008) 453:1239–1243; Nagalakshmi, *et al.*, *Science*. (2008) 320:1344–1349; and Mortazavi, *et al.*, *Nat. Methods*. (2008) 5:621–628.

[0106] In varying embodiments, the biomarkers (*e.g.*, exons or splice variants or whole genes) are detected using RNA sequencing techniques. Methodologies for direct sequencing of RNA, *e.g.*, without an intervening step of producing cDNA are known in the art, and described for example, in Nagalakshmi, *et al.*, *Curr Protoc Mol Biol.* (Jan 2010) Chapter 4:Unit 4.11.1-13; Wang, *et al.*, *Nat Rev Genet.* (2009) 10(1):57-63; Kwok, *et al.*, *Trends Biochem Sci.* (2015) 40(4):221-232; Ramsköld, *et al.*, *Methods Mol Biol.* (2012) 802:259-74; Krupp, *et al.*, *Bioinformatics.* (2012) 28(8):1184-5; Oudejans, *Clin Biochem.* (2015) Mar 16. pii: S0009-9120(15)00081-8; Eija Korpelainen and Jarno Tuimala, “RNA-seq Data Analysis: A Practical Approach (Chapman & Hall/CRC Mathematical and Computational Biology,” Chapman and Hall/CRC (September 19, 2014); Ernesto Picardi, “RNA Bioinformatics (Methods in Molecular Biology),” Humana Press; 2015 edition

(January 11, 2015); and Shashikant Kulkarni and John Pfeifer, "Clinical Genomics," Academic Press; 1 edition (November 21, 2014).

[0107] An alternative means for determining the level of expression of the nucleic acids of the present invention is in situ hybridization. In situ hybridization assays are well known and are generally described in Angerer et al., *Methods Enzymol.* 152:649-660 (1987). In an in situ hybridization assay, cells, preferentially human cells, are fixed to a solid support, typically a glass slide. If DNA is to be probed, the cells are denatured with heat or alkali. The cells are then contacted with a hybridization solution at a moderate temperature to permit annealing of specific probes that are labeled. The probes are preferably labeled with radioisotopes or fluorescent reporters.

[0108] In other embodiments, quantitative RT-PCR is used to detect the expression of a plurality of the biomarkers set forth in one or more of Tables 1A-1E. In one embodiment, quantitative RT-PCR is used to further detect a plurality of the biomarkers useful for the diagnosis of ischemic stroke, cardioembolic stroke, carotid stenosis, atrial fibrillation, transient ischemic attacks, intracerebral hemorrhage and/or hemorrhagic transformation, as described herein and known in the art. A general overview of the applicable technology can be found, for example, in A-Z of Quantitative PCR, Bustin, ed., 2004, International University Line; Quantitative PCR Protocols, Kochanowski and Reischl, eds., 1999, Humana Press; Clinical Applications of PCR, Lo, ed., 2006, Humana Press; PCR Protocols: A Guide to Methods and Applications (Innis et al. eds. (1990)) and PCR Technology: Principles and Applications for DNA Amplification (Erich, ed. (1992)). In addition, amplification technology is described in U.S. Patent Nos. 4,683,195 and 4,683,202. Methods for multiplex PCR, known in the art, are applicable to the present invention.

[0109] In varying embodiments, detection is accomplished by performing reverse transcription (RT) followed by a ligase detection reaction (LDR) with single-pair fluorescence resonance energy transfer (spFRET) (RT-LDR/spFRET). Methods for performing RT-LDR/spFRET are known in the art and described, *e.g.*, in Peng, *et al.*, *Anal Chem.* 2013 Aug 20;85(16):7851-8.

[0110] Accordingly, in one embodiment, provided is a reaction mixture comprising a plurality of polynucleotides which specifically hybridize (*e.g.*, primers) to a plurality of nucleic acid sequences of the genes set forth in one or more of Tables 1A-1E. In some embodiments, the invention provides a reaction mixture further comprising a plurality of

polynucleotides which specifically hybridize (e.g., primers) to a plurality of nucleic acid sequences of the genes useful for the diagnosis of ischemic stroke, cardioembolic stroke, carotid stenosis, atrial fibrillation, transient ischemic attacks, intracerebral hemorrhage and/or hemorrhagic transformation, as described herein and known in the art. In some
5 embodiments, the reaction mixture is a PCR mixture, for example, a multiplex PCR mixture.

[0111] This invention relies on routine techniques in the field of recombinant genetics. Generally, the nomenclature and the laboratory procedures in recombinant DNA technology described below are those well-known and commonly employed in the art.
10 Standard techniques are used for cloning, DNA and RNA isolation, amplification and purification. Generally enzymatic reactions involving DNA ligase, DNA polymerase, restriction endonucleases and the like are performed according to the manufacturer's specifications. Basic texts disclosing the general methods of use in this invention include Green and Sambrook et al., *Molecular Cloning, A Laboratory Manual* (4th ed. 2012);
15 Kriegler, *Gene Transfer and Expression: A Laboratory Manual* (1990); and *Current Protocols in Molecular Biology* (Ausubel et al., eds., 1987-2015, Wiley Interscience)).

[0112] For nucleic acids, sizes are given in either kilobases (kb) or base pairs (bp). These are estimates derived from agarose or acrylamide gel electrophoresis, from sequenced nucleic acids, or from published DNA sequences. For proteins, sizes are given in
20 kilodaltons (kDa) or amino acid residue numbers. Proteins sizes are estimated from gel electrophoresis, from sequenced proteins, from derived amino acid sequences, or from published protein sequences.

[0113] Oligonucleotides that are not commercially available can be chemically synthesized according to the solid phase phosphoramidite triester method first described by
25 Beaucage & Caruthers, *Tetrahedron Letts.* 22:1859-1862 (1981), using an automated synthesizer, as described in Van Devanter et. al., *Nucleic Acids Res.* 12:6159-6168 (1984). Purification of oligonucleotides is by either native acrylamide gel electrophoresis or by anion-exchange HPLC as described in Pearson & Reanier, *J. Chrom.* 255:137-149 (1983).

[0114] In some embodiments, the expression level of the biomarkers described
30 herein are detected at the translational or protein level. Detection of proteins is well known in the art, and methods for protein detection known in the art find use. Exemplary assays for determining the expression levels of a plurality of proteins include, e.g., ELISA, flow cytometry, mass spectrometry (e.g., MALDI or SELDI), surface plasmon resonance (e.g.,

BiaCore), microfluidics and other biosensor technologies. See, e.g., Tothill, *Semin Cell Dev Biol* (2009) 20(1):55-62.

6. Providing Appropriate Treatment and Prevention Regimes to the Patient

[0115] Upon a positive determination or confirmation that a patient has experienced
5 ischemic stroke/ICH, and a determination of the cause of the ischemic stroke/ICH, *e.g.*,
using established clinical procedures and/or the biomarkers provided herein and known in
the art (*e.g.*, employing biomarkers described in co-pending and co-owned U.S. Patent
Publications Nos. 2015/0018234 (“BIOMARKERS FOR DIAGNOSING ISCHEMIA”);
2012/0316076 (“BIOMARKERS FOR THE DIAGNOSIS OF LACUNAR STROKE”);
10 2012/0065087 (“BIOMARKERS FOR DIAGNOSIS OF STROKE AND ITS CAUSES”);
2012/0015904 (“BIOMARKERS FOR DIAGNOSIS OF TRANSIENT ISCHEMIC
ATTACKS”); and 2010/0197518 (“METHODS FOR DIAGNOSING ISCHEMIA”) for the
diagnosis of ischemic stroke/ICH), the methods further provide for the step of prescribing,
providing or administering a regime for the prophylaxis or treatment of ischemic
15 stroke/ICH. By diagnosing the occurrence and/or the cause of ischemic stroke/ICH using
the biomarkers described herein, a patient can rapidly receive treatment that is tailored to
and appropriate for the type of ischemic stroke/ICH that has been experienced, or that the
patient is at risk of experiencing.

[0116] For example, if the expression levels of the plurality of ischemic stroke/ICH-
20 associated biomarkers indicate the occurrence or risk of ischemic stroke/ICH, a positive
diagnosis of ischemic stroke/ICH can be supported or confirmed using methods known in
the art. For example, the patient can be subject to MRI imaging of brain and vessels,
additional blood tests, EKG, and/or echocardiogram. Patients who have experienced
ischemic transient neurological events may undergo extensive evaluation of the heart,
25 vasculature, blood and brain, and may receive stroke prevention therapy such as
antiplatelet/anticoagulation, anti-hypertensive medication and lipid lowering therapy.

[0117] If the expression levels of the plurality of biomarkers indicate the occurrence
or risk of an ischemic transient neurological event (*e.g.*, transient ischemic attacks (TIA) or
transient cerebral ischemia), the patient can be prescribed a regime of medications and/or
30 life-style adjustments (*e.g.*, diet, exercise, stress) to minimize risk factors can be
recommended, including reducing blood pressure and cholesterol levels, and controlling
diabetes. Several medications can be used to decrease the likelihood of a stroke after a
transient ischemic attack. The medication selected will depend on the location, cause,

severity and type of TIA, if TIA has occurred. For example, the patient may be prescribed a regime of an anti-platelet drug. The most frequently used anti-platelet medication is aspirin. An alternative to aspirin is the anti-platelet drug clopidogrel (Plavix). Some studies indicate that aspirin is most effective in combination with another anti-platelet drug. In some
5 embodiments, the patient is prescribed a combination of low-dose aspirin and the anti-platelet drug dipyridamole (Aggrenox), to reduce blood clotting. Ticlopidine (Ticlid) is another anti-platelet medication that finds use to prevent or reduce the risk of stroke in patients who have experienced TIA. In some embodiments, the patient may be prescribed a regime of an anticoagulant. Exemplary anticoagulants include aspirin, heparin, warfarin,
10 and dabigatran. Patients having a moderately or severely narrowed neck (carotid) artery, may require or benefit from carotid endarterectomy to clear carotid arteries of fatty deposits (atherosclerotic plaques) before another TIA or stroke can occur. In some embodiments, the patient may require or benefit from carotid angioplasty, or stenting.

[0118] In cases where a non-ischemic transient neurological event (TNE) is

15 indicated, further evaluation to the cause of the non-ischemic TNE can be performed. For example, the subject can be given tests to determine if a migraine or seizure was experienced, and receive proper treatment. Patients with non-ischemic transient neurological events undergo different diagnostic evaluation and therapy, such as EEG and anti-seizure medication for seizures, and anti-migraine medication for migraines.

20 **[0119]** If the expression levels of the plurality of biomarkers indicate the occurrence or risk of cardioembolic stroke, the patient can be prescribed or administered a regime of an anticoagulant. Exemplary anticoagulants include aspirin, heparin, warfarin, and dabigatran.

[0120] If the expression levels of the plurality of biomarkers indicate the occurrence or risk of carotid stenosis, the patient can be prescribed or administered a regime of an anti-platelet drug. The most frequently used anti-platelet medication is aspirin. An alternative
25 to aspirin is the anti-platelet drug clopidogrel (Plavix). Some studies indicate that aspirin is most effective in combination with another anti-platelet drug. In some embodiments, the patient is prescribed a combination of low-dose aspirin and the anti-platelet drug dipyridamole (Aggrenox), to reduce blood clotting. Ticlopidine (Ticlid) is another anti-platelet medication that finds use. Patients having a moderately or severely narrowed neck
30 (carotid) artery, may require or benefit from carotid endarterectomy. This preventive surgery clears carotid arteries of fatty deposits (atherosclerotic plaques) to prevent a first or subsequent strokes. In some embodiments, the patient may require or benefit from carotid

angioplasty, or stenting. Carotid angioplasty involves using a balloon-like device to open a clogged artery and placing a small wire tube (stent) into the artery to keep it open.

[0121] If the expression levels of the plurality of biomarkers indicate the occurrence or risk of atrial fibrillation, the patient can be prescribed a regime of an anti-coagulant (to prevent stroke) and/or a pharmacological agent to achieve rate control. Exemplary anticoagulants include aspirin, heparin, warfarin, and dabigatran. Exemplary rate control drugs include beta blockers (e.g., metoprolol, atenolol, bisoprolol), non-dihydropyridine calcium channel blockers (e.g., diltiazem or verapamil), and cardiac glycosides (e.g., digoxin).

[0122] If the expression levels of the plurality of ischemic stroke/ICH-associated biomarkers indicate the occurrence or risk of lacunar stroke, a positive diagnosis of lacunar stroke can be supported or confirmed using methods known in the art. For example, the patient can be subject to clinical evaluation (e.g., determination of one or more of the lacunar syndromes, including (1) Pure motor stroke/hemiparesis, (2) Ataxic hemiparesis, (3) Dysarthria/clumsy hand, (4) Pure sensory stroke, and (5) Mixed sensorimotor stroke), radiologic imaging, retinal imaging, evaluation of blood-brain barrier permeability, evidence of microhemorrhage and blood endothelial markers (e.g., (homocysteine, intercellular adhesion molecule 1 (ICAM1), thrombomodulin (TM), tissue factor (TF) and tissue factor pathway inhibitor (TFPI); Hassan, *et al.*, *Brain* (2003) 126(Pt 2):424-32; and Hassan, *et al.*, *Brain*. (2004) 127(Pt 1):212-9). Upon a positive diagnosis of lacunar stroke, the patient may be administered tissue plasminogen activator within three hours of experiencing ischemic stroke/ICH if the patient is without contraindications (*i.e.* a bleeding diathesis such as recent major surgery or cancer with brain metastases). High doses aspirin may be given within 48 hours of experiencing ischemic stroke/ICH. For long term prevention of recurrence, medical regimens may be aimed towards correcting the underlying risk factors for lacunar infarcts such as hypertension, diabetes mellitus and cigarette smoking.

[0123] If the expression levels of the plurality of ischemic stroke/ICH-associated biomarkers indicate the occurrence or risk of hemorrhagic transformation, a positive or negative diagnosis of hemorrhagic transformation of ischemic stroke can be supported or confirmed using methods known in the art. For example, the patient can be subject to MRI imaging of brain and vessels, additional blood tests, EKG, and/or echocardiogram. Patients who have experienced or who are at risk of hemorrhagic transformation of ischemic stroke

may undergo extensive evaluation of the heart, vasculature, blood and brain, and may receive reduced dosages of tissue plasminogen activator (tPA), or administration of tPA may be withdrawn or discontinued. In some embodiments, patients who have experienced or who are at risk of hemorrhagic transformation of ischemic stroke may receive an interventional therapy instead of administration of tPA. In some embodiments, patients who have experienced or who are at risk of hemorrhagic transformation of ischemic stroke may receive tPA co-administered with one or more pharmacological agents to prevent, inhibit, reduce and/or mitigate the symptoms of HT, *e.g.*, minocycline, Edoxaban, Fingolimide (*see*, Campos, *et al.*, *Stroke*. (2013) 44(2):505-11), a matrix metalloproteinase (MMP) inhibitor (*e.g.*, an inhibitor of MMP9), an anti-inflammatory agent and/or an antioxidant. Inhibitors of MMP9 that find use are known in the art and have been described, *e.g.*, in Intl. Appl. Nos. PCT/US2010/023585, PCT/GB2003/002138, PCT/GB2003/000741, in U.S. Patent Publ. Nos. 2004/0147573, 2005/0113344, 2010/0098659, and in Tandon, *et al.*, *Bioinformation*. (2011) 5(8):310-4, Tuccinardi, *et al.*, *Bioorg Med Chem*. (2008) 16(16):7749-58. Patients who have not experienced or who are not at risk of hemorrhagic transformation of ischemic stroke may also undergo extensive evaluation of the heart, vasculature, blood and brain, and may receive tissue plasminogen activator (tPA).

7. Reaction Mixtures

[0124] Further provided are reaction mixtures for diagnosing ischemic stroke/ICH or a predisposition for developing ischemic stroke/ICH. In varying embodiments, the reaction mixtures comprise a plurality of nucleic acid probes or primer sets useful for the amplification of a plurality of biomarkers (*e.g.*, 2, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 biomarkers, or all listed biomarkers in the identified Table, *e.g.*, Table 1A, Table 1B, Table 1C, Table 1D and/or Table 1E) of the biomarkers set forth in Tables 1A-E. In one embodiment, the reaction mixtures comprise a plurality of nucleic acid probes or primer sets that hybridize to a plurality of the biomarkers set forth in Table 1A. In one embodiment, the reaction mixtures comprise a plurality of nucleic acid probes or primer sets that hybridize to a plurality of the biomarkers set forth in Table 1B. In one embodiment, the reaction mixtures comprise a plurality of nucleic acid probes or primer sets that hybridize to a plurality of the biomarkers set forth in Table 1C. In one embodiment, the reaction mixtures comprise a plurality of nucleic acid probes or primer sets that hybridize to a plurality of the biomarkers set forth in Table 1D. In one embodiment, the reaction

mixtures further comprise a plurality of nucleic acid probes or primer sets that hybridize to a plurality of the biomarkers set useful for the diagnosis of ischemic stroke, cardioembolic stroke, atherothrombotic stroke, carotid stenosis, lacunar stroke, atrial fibrillation, transient ischemic attacks (TIA), transient neurological events (TNEs), intracerebral hemorrhage and/or hemorrhagic transformation, as described herein. The probes may be immobilized on an array as described herein.

[0125] In varying embodiments, the reaction mixtures further can comprise appropriate buffers, salts, polymerases, dNTPs and other reagents to facilitate amplification and/or detection reactions (e.g., primers, labels) for amplifying one or more exons of a plurality of the biomarkers set forth in Tables 1A-E.

[0126] In some embodiments, the reaction mixtures can be provided in one or more reaction vessels that have aliquots of some or all of the reaction components of the reaction mixtures in them. Aliquots can be in liquid or dried (e.g., freeze-dried) form. Reaction vessels can include sample processing cartridges or other vessels that allow for the containment, processing and/or amplification of samples in the same vessel.

[0127] Further contemplated are kits comprising the reaction mixtures described above and herein.

8. Solid Supports and Kits

[0128] The invention further provides, a solid support comprising a plurality of nucleic acid probes that hybridize to a plurality (e.g., two or more, or all) of the biomarkers set forth in Tables 1A-E, and optionally stably expressed endogenous reference biomarkers, as described herein. For example, the solid support can be a microarray attached to a plurality of nucleic acid probes that hybridize to a plurality (e.g., two or more, or all) of the biomarkers set forth in Tables 1A-E, and optionally stably expressed endogenous reference biomarkers.

[0129] In various embodiments, the solid supports are configured to exclude genes not associated with or useful to the diagnosis, prediction or confirmation of ischemic stroke or ICH. For example, oligonucleotide probes that hybridize to genes or gene exons/splice variants/isoforms that are overexpressed or underexpressed less than 1.2-fold in subjects with ischemic stroke/ICH in comparison to a control level of expression can be excluded from the present solid supports. In some embodiments, oligonucleotide probes that hybridize to genes or gene exons that are overexpressed or underexpressed less than 1.2-

fold in subjects with ischemic stroke, including transient cerebral ischemia, lacunar stroke, cardioembolic stroke, atherothrombotic stroke, TIA, TNE, carotid stenosis, and stroke subsequent to atrial fibrillation, in comparison to a control level of expression can be excluded from the present solid supports.

5 **[0130]** In various embodiments, the solid supports are configured to include only oligonucleotide probes that hybridize to genes or gene exons associated with or useful to the diagnosis, prediction or confirmation of ischemic stroke and/or ICH. For example, in some embodiments, only oligonucleotide probes that hybridize to genes or gene exons that are overexpressed or underexpressed more than 1.2-fold in subjects with ischemic stroke/ICH
10 in comparison to a control level of expression are included in the present solid supports. In some embodiments, only oligonucleotide probes that hybridize to genes or gene exons that are overexpressed or underexpressed more than 1.2-fold in subjects with ICH or ischemic stroke (*e.g.*, including transient cerebral ischemia, lacunar stroke, cardioembolic stroke, atherothrombotic stroke, TIA, TNE, carotid stenosis and stroke subsequent to atrial
15 fibrillation), in comparison to a control level of expression are included in the present solid supports.

[0131] The solid support may optionally further comprise a plurality of oligonucleotide probes that hybridize to a plurality (*e.g.*, two or more, or all) of the biomarkers useful for the diagnosis of ICH/ischemic stroke (*e.g.*, cardioembolic stroke,
20 carotid stenosis, and/or atrial fibrillation), as described herein. In various embodiments, the solid support comprises 5000, 4000, 3000, 2000, 1000 or fewer (*e.g.*, 900, 800, 700, 600, 500 or fewer) nucleic acid probes that hybridize to a plurality of ischemic stroke/ICH-associated genes, as described herein. The solid support may be a component in a kit.

[0132] The invention also provides kits for diagnosing ischemic stroke/ICH or a
25 predisposition for developing ischemic stroke/ICH. For example, the invention provides kits that include one or more reaction vessels that have aliquots of some or all of the reaction components of the reaction mixtures in them. Aliquots can be in liquid or dried form. Reaction vessels can include sample processing cartridges or other vessels that allow for the containment, processing and/or amplification of samples in the same vessel. The
30 kits may comprise a plurality of nucleic acid probes or primer sets that hybridize to a plurality (*e.g.*, two or more, or all) of the biomarkers set forth in Tables 1A-E. In one embodiment, the kits comprise a plurality of nucleic acid probes or primer sets that hybridize to a plurality of the biomarkers set forth in Table 1A. In one embodiment, the kits

comprise a plurality of nucleic acid probes or primer sets that hybridize to a plurality of the biomarkers set forth in Table 1B. In one embodiment, the kits comprise a plurality of nucleic acid probes or primer sets that hybridize to a plurality of the biomarkers set forth in Table 1C. In one embodiment, the kits comprise a plurality of nucleic acid probes or primer sets that hybridize to a plurality of the biomarkers set forth in Table 1D. In one embodiment, the kits further comprise a plurality of nucleic acid probes or primer sets that hybridize to a plurality of the biomarkers set useful for the diagnosis of ischemic stroke, cardioembolic stroke, atherothrombotic stroke, carotid stenosis, lacunar stroke, atrial fibrillation, transient ischemic attacks (TIA), transient neurological events (TNEs), intracerebral hemorrhage and/or hemorrhagic transformation, as described herein. The probes may be immobilized on an array as described herein.

[0133] In addition, the kit can comprise appropriate buffers, salts and other reagents to facilitate amplification and/or detection reactions (e.g., primers, labels) for determining the expression levels of a plurality of the biomarkers set forth in Tables 1A-E. In one embodiment, the kit comprises appropriate buffers, salts and other reagents to facilitate amplification and/or detection reactions (e.g., primers, labels) for determining the expression levels of a plurality of the biomarkers set forth in Table 1A. In one embodiment, the kit comprises appropriate buffers, salts and other reagents to facilitate amplification and/or detection reactions (e.g., primers) for determining the expression levels of a plurality of the biomarkers set forth in Table 1B. In one embodiment, the kit comprises appropriate buffers, salts and other reagents to facilitate amplification and/or detection reactions (e.g., primers, labels) for determining the expression levels of a plurality of the biomarkers set forth in Table 1C. In one embodiment, the kit comprises appropriate buffers, salts and other reagents to facilitate amplification and/or detection reactions (e.g., primers) for determining the expression levels of a plurality of the biomarkers set forth in Table 1D. In one embodiment, the kit further comprises appropriate buffers, salts and other reagents to facilitate amplification and/or detection reactions (e.g., primers) for determining the expression levels of a plurality of the biomarkers useful for the diagnosis of ischemic stroke, cardioembolic stroke, atherothrombotic stroke, lacunar stroke, carotid stenosis, atrial fibrillation, and/or transient ischemic attacks (TIA), transient neurological events (TNEs) as described herein. The kits can also include written instructions for the use of the kit.

[0134] In one embodiment, the kits comprise a plurality of antibodies that bind to a plurality of the biomarkers set forth in Tables 1A-E. The kits may further comprise a

plurality of antibodies that bind to a plurality of the biomarkers useful for the diagnosis of ischemic stroke, cardioembolic stroke, carotid stenosis, atrial fibrillation, transient ischemic attacks (TIA), transient neurological events (TNEs), intracerebral hemorrhage and/or hemorrhagic transformation, as described herein. The antibodies may or may not be
5 immobilized on a solid support, *e.g.*, an ELISA plate.

EXAMPLES

[0135] The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1

10 Intracerebral Hemorrhage and Ischemic Stroke of Different Etiologies Have Distinct Alternatively Spliced mRNA Profiles in Blood

ABSTRACT

[0136] Background: Whole transcriptome studies have used 3'-biased expression microarrays to study genes regulated in blood of ischemic stroke patients. However,
15 alternatively spliced messenger RNA isoforms have not been investigated for ischemic stroke or intracerebral hemorrhage (ICH) in animals or humans. Alternative splicing is the mechanism whereby a single gene's exons combine to produce distinct mRNA and protein isoforms. RNA-sequencing (RNA-Seq) was used to determine if alternative splicing varies for ICH and different ischemic stroke causes (cardioembolic, large vessel, lacunar) as
20 compared to each other and controls.

[0137] Methods: Paired-end RNA-Seq was performed using Illumina Solexa technology to a depth of 200×10^6 reads for splicing analysis on twenty whole-blood samples. Differential alternative splicing was assessed using 1-way-ANOVA (FDR $p < 0.05$). Differential exon-usage was calculated between each group ($p < 0.0005$; |fold
25 change| > 1.2).

[0138] Results: 412 genes displayed differential alternative splicing among the groups. They were involved in cellular immune response, cell death and cell survival pathways implicated in stroke. Distinct expression signatures based on usage of 308 exons (292 genes) differentiated the groups.

[0139] Conclusions: This pilot study demonstrates alternatively spliced genes from whole blood differ in ICH compared to ischemic stroke, and differ between different ischemic stroke etiologies.

METHODS

5 [0140] Stroke patients and control subjects were randomly selected from all those recruited at the UC Davis Medical Center between 2008 and 2012. Stroke patients were chosen to represent the major ischemic stroke etiologies (cardioembolic, large vessel, lacunar) or had intracerebral hemorrhages (ICH). Control subjects were selected to match the stroke subjects by age, race and sex, to have vascular risk factors and no cardiovascular
10 events. All subjects provided Informed Consent. The UCD Institutional Review Board approved this study. IS diagnosis and causes were assessed as previously described [5, 9]. ICH patients had deep ICH confirmed by CT and/or MRI brain scans, and were associated with hypertension without evidence of vascular malformation, tumor or aneurysm. Controls had vascular risk factors without evidence of stroke. Blood was drawn into PAXgene tubes
15 at 5.8 to 101.2h following IS or ICH. RNA from whole blood was isolated as previously described [3].

[0141] Whole blood RNA was used to prepare mRNA libraries using the TruSeq RNA Sample Prep v2 kit and protocol (Illumina). Paired-end 100bp RNA-Seq reads on whole blood RNA were obtained by Illumina Solexa sequencing by synthesis on Illumina
20 HiSeq2000 to a depth of 200×10^6 reads. Bowtie 2 was used to map reads to a reference genome (Hg19) and generate bam files for analysis [10]. RNA transcript quantification was performed using Hg19 AceView transcripts in Partek Genomics Suite 6.6 RNA-Seq workflow. DAS was determined with ANOVA on Group (FDR $p < 0.05$), and differential exon-usage was assessed between each two groups ($p < 0.0005$, $|\text{fold change}| > 1.2$).

25 [0142] Principal Component Analysis (PCA) and Hierarchical Clustering were performed in Partek. Ingenuity Pathway Analysis (IPA®) and DAVID identified regulated pathways and processes as described previously [6].

RESULTS

[0143] *Subject Demographics.* Subject demographics and clinical characteristics are
30 presented in Table 2. Only Caucasian males were studied because of the small group sizes. Demographics for age, time since event for IS or ICH, and vascular risk factors were not significantly different. Coverage of a wide range of post-stroke biology was obtained by

selecting patients with early (5.8 hours) through late (101.2 hours) blood draw times after stroke event. Although this time range seems wide, means are similar between stroke groups. Cardioembolic post-event blood draw times were, on average, 33.7 hours; large vessel averaged 47.4 hours; lacunar averaged 34.6 hours; and ICH averaged 29.4 hours (Table 2).

TABLE 2**Subjects' Characteristics.**

	Ischemic Stroke			Intracerebral Hemorrhage	Controls
	Cardioembolic	Large Vessel	Lacunar		
Subjects, no. (total n=20)	4	4	4	4	4
Age, years (mean $\pm$ SD)	62.3 $\pm$ 9.6	61.0 $\pm$ 8.2	58.9 $\pm$ 9.0	60.1 $\pm$ 2.3	60.8 $\pm$ 9.2
Time since event, hours (mean $\pm$SD)	33.7 $\pm$ 18.9	47.4 $\pm$ 47.8	34.6 $\pm$ 23.7	29.4 $\pm$ 15.5	N/A
Hypertension, no.	4	3	2	3	3
Diabetes, no.	2	2	0	0	1
Hyperlipidemia, no.	3	2	2	0	2

[0144] *RNA Sequencing Alignments.* RNA sequencing alignments statistics for all samples among the five groups are presented in Table 3. Cardioembolic stroke samples had on average, 1.60E+08 alignments; large vessel had 1.65E+08 alignments; lacunar stroke had 1.64E+08 alignments; and ICH and control each averaged 1.59E+08 alignments.

Table 3. RNA-Seq Reads

All Samples					
Sequence Length	100				
Average Quality per Read PHRED score	37				
Total Sequence Reads Mean $\pm$ SD	1.95E+08 $\pm$ 1.30E+07				
Total Alignments Mean $\pm$ SD	1.61E+08 $\pm$ 1.01E+07				
%GC Alignments Mean $\pm$ SD	54.20 $\pm$ 1.91				
Unmapped Sequences Mean $\pm$ SD	3.33E+07 $\pm$ 4.44E+06				
%GC Unmapped Sequences Mean $\pm$ SD	61.60 $\pm$ 3.45				

Total Sequence Reads		Ischemic Stroke		Intracerebral Hemorrhage	Controls
		Cardioembolic	Large Vessel	Lacunar	
Mean $\pm$ SD		1.93E+08 $\pm$ 1.07E+07	1.99E+08 $\pm$ 1.14E+07	1.99E+08 $\pm$ 1.18E+07	1.92E+08 $\pm$ 1.94E+09
Total Sequence Reads by Sample					
1	177,117,828	203,837,628		203,564,103	185,714,780
2	195,150,937	182,750,587		213,336,146	218,687,770
3	198,658,650	209,078,152		188,188,692	172,555,000
4	200,504,201	198,375,293		190,420,476	192,521,761

Number of Alignments		Ischemic Stroke		Intracerebral Hemorrhage	Controls
		Cardioembolic	Large Vessel	Lacunar	
Mean $\pm$ SD		1.60E+08 $\pm$ 9.73E+06	1.65E+08 $\pm$ 1.25E+07	1.64E+08 $\pm$ 8.34E+06	1.59E+08 $\pm$ 1.18E+07
CV (%)	6.073	7.61352		5.09486	7.46071
Mean %GC $\pm$ SD	54.75 $\pm$ 2.36	55.75 $\pm$ 0.96	53.75 $\pm$ 1.89	52.00 $\pm$ 0.82	54.75 $\pm$ 1.26

Table 3. RNA-Seq Reads

Alignments by Sample				
1	164,675,690	171,375,517	166,034,796	160,755,434
2	164,012,069	146,190,367	174,444,217	168,409,440
3	145,627,854	172,988,643	157,269,390	142,396,412
4	166,272,000	168,785,456	156,892,385	166,405,048
				157,275,379
				174,121,248
				145,330,668
				157,539,078

Number of Unmapped Sequences	Ischemic Stroke			Controls
	Cardioembolic	Large Vessel	Lacunar	
Mean $\pm$ SD	3.27E+07 $\pm$ 3.14E+06	3.37E+07 $\pm$ 3.28E+06	3.52E+07 $\pm$ 3.66E+06	3.38E+07 $\pm$ 7.94E+
Mean %GC $\pm$ SD	63.25 $\pm$ 2.63	62.25 $\pm$ 1.26	61.75 $\pm$ 1.89	63.5 $\pm$ 2.38
Unmapped Sequences by Sample				
	1	32,462,111	37,529,307	28,439,401
	2	36,560,220	38,891,929	44,566,522
	3	36,089,509	30,919,302	27,224,332
4	28,878,937	29,589,837	33,528,091	34,982,683

[0145] *Distinct Alternatively Spliced Transcriptomes from Whole Blood of Patients with ICH, Different IS Etiologies and Controls.* 412 genes display DAS in the whole blood transcriptomes of patients with IS (cardioembolic, large vessel, and lacunar), ICH and controls (FDR $p < 0.05$; Table 4). These genes are involved in cellular immunity, cytokine signaling and cell death and survival pathways (Table 5). Pathways with higher over-representation of DAS genes between groups include: CD28 signaling in T helper cells, CDC42 signaling, Nur77 signaling in T lymphocytes, fMLP signaling in neutrophils, and interferon signaling (Table 5). Molecular and cellular functions best representing the DAS genes are: cell death/survival of immune cells/leukocytes, cell-to-cell signaling and interaction, including activation, recruitment and adhesion of leukocytes, antigen presenting cells, activation of T lymphocytes, adhesion of vascular endothelial cells and immune response of neutrophils (Table 6).

[0146] *Specific Exon-Usage Profiles for IS and ICH.* Distinct differential expression signatures based on 308 exons (292 genes) ($p < 0.0005$, fold change $> |1.2|$; Table 1) separated the three causes of IS, as well as ICH and controls (PCA Figure 2A; Unsupervised Hierarchical Clustering Figure 2B). Biological functions and networks represented by genes with highly expressed exons in each group (in Figure 2B) are displayed in Table 8. Cardioembolic stroke genes with differential exon usage are involved in ion binding and transport, cellular assembly and organization. Large vessel genes are associated with cell death, transcription and chromatin remodeling. Lacunar stroke genes are associated with cellular compromise, cell cycle, cell death and survival. ICH genes are involved with protein transport and localization (Table 8).

TABLE 4. Genes (412) with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls

Gene Symbol	Gene Name	alt-splicing (Dx)	stepup (alt-splicing (Dx))
MARCH7	membrane-associated ring finger (C3HC4) 7	1.18E-05	9.07E-04
SEPT15	septin 5	3.38E-05	2.16E-03
ABCA7	ATP-binding cassette, sub-family A (ABC1), member 7	3.37E-08	7.73E-06
ACSL4/KCNE1L	acyl-CoA synthetase long-chain family member 4/KCNE1-like	6.77E-05	3.66E-03
ACTR2	ARP2 actin-related protein 2 homolog (yeast)	5.76E-20	2.57E-16
ACTR3	ARP3 actin-related protein 3 homolog (yeast)	1.29E-03	3.34E-02
ADCK2/NDUFB2	aarF domain containing kinase 2/NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8kDa	6.16E-05	3.42E-03
ADCY7	adenylate cyclase 7	6.29E-09	1.76E-06
ADD3	adducin 3 (gamma)	1.14E-05	8.90E-04
ADSS/TGIF2P1	adenylosuccinate synthase/TGFB-induced factor homeobox 2 pseudogene 1	4.63E-05	2.67E-03
AKAP8	A kinase (PRKA) anchor protein 8	1.29E-03	3.34E-02
ANAPC13	anaphase promoting complex subunit 13	1.50E-03	3.70E-02
ANKRD12	ankyrin repeat domain 12	3.96E-06	3.97E-04
ANKRD13A	ankyrin repeat domain 13A	7.49E-05	3.95E-03
ANXA1	annexin A1	8.66E-08	1.65E-05
ANXA7	annexin A7	8.70E-06	7.20E-04
AP1S2	adaptor-related protein complex 1, sigma 2 subunit pseudogene; adaptor-related protein complex 1, sigma 2 subunit	1.11E-03	2.93E-02
APAF1	apoptotic peptidase activating factor 1	1.80E-03	4.20E-02
APH1A	anterior pharynx defective 1 homolog A (C. elegans)	1.32E-03	3.40E-02
APIP	APAF1 interacting protein; similar to APAF1 interacting protein	1.35E-03	3.45E-02
APOBEC3A/APOBEC3B	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A/apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B	5.87E-04	1.81E-02
ARCN1	archain 1	2.53E-04	9.85E-03
ARFIP1/FHDC1	ADP-ribosylation factor interacting protein 1/FH2 domain containing 1	1.69E-05	1.24E-03
ARID4B/RBM34	AT rich interactive domain 4B (RBP1-like)/RNA binding motif protein 34	4.36E-05	2.56E-03
ARL6IP5	ADP-ribosylation-like factor 6 interacting protein 5	2.89E-05	1.91E-03
ARNTL	aryl hydrocarbon receptor nuclear translocator-like	1.83E-05	1.32E-03
ARPC3/ANAPC7	actin related protein 2/3 complex, subunit 3, 21kDa/anaphase promoting complex subunit 7	5.80E-11	3.45E-08
ARPC4/TLL3	actin related protein 2/3 complex, subunit 4, 20kDa/tubulin tyrosine ligase-like family member 3	3.14E-11	2.16E-08
ARPC5L	actin related protein 2/3 complex, subunit 5-like	2.44E-04	9.56E-03
ATM	similar to Serine-protein kinase ATM (Ataxia telangiectasia mutated) (A-T, mutated); ataxia telangiectasia mutated	6.24E-05	3.42E-03

TABLE 4. Genes (412) with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls

Gene Symbol	Gene Name	alt-splicing (Dx)	stepup (alt-splicing (Dx))
ATP2B4	ATPase, Ca ⁺⁺ transporting, plasma membrane 4	2.42E-04	9.54E-03
ATP5B/SNORD59A/SNORD59B	ATP synthase, H ⁺ transporting, mitochondrial F1 complex, beta polypeptide/small nucleolar RNA, C/D box 59A/small nucleolar RNA, C/D box 59B	3.76E-10	1.46E-07
ATP6V1G2/BAT1(DDX39B)/SNORD84	ATPase, H ⁺ transporting, lysosomal 13kDa, V1 subunit G2/DEAD (Asp-Glu-Ala-Asp) box polypeptide 39B/small nucleolar RNA, C/D box 84	2.39E-06	2.51E-04
ATXN1L/KIAA0174(IST1)	ataxin 1-like/increased sodium tolerance 1 homolog (yeast)	8.77E-05	4.38E-03
AZIN1	antizyme inhibitor 1	8.54E-04	2.38E-02
baboy		5.62E-04	1.76E-02
BAZ1A	bromodomain adjacent to zinc finger domain, 1A	7.63E-04	2.21E-02
BAZ2B	bromodomain adjacent to zinc finger domain, 2B	4.42E-04	1.49E-02
BTN2A2/BTN3A1	butyrophilin, subfamily 2, member A2/butyrophilin, subfamily 3, member A1	3.13E-06	3.21E-04
C11orf73	chromosome 11 open reading frame 73	1.71E-03	4.08E-02
C15orf29	chromosome 15 open reading frame 29	5.37E-08	1.17E-05
C1orf59	chromosome 1 open reading frame 59	5.42E-05	3.03E-03
C1orf63	chromosome 1 open reading frame 63	1.10E-12	1.40E-09
C5orf15	chromosome 5 open reading frame 15	5.26E-04	1.67E-02
C6orf62	chromosome 6 open reading frame 62	1.51E-04	6.62E-03
C7orf27	chromosome 7 open reading frame 27	7.25E-04	2.11E-02
C9orf114	chromosome 9 open reading frame 114	2.31E-04	9.15E-03
C9orf72	chromosome 9 open reading frame 72	5.43E-04	1.71E-02
CAB39	calcium binding protein 39	9.34E-05	4.56E-03
CALM1	calmodulin 3 (phosphorylase kinase, delta); calmodulin 2 (phosphorylase kinase, delta); calmodulin 1 (phosphorylase kinase, delta)	2.24E-07	3.77E-05
CALM2/C2orf61	calmodulin 2 (phosphorylase kinase, delta)/chromosome 2 open reading frame 61	3.70E-12	3.00E-09
CAPZA2	capping protein (actin filament) muscle Z-line, alpha 2	6.35E-04	1.91E-02
CARD8	caspase recruitment domain family, member 8	5.51E-08	1.17E-05
CBARA1	calcium binding atopy-related autoantigen 1	2.87E-04	1.08E-02
CCAR1	cell division cycle and apoptosis regulator 1	1.61E-05	1.19E-03
CCNDBP1	cyclin D-type binding-protein 1	3.17E-10	1.29E-07
CCNY	cyclin Y	1.68E-04	7.13E-03
CCT8	similar to chaperonin containing TCP1, subunit 8 (theta); chaperonin containing TCP1, subunit 8 (theta)	2.19E-03	4.80E-02
CD164	CD164 molecule, sialomucin	1.82E-05	1.32E-03
CD244	CD244 molecule, natural killer cell receptor 2B4	6.82E-04	2.03E-02
CD300E	CD300e molecule	1.05E-04	4.97E-03
CD36	CD36 molecule (thrombospondin receptor)	2.83E-07	4.60E-05

TABLE 4. Genes (412) with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls

Gene Symbol	Gene Name	alt-splicing (Dx)	stepup (alt-splicing (Dx))
CD46	CD46 molecule, complement regulatory protein	4.46E-06	4.29E-04
CD47	CD47 molecule	4.97E-15	9.66E-12
CD53	CD53 molecule	1.52E-04	6.62E-03
CD58	CD58 molecule	2.07E-04	8.41E-03
CD74	CD74 molecule, major histocompatibility complex, class II invariant chain	6.89E-04	2.03E-02
CD86	CD86 molecule	1.60E-03	3.88E-02
CDC42SE1	CDC42 small effector 1	1.70E-06	1.97E-04
CDC42SE2	CDC42 small effector 2	3.58E-04	1.26E-02
CDKL3/PPP2CA	cyclin-dependent kinase-like 3/protein phosphatase 2, catalytic subunit, alpha isozyme	3.66E-05	2.26E-03
CDKN1C	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	2.33E-05	1.59E-03
CECR1	cat eye syndrome chromosome region, candidate 1	6.88E-06	5.97E-04
CELF2	CUG triplet repeat, RNA binding protein 2	3.17E-04	1.14E-02
CFLAR/RNU7-45P	CASP8 and FADD-like apoptosis regulator/RNA, U7 small nuclear 45 pseudogene	1.42E-08	3.64E-06
CGGBP1	CGG triplet repeat binding protein 1	7.87E-05	4.06E-03
CHMP2B	chromatin modifying protein 2B	1.42E-03	3.57E-02
CLDND1	claudin domain containing 1	2.13E-06	2.32E-04
CLEC7A	C-type lectin domain family 7, member A	8.25E-10	3.02E-07
CLTC	clathrin, heavy chain (Hc)	2.74E-04	1.04E-02
CNIH	cornichon homolog (Drosophila)	1.84E-04	7.55E-03
CNOT6L	CCR4-NOT transcription complex, subunit 6-like	6.04E-04	1.85E-02
CNOT7	CCR4-NOT transcription complex, subunit 7	2.15E-03	4.75E-02
CNOT8	CCR4-NOT transcription complex, subunit 8	3.00E-04	1.10E-02
COMMD2	canopy 2 homolog (zebrafish)	1.41E-03	3.55E-02
CRKL	COMM domain containing 2	1.14E-03	3.00E-02
CSGALNACT2	chondroitin sulfate N-acetylgalactosaminyltransferase 2; novel protein similar to chondroitin sulfate GalNAcT-2 (GALNACT-2)	3.60E-05	2.26E-03
CTDSP2	similar to hCG2013701; CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase 2	5.61E-04	1.76E-02
CTSS	cathepsin S	1.46E-06	1.76E-04
CYBB	cytochrome b-245, beta polypeptide	7.15E-09	1.94E-06
CYBRD1	cytochrome b reductase 1	2.31E-05	1.59E-03
CYLD	cylindromatosis (turban tumor syndrome)	1.37E-03	3.47E-02
DAP3	death associated protein 3	2.13E-03	4.74E-02
DCP2	DCP2 decapping enzyme homolog (S. cerevisiae)	3.88E-07	5.69E-05
DDX19B/DDX19A	DEAD (Asp-Glu-Ala-Asp) box polypeptide 19B/DEAD (Asp-Glu-Ala-Asp) box polypeptide 19A	3.10E-04	1.13E-02
DDX3X	DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, X-linked	1.37E-12	1.53E-09

TABLE 4. Genes (412) with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls

Gene Symbol	Gene Name	alt-splicing (Dx)	stepup (alt-splicing (Dx))
DDX60L	DEAD (Asp-Glu-Ala-Asp) box polypeptide 60-like	4.35E-06	4.27E-04
DEGS1	degenerative spermatocyte homolog 1, lipid desaturase (Drosophila)	1.25E-04	5.67E-03
DENND5A	DENN/MADD domain containing 5A	3.64E-07	5.45E-05
DHX40	similar to DEAH (Asp-Glu-Ala-His) box polypeptide 40; DEAH (Asp-Glu-Ala-His) box polypeptide 40	7.11E-04	2.08E-02
DMXL2	Dmx-like 2	7.29E-12	5.43E-09
DNAJB6	DnaJ (Hsp40) homolog, subfamily B, member 6	1.20E-04	5.52E-03
DNTTIP1	deoxynucleotidyltransferase, terminal, interacting protein 1	1.88E-03	4.29E-02
DPEP2/DPEP3	dipeptidase 2/dipeptidase 3	5.43E-05	3.03E-03
DPY30/MEMO1	dpy-30 homolog (C. elegans)/mediator of cell motility 1	2.26E-03	4.91E-02
DPYD	dihydropyrimidine dehydrogenase	8.13E-08	1.61E-05
DTX3L	deltex 3-like (Drosophila)	3.95E-04	1.37E-02
DUSP22	similar to mitogen-activated protein kinase phosphatase x; dual specificity phosphatase 22	7.74E-04	2.21E-02
DYNC1LI1	dynein, cytoplasmic 1, light intermediate chain 1	7.00E-04	2.06E-02
DYNC1LI2	dynein, cytoplasmic 1, light intermediate chain 2	3.68E-05	2.26E-03
DYX1C1/CCPG1	dyslexia susceptibility 1 candidate 1/cell cycle progression 1	7.61E-05	3.95E-03
EAPP	E2F-associated phosphoprotein	5.17E-04	1.67E-02
ECHDC1	enoyl Coenzyme A hydratase domain containing 1	7.45E-06	6.34E-04
ECHDC2	enoyl Coenzyme A hydratase domain containing 2	9.29E-04	2.55E-02
EGLN1	egl nine homolog 1 (C. elegans)	2.12E-04	8.51E-03
EIF2AK2	eukaryotic translation initiation factor 2-alpha kinase 2	1.63E-03	3.91E-02
EIF2S1	eukaryotic translation initiation factor 2, subunit 1 alpha, 35kDa	4.13E-04	1.42E-02
ELP2	elongation protein 2 homolog (S. cerevisiae)	1.01E-05	8.06E-04
EMB	embigin homolog (mouse)	1.03E-10	5.41E-08
EPHB4	EPH receptor B4	1.48E-03	3.67E-02
ERAP1	endoplasmic reticulum aminopeptidase 1	8.18E-05	4.13E-03
ERBB2IP	erbb2 interacting protein	6.97E-05	3.73E-03
ERN1	endoplasmic reticulum to nucleus signaling 1	1.70E-03	4.07E-02
ETNK1	ethanolamine kinase 1	1.83E-03	4.23E-02
FAM111B/FAM111A	family with sequence similarity 111, member B/family with sequence similarity 111, member A	1.78E-03	4.16E-02
FAM118A	family with sequence similarity 118, member A	9.23E-10	3.13E-07
FAM198B	chromosome 4 open reading frame 18	2.90E-04	1.08E-02
FAM45A	family with sequence similarity 45, member A	2.11E-04	8.51E-03
FBXL3	F-box and leucine-rich repeat protein 3	2.01E-04	8.22E-03
FBXL5	F-box and leucine-rich repeat protein 5	1.40E-06	1.71E-04
FCER1A	Fc fragment of IgE, high affinity I, receptor for; alpha	6.21E-07	8.53E-05

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Gene Symbol	Gene Name	alt-splicing (Dx)	stepup (alt-splicing (Dx))
	polypeptide		
FKBP1A/SDCBP2	FK506 binding protein 1A, 12kDa/syndecan binding protein (syntenin) 2	1.09E-03	2.89E-02
FNTA	farnesyltransferase, CAAX box, alpha	2.84E-08	6.86E-06
GALNT1	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 13 (GalNAc-T13); UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 1 (GalNAc-T1)	3.80E-09	1.13E-06
GBP4/GBP7/GBP2	guanylate binding protein 4/guanylate binding protein 7/guanylate binding protein 2, interferon-inducible	3.67E-05	2.26E-03
GCA	grancalcin, EF-hand calcium binding protein	2.92E-07	4.66E-05
GGNBP2	gametogenetin binding protein 2	1.12E-04	5.26E-03
GHITM	growth hormone inducible transmembrane protein	9.44E-07	1.22E-04
GIT2	G protein-coupled receptor kinase interacting ArfGAP 2	5.73E-04	1.78E-02
GLRX	glutaredoxin (thioltransferase)	5.22E-04	1.67E-02
GLUD1	glutamate dehydrogenase 1	4.22E-05	2.52E-03
GMCL1	germ cell-less homolog 1 (Drosophila)-like; germ cell-less homolog 1 (Drosophila)	4.91E-04	1.62E-02
GPX1	glutathione peroxidase 1	1.77E-03	4.15E-02
GSTK1	glutathione S-transferase kappa 1	1.77E-04	7.34E-03
GSTO1	glutathione S-transferase omega 1	4.25E-04	1.44E-02
GTF2I	general transcription factor II, i; general transcription factor II, i, pseudogene	1.39E-05	1.04E-03
GZMA	granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3)	1.27E-03	3.31E-02
H2AFZ	H2A histone family, member Z	8.03E-04	2.26E-02
H3F3B	H3 histone, family 3B (H3.3B); H3 histone, family 3A pseudogene; H3 histone, family 3A; similar to H3 histone, family 3B; similar to histone H3.3B	1.90E-03	4.32E-02
HBP1	HMG-box transcription factor 1	7.69E-04	2.21E-02
HDC	histidine decarboxylase	1.26E-03	3.28E-02
HERC3	hect domain and RLD 3	4.70E-07	6.67E-05
HERC5	hect domain and RLD 5	1.03E-05	8.14E-04
hetira		7.84E-04	2.22E-02
HEXB	hexosaminidase B (beta polypeptide)	3.00E-04	1.10E-02
HIPK3	homeodomain interacting protein kinase 3	2.01E-10	9.45E-08
HLA-DMA/HLA-DMB	major histocompatibility complex, class II, DM alpha/major histocompatibility complex, class II, DM beta	5.32E-05	3.01E-03
HLA-DQA1	similar to hCG2042724; similar to HLA class II histocompatibility antigen, DQ(1) alpha chain precursor (DC-4 alpha chain); major histocompatibility complex, class II, DQ alpha 1	1.89E-03	4.31E-02

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Gene Symbol	Gene Name	alt-splicing (Dx)	stepup (alt-splicing (Dx))
HLA-DRB1	major histocompatibility complex, class II, DR beta 4; major histocompatibility complex, class II, DR beta 1	2.35E-06	2.49E-04
HMGB1	high-mobility group box 1; high-mobility group box 1-like 10	1.45E-03	3.64E-02
HMGCL/GALE	3-hydroxymethyl-3-methylglutaryl-CoA lyase/UDP-galactose-4-epimerase	1.02E-03	2.73E-02
HMGN4	high mobility group nucleosomal binding domain 4	7.64E-06	6.44E-04
HNRNPA2B1	heterogeneous nuclear ribonucleoprotein A2/B1	5.52E-06	4.93E-04
HNRNPAB	heterogeneous nuclear ribonucleoprotein A/B	3.04E-04	1.11E-02
HNRNPH3	heterogeneous nuclear ribonucleoprotein H3 (2H9)	2.16E-06	2.32E-04
HP1BP3	heterochromatin protein 1, binding protein 3	1.62E-03	3.90E-02
HSD17B11/HSD17B13	hydroxysteroid (17-beta) dehydrogenase 11/hydroxysteroid (17-beta) dehydrogenase 13	6.11E-04	1.86E-02
HSD17B4/FAM170A	hydroxysteroid (17-beta) dehydrogenase 4/family with sequence similarity 170, member A	2.19E-05	1.52E-03
HSPC157 (LINC00339)/CDC42	long intergenic non-protein coding RNA 339 / cell division cycle 42	1.01E-03	2.72E-02
IDH1	isocitrate dehydrogenase 1 (NADP+), soluble	7.39E-06	6.34E-04
IFIH1	interferon induced with helicase C domain 1	5.00E-04	1.65E-02
IFNAR1	interferon (alpha, beta and omega) receptor 1	3.13E-04	1.13E-02
IFNGR1	interferon gamma receptor 1	3.75E-11	2.39E-08
IFRD1/C7orf53 (LSMEM1)	interferon-related developmental regulator 1/leucine-rich single-pass membrane protein 1	8.87E-04	2.44E-02
IGFBP7	insulin-like growth factor binding protein 7	3.17E-04	1.14E-02
IKZF1	IKAROS family zinc finger 1 (Ikaro)	1.72E-03	4.10E-02
ING4	inhibitor of growth family, member 4	1.09E-06	1.39E-04
IPMK	inositol polyphosphate multikinase	5.25E-04	1.67E-02
IQGAP2	IQ motif containing GTPase activating protein 2	8.51E-04	2.38E-02
ITGA4	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	5.23E-06	4.77E-04
JAK2	Janus kinase 2	5.67E-07	7.92E-05
JMJD1C	jumonji domain containing 1C	1.42E-05	1.05E-03
KIAA1033	KIAA1033	7.58E-05	3.95E-03
kihire		2.02E-03	4.56E-02
KLF13	Kruppel-like factor 13	1.75E-03	4.14E-02
LACTB	lactamase, beta	2.22E-07	3.77E-05
LAPTM4A	lysosomal protein transmembrane 4 alpha	1.81E-03	4.20E-02
LEMD3	LEM domain containing 3	4.59E-04	1.54E-02
LILRA3	leukocyte immunoglobulin-like receptor, subfamily A (without TM domain), member 3	6.01E-04	1.84E-02
LMBRD1	LMBR1 domain containing 1	1.82E-03	4.21E-02
LMO4	LIM domain only 4	1.07E-04	5.08E-03

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Gene Symbol	Gene Name	alt-splicing (Dx)	stepup (alt-splicing (Dx))
LOC100093631	general transcription factor II, i; general transcription factor II, i, pseudogene	1.74E-04	7.26E-03
LOC100132062	hypothetical LOC100132062	2.07E-03	4.63E-02
LOC100288778	similar to WAS protein family homolog 1	1.53E-04	6.62E-03
LOC146880	hypothetical LOC146880	5.27E-04	1.67E-02
LOC728054	hypothetical LOC728054	1.76E-06	2.01E-04
LPCAT2/CAPNS2	lysophosphatidylcholine acyltransferase 2/calpain, small subunit 2	1.01E-04	4.87E-03
LRMP	lymphoid-restricted membrane protein	8.68E-04	2.42E-02
LRRFIP2	leucine rich repeat (in FLII) interacting protein 2	6.70E-07	9.07E-05
LRRK2	leucine-rich repeat kinase 2	2.43E-05	1.64E-03
LTA4H	leukotriene A4 hydrolase	8.88E-05	4.41E-03
LY75/CD302	lymphocyte antigen 75/CD302 molecule	6.74E-18	2.01E-14
MALAT1	metastasis associated lung adenocarcinoma transcript 1 (non-protein coding)	1.73E-04	7.26E-03
MAN1A1	mannosidase, alpha, class 1A, member 1	6.62E-05	3.61E-03
MAT2B	methionine adenosyltransferase II, beta	1.16E-04	5.41E-03
MCL1	myeloid cell leukemia sequence 1 (BCL2-related)	2.05E-03	4.60E-02
MED4	mediator complex subunit 4	6.30E-06	5.52E-04
MEGF9	multiple EGF-like-domains 9	1.54E-03	3.77E-02
METTL9	methyltransferase like 9	7.05E-08	1.46E-05
MFSD1	major facilitator superfamily domain containing 1	2.99E-05	1.95E-03
MGST1	microsomal glutathione S-transferase 1	3.86E-05	2.33E-03
MIAT	myocardial infarction associated transcript (non-protein coding)	9.16E-08	1.70E-05
MICA/HCP5	MHC class I polypeptide-related sequence A/HLA complex P5 (non-protein coding)	2.15E-05	1.50E-03
MLX	MAX-like protein X	2.24E-03	4.89E-02
MMADHC	methylmalonic aciduria (cobalamin deficiency) cblD type, with homocystinuria	1.65E-04	7.08E-03
MOBK1B	MOB1, Mps One Binder kinase activator-like 1B (yeast)	7.62E-11	4.25E-08
MPPE1	metallophosphoesterase 1	4.29E-13	6.39E-10
MRPL15	mitochondrial ribosomal protein L15	6.55E-04	1.96E-02
MS4A6E/MS4A7/MS4A14	membrane-spanning 4-domains, subfamily A, member 6E/membrane-spanning 4-domains, subfamily A, member 7/membrane-spanning 4-domains, subfamily A, member 14	1.84E-04	7.55E-03
MSMB/NCOA4	microseminoprotein, beta-/nuclear receptor coactivator 4	9.13E-06	7.48E-04
MTCH1	mitochondrial carrier homolog 1 (C. elegans)	1.04E-03	2.76E-02
MTMR1	myotubularin related protein 1	7.73E-04	2.21E-02
MTMR6	myotubularin related protein 6	5.13E-04	1.67E-02
MTO1	mitochondrial translation optimization 1 homolog (S. cerevisiae)	3.83E-05	2.33E-03

TABLE 4. Genes (412) with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls

Gene Symbol	Gene Name	alt-splicing (Dx)	stepup (alt-splicing (Dx))
MTPN/LUZP6	myotrophin/leucine zipper protein 6	5.15E-04	1.67E-02
MX1	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)	3.36E-12	3.00E-09
MYL12A	myosin, light chain 12A, regulatory, non-sarcomeric	1.66E-06	1.95E-04
MYLIP	myosin regulatory light chain interacting protein	1.61E-03	3.88E-02
NAB1	NGFI-A binding protein 1 (EGR1 binding protein 1)	7.51E-05	3.95E-03
NAP1L1	nucleosome assembly protein 1-like 1	1.58E-03	3.84E-02
NAPSB	napsin B aspartic peptidase pseudogene	5.81E-06	5.14E-04
NARS	asparaginyl-tRNA synthetase	1.26E-04	5.70E-03
NBPF9/NOTCH2NL/NBPF10	neuroblastoma breakpoint family, member 9/notch 2 N-terminal like/neuroblastoma breakpoint family, member 10	7.79E-04	2.21E-02
NBR2/NBR1	neighbor of BRCA1 gene 2 (non-protein coding)/neighbor of BRCA1 gene 1	1.77E-03	4.15E-02
NCRNA00189 (LINC00189)/GAPDHP14/BACH1	long intergenic non-protein coding RNA 189/glyceraldehyde-3-phosphate dehydrogenase pseudogene 14/BTB and CNC homology 1, basic leucine zipper transcription factor 1	4.89E-06	4.50E-04
NDFIP1	Nedd4 family interacting protein 1	2.26E-03	4.91E-02
NEK9	NIMA (never in mitosis gene a)- related kinase 9	2.94E-04	1.09E-02
NFE2L2	nuclear factor (erythroid-derived 2)-like 2	3.18E-04	1.14E-02
NR3C1	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	3.02E-06	3.14E-04
NSUN2	NOL1/NOP2/Sun domain family, member 2	8.40E-06	7.02E-04
OAS2	2'-5'-oligoadenylate synthetase 2, 69/71kDa	2.12E-04	8.51E-03
OAS3	2'-5'-oligoadenylate synthetase 3, 100kDa	1.07E-03	2.84E-02
OAZ2	ornithine decarboxylase antizyme 2	7.72E-04	2.21E-02
OGFRL1	opioid growth factor receptor-like 1	4.09E-04	1.42E-02
PAFAH1B1	platelet-activating factor acetylhydrolase, isoform lb, subunit 1 (45kDa)	4.60E-05	2.67E-03
PAN2/CNPY2/CS	PAN2 poly(A) specific ribonuclease subunit/canopy FGF signaling regulator 2/ citrate synthase	2.94E-05	1.93E-03
PAPOLA	poly(A) polymerase alpha	1.41E-03	3.55E-02
PARP14	poly (ADP-ribose) polymerase family, member 14	3.54E-08	7.91E-06
PARP9	poly (ADP-ribose) polymerase family, member 9	1.25E-04	5.67E-03
PCMTD2	protein-L-isoaspartate (D-aspartate) O-methyltransferase domain containing 2	9.19E-05	4.51E-03
PDPR	pyruvate dehydrogenase phosphatase regulatory subunit	3.87E-04	1.35E-02
PELI1	pellino homolog 1 (Drosophila)	2.46E-07	4.07E-05
PGK1	phosphoglycerate kinase 1	2.08E-05	1.48E-03
PHB2/SCARNA12	prohibitin 2/SCARNA12	6.25E-04	1.89E-02
PHIP/TRNAF13P (TRF-GAA8-1)	pleckstrin homology domain interacting protein/ transfer RNA-Phe (GAA) 8-1	2.70E-04	1.04E-02

TABLE 4. Genes (412) with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls

Gene Symbol	Gene Name	alt-splicing (Dx)	stepup (alt-splicing (Dx))
PJA2	praja ring finger 2	4.33E-06	4.27E-04
PLCL2	phospholipase C-like 2	1.94E-03	4.40E-02
PLDN (BLOC1S6)/SQRD	biogenesis of lysosomal organelles complex-1, subunit 6, pallidin/sulfide quinone reductase-like (yeast)	2.21E-03	4.84E-02
PLEK	pleckstrin	1.86E-09	5.93E-07
PLEKHB2	pleckstrin homology domain containing, family B (evectins) member 2	3.65E-07	5.45E-05
PLEKHM1P	pleckstrin homology domain containing, family M (with RUN domain) member 1 pseudogene	4.23E-04	1.44E-02
PNRC1	proline-rich nuclear receptor coactivator 1	1.57E-03	3.82E-02
PPIL3/CLK1	peptidylprolyl isomerase (cyclophilin)-like 3/CDC-like kinase 1	5.88E-04	1.81E-02
PPP1CB/SPDYA	protein phosphatase 1, catalytic subunit, beta isozyme/speedy/RINGO cell cycle regulator family member A	4.45E-06	4.29E-04
PPP1CC	protein phosphatase 1, catalytic subunit, gamma isoform	8.17E-05	4.13E-03
PPP1R15B	protein phosphatase 1, regulatory (inhibitor) subunit 15B	1.38E-03	3.50E-02
PPP2R5A	protein phosphatase 2, regulatory subunit B', alpha isoform	1.25E-07	2.24E-05
PPP3CB	protein phosphatase 3 (formerly 2B), catalytic subunit, beta isoform	2.19E-04	8.68E-03
PPP3R1/WDR92	protein phosphatase 3, regulatory subunit B, alpha/WD repeat domain 92	1.50E-06	1.79E-04
PPP4R1	protein phosphatase 4, regulatory subunit 1	5.17E-04	1.67E-02
PPP6C	protein phosphatase 6, catalytic subunit	1.84E-04	7.55E-03
PPTC7	PTC7 protein phosphatase homolog (S. cerevisiae)	4.64E-05	2.67E-03
PRCP	prolylcarboxypeptidase (angiotensinase C)	1.01E-03	2.72E-02
PRMT2	protein arginine methyltransferase 2	1.75E-03	4.14E-02
PRNP	prion protein	5.70E-04	1.77E-02
PRPF38B	PRP38 pre-mRNA processing factor 38 (yeast) domain containing B	7.61E-04	2.21E-02
PSMA1/COPB1	proteasome (prosome, macropain) subunit, alpha type, 1/coatome protein complex, subunit beta 1	2.16E-03	4.76E-02
PSMB3	proteasome (prosome, macropain) subunit, beta type, 3	2.03E-03	4.56E-02
PSMB8	proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional peptidase 7)	6.21E-05	3.42E-03
PSMD13	proteasome (prosome, macropain) 26S subunit, non-ATPase, 13	8.66E-07	1.14E-04
PSMD6	proteasome (prosome, macropain) 26S subunit, non-ATPase, 6	3.66E-07	5.45E-05
PTGER4	prostaglandin E receptor 4 (subtype EP4)	6.30E-04	1.90E-02
PTPRC	protein tyrosine phosphatase, receptor type, C	1.77E-23	1.59E-19
PXK	PX domain containing serine/threonine kinase	2.74E-04	1.04E-02
RAB10	RAB10, member RAS oncogene family	8.67E-07	1.14E-04

TABLE 4. Genes (412) with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls

Gene Symbol	Gene Name	alt-splicing (Dx)	stepup (alt-splicing (Dx))
RAB1A	RAB1A, member RAS oncogene family	1.18E-04	5.47E-03
RAB32	RAB32, member RAS oncogene family	1.48E-03	3.67E-02
RAB6A	RAB6C, member RAS oncogene family; RAB6A, member RAS oncogene family; hypothetical LOC100130819; RAB6C-like	1.20E-04	5.51E-03
RAB8B	RAB8B, member RAS oncogene family	2.86E-04	1.08E-02
RAD21	RAD21 homolog (S. pombe)	2.14E-03	4.74E-02
RAF1	v-raf-1 murine leukemia viral oncogene homolog 1	4.83E-04	1.61E-02
RAP1A	RAP1A, member of RAS oncogene family	4.21E-09	1.21E-06
RAP1B	RAP1B, member of RAS oncogene family	3.01E-12	2.99E-09
RASSF3	Ras association (RaGDS/AF-6) domain family member 3	1.51E-03	3.70E-02
RBBP4	hypothetical LOC642954; retinoblastoma binding protein 4	9.69E-04	2.64E-02
RBL2	retinoblastoma-like 2 (p130)	4.62E-06	4.30E-04
RECQL	RecQ protein-like (DNA helicase Q1-like)	4.93E-05	2.82E-03
RFWD2	ring finger and WD repeat domain 2	9.23E-06	7.50E-04
RGS18	regulator of G-protein signaling 18	8.81E-04	2.43E-02
RICTOR	RPTOR independent companion of MTOR, complex 2	3.07E-08	7.22E-06
RILPL2	Rab interacting lysosomal protein-like 2	4.59E-06	4.30E-04
RIT1	Ras-like without CAAX 1	1.18E-04	5.47E-03
RNF103/VPS24 (CHMP3)	ring finger protein 103/charged multivesicular body protein 3	5.29E-04	1.67E-02
RNF13	ring finger protein 13	1.73E-08	4.30E-06
RNF141	ring finger protein 141	1.20E-05	9.15E-04
RNF145	ring finger protein 145	7.82E-09	2.06E-06
RNF213	ring finger protein 213	1.13E-10	5.60E-08
RNF31/IRF9	ring finger protein 31/interferon regulatory factor 9	2.70E-04	1.04E-02
RNF5	ring finger protein 5; ring finger protein 5 pseudogene 1	1.97E-03	4.45E-02
RNF6	ring finger protein (C3H2C3 type) 6	4.21E-04	1.44E-02
ROCK1	similar to Rho-associated, coiled-coil containing protein kinase 1; Rho-associated, coiled-coil containing protein kinase 1	1.46E-03	3.65E-02
RPL14.1	ribosomal protein L14	1.80E-03	4.19E-02
S100A6	S100 calcium binding protein A6	1.51E-03	3.70E-02
SACM1L	SAC1 suppressor of actin mutations 1-like (yeast)	5.04E-04	1.66E-02
SAR1A/TYSND1/AIFM2	secretion associated, Ras related GTPase 1A/trypsin domain containing 1/apoptosis-inducing factor, mitochondrion-associated, 2	3.26E-07	5.12E-05
SCP2	sterol carrier protein 2	4.97E-05	2.83E-03
SCPEP1	serine carboxypeptidase 1	8.05E-05	4.11E-03
SDHD	succinate dehydrogenase complex, subunit D, integral membrane protein	2.18E-03	4.80E-02
SEC22B	SEC22 vesicle trafficking protein homolog B (S.	4.13E-04	1.42E-02

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Gene Symbol	Gene Name	alt-splicing (Dx)	stepup (alt-splicing (Dx))
	cerevisiae)		
SEC61B	Sec61 beta subunit	8.05E-05	4.11E-03
SELE/SELL	selectin E/selectin L	2.96E-04	1.10E-02
SEN6	SUMO1/sentrin specific peptidase 6	1.73E-03	4.10E-02
SEPT5/GP1BB	septin 5/glycoprotein Ib (platelet), beta polypeptide	1.31E-03	3.38E-02
SERINC1	serine incorporator 1	1.36E-07	2.39E-05
SERINC3	serine incorporator 3	1.02E-04	4.88E-03
SKAP2	src kinase associated phosphoprotein 2	1.03E-03	2.76E-02
SKIV2L2	superkiller viralicidic activity 2-like 2 (S. cerevisiae)	1.61E-04	6.94E-03
SLA	Src-like-adaptor	3.32E-04	1.18E-02
SLBP	stem-loop binding protein	1.87E-03	4.29E-02
SLC12A7	solute carrier family 12 (potassium/chloride transporters), member 7	2.26E-03	4.91E-02
SLC25A37	solute carrier family 25, member 37	9.13E-05	4.51E-03
SLK	STE20-like kinase (yeast)	1.49E-04	6.55E-03
SLU7	SLU7 splicing factor homolog (S. cerevisiae)	8.40E-04	2.36E-02
SMAP2	small ArfGAP2	1.92E-03	4.35E-02
SMARCA5	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 5	9.51E-04	2.60E-02
SMCHD1	structural maintenance of chromosomes flexible hinge domain containing 1	2.21E-10	9.86E-08
SNX10	sorting nexin 10	1.40E-06	1.71E-04
SNX14	sorting nexin 14	2.09E-06	2.30E-04
SNX2	sorting nexin 2	1.60E-03	3.88E-02
SNX6	sorting nexin 6	3.38E-05	2.16E-03
SP140L/SP100/HMGB1L3	SP140 nuclear body protein-like/SP100 nuclear antigen/high mobility group box 1 pseudogene 3	1.69E-04	7.17E-03
SPATA13/C1QTNF9	spermatogenesis associated 13/C1q and tumor necrosis factor related protein 9	1.80E-06	2.01E-04
SPCS3	signal peptidase complex subunit 3 homolog (S. cerevisiae)	4.54E-06	4.30E-04
SPOPL	speckle-type POZ protein-like	8.45E-10	3.02E-07
SPPL2A	signal peptide peptidase-like 2A	3.22E-05	2.08E-03
SRI	sorcin	3.49E-06	3.54E-04
SRP9/EPHX1	signal recognition particle 9kDa/epoxide hydrolase 1, microsomal (xenobiotic)	7.37E-08	1.50E-05
SSFA2	sperm specific antigen 2	9.73E-04	2.64E-02
ST8SIA4	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 4	1.14E-03	3.00E-02
STAT1	signal transducer and activator of transcription 1, 91kDa	8.77E-04	2.43E-02
STOM	stomatin	4.35E-05	2.56E-03
STXBP3	syntaxin binding protein 3	1.24E-06	1.56E-04

TABLE 4. Genes (412) with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls

Gene Symbol	Gene Name	alt-splicing (Dx)	stepup (alt-splicing (Dx))
SURF4	surfeit 4	1.20E-03	3.15E-02
SYTL2	synaptotagmin-like 2	9.74E-04	2.64E-02
TAF1	TAF1 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 250kDa	4.42E-04	1.49E-02
TAGAP	T-cell activation RhoGTPase activating protein	1.01E-04	4.87E-03
TAX1BP1	Tax1 (human T-cell leukemia virus type I) binding protein 1	1.91E-05	1.36E-03
TBC1D2B	TBC1 domain family, member 2B	6.79E-05	3.66E-03
TCF25/MC1R/TUBB3	transcription factor 25 (basic helix-loop-helix)/melanocortin 1 receptor (alpha melanocyte stimulating hormone receptor)/tubulin, beta 3 class III	2.12E-09	6.52E-07
TCP11L2	t-complex 11 (mouse)-like 2	3.73E-04	1.31E-02
TDG	similar to G/T mismatch-specific thymine DNA glycosylase; thymine-DNA glycosylase	1.87E-03	4.29E-02
TDP2	tyrosyl-DNA phosphodiesterase 2	1.70E-03	4.07E-02
TES	testis derived transcript (3 LIM domains)	2.74E-04	1.04E-02
TGFBR2	transforming growth factor, beta receptor II (70/80kDa)	1.05E-04	4.97E-03
TM9SF2	transmembrane 9 superfamily member 2	2.95E-10	1.25E-07
TM9SF3	transmembrane 9 superfamily member 3	1.74E-04	7.26E-03
TMCC1	transmembrane and coiled-coil domain family 1	2.13E-04	8.52E-03
TMCO3	transmembrane and coiled-coil domains 3	7.11E-05	3.78E-03
TMEM167B	transmembrane protein 167B	2.78E-05	1.85E-03
TMEM222	transmembrane protein 222	1.41E-04	6.27E-03
TMEM49	transmembrane protein 49	5.38E-06	4.86E-04
TMEM59	transmembrane protein 59	8.49E-05	4.26E-03
TMSB4X	thymosin-like 2 (pseudogene); thymosin-like 1 (pseudogene); thymosin beta 4, X-linked	6.06E-04	1.85E-02
TNFSF13B	tumor necrosis factor (ligand) superfamily, member 13b	3.47E-04	1.23E-02
TNKS2	tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase 2	8.73E-04	2.42E-02
TNPO3	transportin 3	4.02E-05	2.41E-03
TOPORS/DDX58	topoisomerase I binding, arginine/serine-rich, E3 ubiquitin protein ligase/DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	6.89E-04	2.03E-02
TOR1A	torsin family 1, member A (torsin A)	1.11E-07	2.02E-05
TOR1AIP1	torsin A interacting protein 1	5.49E-04	1.73E-02
TPM3	tropomyosin 3	4.32E-07	6.23E-05
TRAM1	translocation associated membrane protein 1	1.79E-06	2.01E-04
TRPC4AP	transient receptor potential cation channel, subfamily C, member 4 associated protein	1.30E-05	9.81E-04
TSNAX/DISC1	translin-associated factor X/disrupted in schizophrenia 1	4.89E-04	1.62E-02
TSPAN14	tetraspanin 14	1.16E-05	8.98E-04
TXNRD1	thioredoxin reductase 1; hypothetical LOC100130902	8.52E-08	1.65E-05
U2AF1	U2 small nuclear RNA auxiliary factor 1	3.82E-05	2.33E-03

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Gene Symbol	Gene Name	alt-splicing (Dx)	stepup (alt-splicing (Dx))
UBE2B	ubiquitin-conjugating enzyme E2B (RAD6 homolog)	2.65E-04	1.02E-02
UBE2E3	ubiquitin-conjugating enzyme E2E 3 (UBC4/5 homolog, yeast)	6.50E-04	1.95E-02
UBL7	ubiquitin-like 7 (bone marrow stromal cell-derived)	2.09E-03	4.66E-02
UBR2	ubiquitin protein ligase E3 component n-recognin 2	7.78E-04	2.21E-02
UHMK1	U2AF homology motif (UHM) kinase 1	1.28E-03	3.32E-02
USP1	ubiquitin specific peptidase 1	1.36E-03	3.47E-02
USP15	ubiquitin specific peptidase 15	2.60E-05	1.75E-03
USP33	ubiquitin specific peptidase 33	7.17E-04	2.09E-02
UTRN	utrophin	5.40E-15	9.66E-12
VAMP3	vesicle-associated membrane protein 3 (cellubrevin)	1.62E-04	6.94E-03
VCP	valosin-containing protein	6.72E-04	2.00E-02
VNN2	vanin 2	1.49E-03	3.69E-02
VPS13C	vacuolar protein sorting 13 homolog C (S. cerevisiae)	3.31E-04	1.18E-02
WARS	tryptophanyl-tRNA synthetase	1.44E-04	6.37E-03
WDFY2	WD repeat and FYVE domain containing 2	1.87E-03	4.29E-02
WSB1	WD repeat and SOCS box-containing 1	1.39E-04	6.20E-03
yakeme		5.07E-04	1.66E-02
YIPF4	Yip1 domain family, member 4	2.65E-04	1.02E-02
YWHAE	similar to 14-3-3 protein epsilon (14-3-3E) (Mitochondrial import stimulation factor L subunit) (MSF L); tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide	9.45E-10	3.13E-07
ZBED5/EIF4G2/SNORD97	zinc finger, BED-type containing 5/eukaryotic translation initiation factor 4 gamma, 2/small nucleolar RNA, C/D box 97	4.27E-04	1.45E-02
ZCCHC6	zinc finger, CCHC domain containing 6	3.66E-05	2.26E-03
ZEB2/GTDC1	zinc finger E-box binding homeobox 2/glycosyltransferase-like domain containing 1	1.36E-04	6.12E-03
ZFAND5	zinc finger, AN1-type domain 5	2.10E-05	1.48E-03
ZFP91-CNTF	zinc finger protein 91 homolog (mouse); ZFP91-CNTF readthrough transcript; ciliary neurotrophic factor	9.98E-06	8.03E-04
ZNF516	zinc finger protein 516	2.98E-04	1.10E-02
ZNF592	zinc finger protein 592	1.35E-03	3.45E-02

TABLE 5. Canonical Pathways of the 412 Genes with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls. B-H-Benjamini-Hochberg corrected p-value				
Ingenuity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules
CD28 Signaling in T Helper Cells	8.11E00	5.54E00	1.36E-01	CDC42,ACTR2,CALM1 (includes others),ARPC3,HLA-DQA1,ATM,PPP3CB,ARPC5L,ACTR3,HLA-DRB1,PPP3R1,HLA-DMA,ARPC4,HLA-DMB,PTPRC,CD86
Cdc42 Signaling	5.99E00	3.72E00	9.58E-02	CDC42,ACTR2,ARPC3,HLA-DQA1,RAF1,CDC42SE1,MYL12A,ARPC5L,ACTR3,HLA-DRB1,HLA-DMA,ARPC4,HLA-DMB,PPP1CB,ITGA4,IQGAP2
Nur77 Signaling in T Lymphocytes	5.38E00	3.33E00	1.58E-01	HLA-DRB1,CALM1 (includes others),PPP3R1,APAF1,HLA-DMA,HLA-DQA1,HLA-DMB,PPP3CB,CD86
fMLP Signaling in Neutrophils	5.3E00	3.33E00	1.11E-01	CDC42,ACTR2,CALM1 (includes others),PPP3R1,ARPC3,RAF1,ARPC4,ATM,PPP3CB,ARPC5L,CYBB,ACTR3
Interferon Signaling	4.92E00	3.04E00	1.94E-01	IFNGR1,IRF9,JAK2,STAT1,MX1,IFNAR1,PSMB8
Rac Signaling	4.7E00	2.91E00	1.06E-01	CDC42,ACTR2,ARPC3,RAF1,ARPC4,ATM,ITGA4,IQGAP2,ARPC5L,CYBB,ACTR3
Actin Nucleation by ARP-WASP Complex	4.51E00	2.83E00	1.43E-01	CDC42,ACTR2,ARPC3,ARPC4,ROCK1,ITGA4,ARPC5L,ACTR3
Regulation of Actin-based Motility by Rho	4.47E00	2.83E00	1.1E-01	CDC42,ACTR2,ARPC3,ARPC4,MYL12A,PPP1CB,ROCK1,ITGA4,ARPC5L,ACTR3
Ephrin Receptor Signaling	4.45E00	2.83E00	8.05E-02	CDC42,ACTR2,JAK2,ARPC3,EPHB4,CRKL,RAF1,ARPC5L,RAP1A,ACTR3,ARPC4,RAP1B,ROCK1,ITGA4
Integrin Signaling	4.32E00	2.75E00	7.43E-02	CDC42,ACTR2,ARPC3,CRKL,RAF1,ATM,MYL12A,ARPC5L,RAP1A,ACTR3,ARPC4,RAP1B,PPP1CB,ROCK1,ITGA4

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Ingenuity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules
Protein Kinase A Signaling	4.28E00	2.75E00	5.73E-02	ANAPC13,PPP1CC,TDP2,CALM1 (includes others),MPPE1,ADCY7,RAF1,AKAP8,MYL12A,H3F3A/H3F3B,PPP3CB,YWHAE,RAP1A,ADD3,TGFBR2,PPP3R1,RAP1B,PPP1CB,ROCK1,PLCL2,PTPRC,ANAPC7
B Cell Development	4.04E00	2.54E00	1.76E-01	HLA-DRB1,HLA-DMA,HLA-DQA1,HLA-DMB,PTPRC,CD86
Actin Cytoskeleton Signaling	3.97E00	2.51E00	6.91E-02	CDC42,ACTR2,ARPC3,CRKL,RAF1,ATM,MYL12A,ARPC5L,ACTR3,ARPC4,PPP1CB,ROCK1,ITGA4,IQGAP2,TMSB10/TMSB4X
Antigen Presentation Pathway	3.83E00	2.4E00	1.62E-01	HLA-DRB1,CD74,HLA-DMA,HLA-DQA1,HLA-DMB,PSMB8
Role of JAK1, JAK2 and TYK2 in Interferon Signaling	3.8E00	2.4E00	2.08E-01	IFNGR1,JAK2,STAT1,RAF1,IFNAR1
T Helper Cell Differentiation	3.76E00	2.39E00	1.13E-01	IFNGR1,TGFBR2,HLA-DRB1,HLA-DMA,HLA-DQA1,STAT1,HLA-DMB,CD86
Calcium-induced T Lymphocyte Apoptosis	3.28E00	1.96E00	1.09E-01	HLA-DRB1,CALM1 (includes others),PPP3R1,HLA-DMA,HLA-DQA1,HLA-DMB,PPP3CB
Retinoic acid Mediated Apoptosis Signaling	3.28E00	1.96E00	1.09E-01	CFLAR,APAF1,TNKS2,PARP9,PARP14,DAP3,IFNAR1

TABLE 5. Canonical Pathways of the 412 Genes with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls. B-H-Benjamini-Hochberg corrected p-value				
Inguity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules
iCOS-iCOSL Signaling in T Helper Cells	3.17E00	1.9E00	8.33E-02	HLA-DRB1,CALM1 (includes others),PPP3R1,HLA-DMA,HLA-DQA1,ATM,HLA-DMB,PPP3CB,PTPRC
Dendritic Cell Maturation	3.17E00	1.9E00	6.7E-02	HLA-DRB1,JAK2,HLA-DMA,HLA-DQA1,CD58,STAT1,ATM,HLA-DMB,PLCL2,LY75,CD86,IFNAR1
NRF2-mediated Oxidative Stress Response	3.15E00	1.9E00	6.67E-02	GSTO1,BACH1,RAF1,ATM,UBE2E3,TXNRD1,EPHX1,DNAJB6,VCP,GSTK1,MGST1,NFE2L2
Type I Diabetes Mellitus Signaling	3.11E00	1.88E00	8.18E-02	IFNGR1,HLA-DRB1,APAF1,JAK2,HLA-DMA,HLA-DQA1,STAT1,HLA-DMB,CD86
IL-3 Signaling	3.01E00	1.81E00	9.86E-02	PPP3R1,JAK2,CRKL,STAT1,RAF1,ATM,PPP3CB
ERK/MAPK Signaling	3E00	1.81E00	6.42E-02	PPP1CC,PPP2R5A,CRKL,STAT1,RAF1,ATM,RAP1B,H3F3A/H3F3B,PPP1CB,ITGA4,RAP1A,PPP2CA
Breast Cancer Regulation by Stathmin1	2.92E00	1.75E00	6.28E-02	PPP1CC,CDC42,CALM1 (includes others),UHMK1,PPP2R5A,TUBB3,ADCY7,RAF1,ATM,PPP1CB,ROCK1,PPP2CA
Synaptic Long Term Potentiation	2.87E00	1.71E00	7.56E-02	PPP1CC,CALM1 (includes others),PPP3R1,RAF1,RAP1B,PPP3CB,PPP1CB,PLCL2,RAP1A
Ascorbate Recycling (Cytosolic)	2.84E00	1.71E00	6.67E-01	GSTO1,GLRX

TABLE 5. Canonical Pathways of the 412 Genes with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls. B-H-Benjamini-Hochberg corrected p-value				
Ingenuity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules
IL-4 Signaling	2.83E00	1.71E00	9.21E-02	HLA-DRB1,JAK2,HLA-DMA,HLA-DQA1,NR3C1,ATM,HLA-DMB
Role of NFAT in Regulation of the Immune Response	2.81E00	1.71E00	6.43E-02	HLA-DRB1,CALM1 (includes others),PPP3R1,HLA-DMA,HLA-DQA1,RAF1,ATM,HLA-DMB,PPP3CB,FCER1A,CD86
Epithelial Adherens Junction Signaling	2.8E00	1.71E00	6.85E-02	TGFBR2,CDC42,ACTR2,ARPC3,TUBB3,ARPC4,RAP1B,ARPC5L,RAP1A,ACTR3
RhoA Signaling	2.79E00	1.71E00	7.38E-02	ACTR2,ARPC3,ARPC4,MYL12A,PPP1CB,ROCK1,ARPC5L,ACTR3,SEPT5
Signaling by Rho Family GTPases	2.64E00	1.57E00	5.56E-02	CDC42,ACTR2,ARPC3,RAF1,ATM,MYL12A,ARPC5L,ACTR3,SEPT5,ARPC4,ROCK1,ITGA4,CYBB
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	2.63E00	1.57E00	6.11E-02	PPP1CC,IFNGR1,JAK2,PPP2R5A,STAT1,ATM,RAP1B,PPP1CB,CYBB,RAP1A,PPP2CA
GM-CSF Signaling	2.61E00	1.56E00	9.68E-02	PPP3R1,JAK2,STAT1,RAF1,ATM,PPP3CB
Leukotriene Biosynthesis	2.48E00	1.47E00	2.14E-01	DPEP3,DPEP2,LTA4H
Vitamin-C Transport	2.48E00	1.47E00	2.14E-01	GSTO1,GLRX,TXNRD1
Mitotic Roles of Polo-Like Kinase	2.47E00	1.47E00	9.09E-02	SLK,ANAPC13,RAD21,PPP2R5A,ANAPC7,PPP2CA

TABLE 5. Canonical Pathways of the 412 Genes with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls. B-H-Benjamini-Hochberg corrected p-value				
Inguinity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules
CTLA4 Signaling in Cytotoxic T Lymphocytes	2.47E00	1.47E00	7.95E-02	JAK2,PPP2R5A,CLTC,ATM,AP1S2,CD86,PPP2CA
cAMP-mediated signaling	2.43E00	1.45E00	5.48E-02	RGS18,TDP2,CALM1 (includes others),PPP3R1,ADCY7,MPPE1,RAF1,AKAP8,PPP3CB,PTGER4,RAP1A,MC1R
Axonal Guidance Signaling	2.41E00	1.44E00	4.39E-02	CDC42,ACTR2,ARPC3,EPHB4,TUBB3,CRKL,RAF1,ATM,MYL12A,PPP3CB,ARPC5L,RAP1A,ACTR3,PPP3R1,ARPC4,RAP1B,ROCK1,ITGA4,PLCL2
Remodeling of Epithelial Adherens Junctions	2.4E00	1.44E00	8.82E-02	ACTR2,ARPC3,TUBB3,ARPC4,ARPC5L,ACTR3
Graft-versus-Host Disease Signaling	2.39E00	1.43E00	1.04E-01	HLA-DRB1,HLA-DMA,HLA-DQA1,HLA-DMB,CD86
Autoimmune Thyroid Disease Signaling	2.35E00	1.41E00	1.02E-01	HLA-DRB1,HLA-DMA,HLA-DQA1,HLA-DMB,CD86
Fcy Receptor-mediated Phagocytosis in Macrophages and Monocytes	2.33E00	1.4E00	7.53E-02	CDC42,ACTR2,VAMP3,ARPC3,ARPC4,ARPC5L,ACTR3
Protein Ubiquitination Pathway	2.32E00	1.4E00	5.1E-02	UBR2,UBE2E3,PSMD6,USP1,USP15,UBE2B,PSMD13,DNAJB6,PSMB3,PAN2,PSMA1,USP33,PSMB8

TABLE 5. Canonical Pathways of the 412 Genes with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls. B-H-Benjamini-Hochberg corrected p-value				
Ingenuity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules
PKC θ Signaling in T Lymphocytes	2.32E00	1.4E00	6.78E-02	HLA-DRB1,PPP3R1,HLA-DMA,HLA-DQA1,ATM,HLA-DMB,PPP3CB,CD86
Glucocorticoid Receptor Signaling	2.24E00	1.34E00	4.98E-02	JAK2,RAF1,ATM,PPP3CB,SELE,ANXA1,TGFB2,HMGB1,PPP3R1,NR3C1,STAT1,CDKN1C,TAF1
Glutathione Redox Reactions I	2.16E00	1.27E00	1.67E-01	GPX1,GSTK1,MGST1
PDGF Signaling	2.14E00	1.27E00	7.79E-02	EIF2AK2,JAK2,CRKL,STAT1,RAF1,ATM
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	2.13E00	1.27E00	6.3E-02	EIF2AK2,EIF2S1,IFIH1,OAS3,ATM,OAS2,DDX58,CLEC7A
D-myo-inositol (1,4,5,6)-Tetrakisphosphate Biosynthesis	2.13E00	1.27E00	6.3E-02	PPP1CC,PPTC7,PPP2R5A,PPP4R1,SACM1L,IPMK,PTPRC,MTMR6
D-myo-inositol (3,4,5,6)-tetrakisphosphate Biosynthesis	2.13E00	1.27E00	6.3E-02	PPP1CC,PPTC7,PPP2R5A,PPP4R1,SACM1L,IPMK,PTPRC,MTMR6
Clathrin-mediated Endocytosis Signaling	2.07E00	1.22E00	5.41E-02	CDC42,ACTR2,PPP3R1,ARPC3,CLTC,ARPC4,ATM,PPP3CB,ARPC5L,ACTR3
HGF Signaling	2.05E00	1.21E00	6.67E-02	CDC42,CRKL,RAF1,ATM,RAP1B,ITGA4,RAP1A

TABLE 5. Canonical Pathways of the 412 Genes with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls. B-H-Benjamini-Hochberg corrected p-value				
Inguenuity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules
Cardiac β -adrenergic Signaling	2.01E00	1.18E00	6.02E-02	PPP1CC,TDP2,PPP2R5A,ADCY7,MPPE1,AKAP8,PPP1CB,PPP2CA
Dopamine-DARPP32 Feedback in cAMP Signaling	2E00	1.18E00	5.59E-02	PPP1CC,CALM1 (includes others),PPP3R1,PPP2R5A,ADCY7,PPP3CB,PPP1CB,PLCL2,PPP2CA
Cardiac Hypertrophy Signaling	1.95E00	1.13E00	4.93E-02	TGFBR2,CALM1 (includes others),PPP3R1,ADCY7,RAF1,ATM,MYL12A,PPP3CB,ROCK1,PLCL2,ADSS
Role of PKR in Interferon Induction and Antiviral Response	1.93E00	1.12E00	1E-01	EIF2AK2,EIF2S1,APAF1,STAT1
HIPPO signaling	1.91E00	1.11E00	6.98E-02	PPP1CC,PPP2R5A,MOB1A,PPP1CB,YWHAE,PPP2CA
Salvage Pathways of Pyrimidine Deoxyribonucleotides	1.9E00	1.1E00	2.5E-01	APOBEC3B,APOBEC3A
Altered T Cell and B Cell Signaling in Rheumatoid Arthritis	1.87E00	1.09E00	6.82E-02	TNFSF13B,HLA-DRB1,HLA-DMA,HLA-DQA1,HLA-DMB,CD86
UVA-Induced MAPK Signaling	1.87E00	1.09E00	6.82E-02	STAT1,ATM,TNKS2,PARP9,PLCL2,PARP14
Activation of IRF by Cytosolic Pattern Recognition Receptors	1.86E00	1.09E00	7.81E-02	IRF9,STAT1,IFIH1,DDX58,IFNAR1

TABLE 5. Canonical Pathways of the 412 Genes with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls. B-H-Benjamini-Hochberg corrected p-value				
Ingenuity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules
3-phosphoinositide Degradation	1.82E00	1.05E00	5.56E-02	PPP1CC,MTMR1,PPTC7,PPP2R5A,PPP4R1,SACM1L,PTPRC,MTMR6
RhoGDI Signaling	1.81E00	1.05E00	5.2E-02	CDC42,ACTR2,ARPC3,ARPC4,MYL12A,ROCK1,ITGA4,ARPC5L,ACTR3
iNOS Signaling	1.79E00	1.04E00	9.09E-02	IFNGR1,CALM1 (includes others),JAK2,STAT1
Death Receptor Signaling	1.78E00	1.03E00	6.52E-02	CFLAR,APAF1,TNKS2,ROCK1,PARP9,PARP14
B Cell Receptor Signaling	1.77E00	1.03E00	5.11E-02	CDC42,CALM1 (includes others),PPP3R1,RAF1,ATM,RAP1B,PPP3CB,PTPRC,RAP1A
PI3K/AKT Signaling	1.7E00	9.65E-01	5.69E-02	JAK2,PPP2R5A,MCL1,RAF1,ITGA4,YWHAE,PPP2CA
T Cell Receptor Signaling	1.68E00	9.48E-01	6.19E-02	CALM1 (includes others),PPP3R1,RAF1,ATM,PPP3CB,PTPRC
Histamine Biosynthesis	1.65E00	9.38E-01	1E00	HDC
UDP-N-acetyl-D-galactosamine Biosynthesis I	1.65E00	9.38E-01	1E00	GALE
3-phosphoinositide Biosynthesis	1.65E00	9.38E-01	5.16E-02	PPP1CC,PPTC7,PPP2R5A,PPP4R1,ATM,SACM1L,PTPRC,MTMR6
CDK5 Signaling	1.64E00	9.38E-01	6.06E-02	PPP1CC,PPP2R5A,ADCY7,RAF1,PPP1CB,PPP2CA
Prolactin Signaling	1.64E00	9.38E-01	6.85E-02	JAK2,STAT1,NR3C1,RAF1,ATM
Glutathione-mediated Detoxification	1.63E00	9.34E-01	1.07E-01	GSTO1,GSTK1,MGST1

TABLE 5. Canonical Pathways of the 412 Genes with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls. B-H-Benjamini-Hochberg corrected p-value				
Ingenuity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules
Superpathway of Inositol Phosphate Compounds	1.55E00	8.69E-01	4.69E-02	PPP1CC,PPTC7,PPP2R5A,PPP4R1,ATM,SACM1L,IPMK,PTPRC,MTMR6
CNTF Signaling	1.55E00	8.69E-01	7.69E-02	JAK2,STAT1,RAF1,ATM
Dopamine Receptor Signaling	1.53E00	8.51E-01	6.41E-02	PPP1CC,PPP2R5A,ADCY7,PPP1CB,PPP2CA
Pancreatic Adenocarcinoma Signaling	1.51E00	8.41E-01	5.66E-02	TGFBR2,CDC42,JAK2,STAT1,RAF1,ATM
Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes	1.51E00	8.41E-01	6.33E-02	TGFBR2,CALM1 (includes others),PPP3R1,RAF1,PPP3CB
NGF Signaling	1.49E00	8.34E-01	5.61E-02	CDC42,RAF1,ATM,RAP1B,ROCK1,RAP1A
Thrombopoietin Signaling	1.47E00	8.18E-01	7.27E-02	JAK2,STAT1,RAF1,ATM
Aryl Hydrocarbon Receptor Signaling	1.43E00	7.84E-01	5E-02	GSTO1,APAF1,RBL2,ATM,GSTK1,MGST1,NFE2L2
Oncostatin M Signaling	1.41E00	7.68E-01	8.82E-02	JAK2,STAT1,RAF1
Inhibition of Angiogenesis by TSP1	1.41E00	7.68E-01	8.82E-02	CD47,TGFBR2,CD36

TABLE 5. Canonical Pathways of the 412 Genes with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls. B-H-Benjamini-Hochberg corrected p-value				
Ingenuity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules
D-myo-inositol-5-phosphate Metabolism	1.39E00	7.6E-01	4.9E-02	PPP1CC,PPTC7,PPP2R5A,PPP4R1,SACM1L,PTPRC,MTMR6
Phospholipase C Signaling	1.38E00	7.6E-01	4.18E-02	CALM1 (includes others),PPP3R1,ADCY7,RAF1,MYL12A,RAP1B,PPP3CB,PPP1CB,ITGA4,RAP1A
Cell Cycle Regulation by BTG Family Proteins	1.38E00	7.6E-01	8.57E-02	PPP2R5A,CNOT7,PPP2CA
Allograft Rejection Signaling	1.37E00	7.6E-01	5.81E-02	HLA-DRB1,HLA-DMA,HLA-DQA1,HLA-DMB,CD86
Telomere Extension by Telomerase	1.37E00	7.6E-01	1.33E-01	TNKS2,HNRNPA2B1
Spliceosomal Cycle	1.36E00	7.6E-01	5E-01	LOC102724594/U2AF1
S-methyl-5-thio- α -D-ribose 1-phosphate Degradation	1.36E00	7.6E-01	5E-01	APIP
Glutamate Biosynthesis II	1.36E00	7.6E-01	5E-01	GLUD1
Glutamate Degradation X	1.36E00	7.6E-01	5E-01	GLUD1
Regulation of eIF4 and p70S6K Signaling	1.35E00	7.59E-01	4.79E-02	EIF2S1,PPP2R5A,RAF1,ATM,ITGA4,EIF4G2,PPP2CA

TABLE 5. Canonical Pathways of the 412 Genes with Differential Alternative Splicing Among Large Vessel Ischemic Stroke (IS), Cardioembolic IS, Lacunar IS, Intracerebral Hemorrhage and Controls. B-H-Benjamini-Hochberg corrected p-value				
Ingenuity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules
Calcium Signaling	1.34E00	7.57E-01	4.49E-02	TPM3,ATP2B4,CALM1 (includes others),PPP3R1,RAP1B,PPP3CB,MICU1,RAP1A
Gαq Signaling	1.34E00	7.57E-01	4.76E-02	RGS18,CALM1 (includes others),PPP3R1,RAF1,ATM,PPP3CB,ROCK1
RANK Signaling in Osteoclasts	1.34E00	7.57E-01	5.68E-02	CALM1 (includes others),PPP3R1,RAF1,ATM,PPP3CB
Role of NFAT in Cardiac Hypertrophy	1.33E00	7.56E-01	4.47E-02	TGFBR2,CALM1 (includes others),PPP3R1,ADCY7,RAF1,ATM,PPP3CB,PLCL2
PAK Signaling	1.32E00	7.48E-01	5.62E-02	CDC42,RAF1,ATM,MYL12A,ITGA4
p70S6K Signaling	1.31E00	7.39E-01	5.04E-02	PPP2R5A,RAF1,ATM,PLCL2,YWHAE,PPP2CA

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Alternately Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell Death and Survival	cell death	1.32E-09	ACSL4,AIFM2,AKAP8,ANXA1,ANXA7,APAF1,APH1A,APIP,APOBEC3B,ARL6IP5,ARNTL,ATM,ATP2B4,ATP6V1G2,BAZ1A,BRAT1,C1QTNF9,CALM1 (includes others), CARD8,CCAR1,CCT8,CD164,CD244,CD36,CD46,CD47,CD53,CD74,CD86,CDC42,CDKN1C,CFLAR,CHMP3,CNPY2,CTSS,CYBB,CYLD,DAP3,DDX19A,DDX3X,DDX58,DNAJB6,DPYD,DUSP22,EGIN1,EIF2AK2,EIF2S1,EIF4G2,EPHB4,EPHX1,ERN1,FCER1A,FKBP1A,FNTA,GLRX,GLUD1,GMCL1,GPX1,GZMA,HEXB,HIPK3,HLA-DMA,HLA-DRB1, HMGB1,IFIH1,IFNAR1,IFNGR1,IFRD1,IGFBP7,ING4,IPMK,IQGAP2,ITGA4,JAK2,KLF13,LMO4,LRRK2,MC1R,MCL1,MICA,MOB1A,MTCH1,MTMR6,MTPN,MX1,NCOA4,NFE2L2,NR3C1,OAS3, PAFAH1B1,PARP14,PHB2,PHIP,PPP1CC,PPP1R15B,PPP2CA,PPP2R5A,PPP3CB,PPP3R1,PRMT2,PRNP,PSMB8,PSMD6,PTGER4,PTPRC, RAB1A,RAB32,RAD21,RAF1,RAP1A,RAP1B,RASSF3,RBBP4,RBL2,RECQL,RFWD2,RICTOR,RIT1,RNF13,RNF31,RNF5,ROCK1,S100A6,SCP2,SELL,SERINC3, SLC12A7,SLK,SMARCA5,SRI,ST8SIA4,STAT1,TAX1BP1,TDP2,TGFBP2,TMSB10/TMSB4X,TNFSF13B,TNKS2,TOPORS,TPM3,TUBB3,TXNRD1,UBE2B,VAMP3,VCP,YWHAE,ZEB2,ZFAND5 ACSL4,AIFM2,AKAP8,ANXA1,ANXA7,APAF1,APH1A,APIP,APOBEC3B,ARL6IP5,ATM,ATP2B4,ATP6V1G2,BAZ1A,BRAT1,C1QTNF9,CARD8,CCAR1,CD164,CD36,CD47,CD53,CD74,CDC42,CDKN1C,CFLAR,CTSS,CYBB,CYLD,DAP3,DDX19A,DDX3X,DDX58,DUSP22,EIF2AK2,EIF2S1,EIF4G2,EPHB4,EPHX1,ERN1,FCER1A,FKBP1A,FNTA, GLRX,GLUD1,GMCL1,GPX1,GZMA,HEXB,HIPK3,HLA-DMA,HMGB1,IFIH1,IFNAR1,IFNGR1,IGFBP7, ING4,IQGAP2,ITGA4,JAK2,KLF13,LMO4,LRRK2,MC1R,MCL1,MOB1A, MTCH1,MTMR6,MTPN,MX1,NCOA4,NFE2L2,NR3C1,OAS3,PAFAH1B1,PARP14,PHB2,PHIP,PPP1CC,PPP2CA, PPP3CB,PPP3R1,PRMT2,PRNP,PSMB8,PSMD6,PTGER4,PTPRC,RAB32,RAD21,RAF1,RAP1A,RAP1B,RASSF3,R BBP4,RBL2,RFWD2,RICTOR,RIT1,RNF13,RNF31,RNF5,ROCK1,S100A6,SELL,SERINC3,SLK,SRI,ST8SIA4,STAT1, TAX1BP1,TDP2,TGFBP2,TMSB10/TMSB4X,TNFSF13B,TPORS,TXNRD1,UBE2B,VCP,YWHAE,ZEB2,ZFAND5	148
Cell Death and Survival	apoptosis	4.11E-09		122

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Alternately Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell Death and Survival	necrosis	6.80E-05	ANXA1,APAF1,APIP,APOBEC3B,ATM,ATP2B4,ATP6V1G2,BAZ1A,BRAT1,C1QTNF9,CARD8,CCAR1,CCT8,CD36,CD47,CD74,CD86,CDC42,CDKN1C,CFLAR,CNPY2,CTSS,CYBB,CYLD,DAP3,DDX3X,DDX58,DYPD,EGLN1,EIF2A,K2,EIF2S1,EIF4G2,EPHB4,EPHX1,ERN1,FCER1A,FKBP1A,FNTA,GLRX,GLUD1,GPX1,GZMA,HLA-DMA,HMGB1,IFIH1,IFNAR1,IFNGR1,IFRD1,IGFBP7,IPMK,IQGAP2,ITGA4,JAK2,KLF13,LMO4,LRRK2,MCIR,MCL1,MTMR6,MTPN,MX1,NFE2L2,NR3C1,OAS3,PAFAH1B1,PARP14,PHIP,PPP1CC,PPP2CA,PPP3CB,PPP3R1,PRMT2,PRNP,PSMB8,PSMD6,PTGER4,PTPRC,RAB32,RAD21,RAF1,RASSF3,RBBP4,RBL2,RECQL,RFWD2,RIT1,RIT2,RIT3,RNF13,RNF31,RNF5,ROCK1,S100A6,SCP2,SELL,SLK,SRI,STAT1,TAX1BP1,TDP2,TGFB2,TMSB10/TMSB4X,TNFSF13B,TUBB3,TXNRD1,VCP,YWHA	106
Cell Death and Survival	cell viability	2.26E-04	APAF1,APOBEC3A,ATM,C1QTNF9,CD47,CD74,CD86,CDC42,CDKL3,CDKN1C,CFLAR,CYBB,CYLD,DYPD,DUSP2,EPHB4,ERN1,FCER1A,GLUD1,GPX1,HMGB1,IFIH1,IGFBP7,IRF9,JAK2,LRRK2,MCL1,MGST1,MTMR1,MTMR6,MX1,NFE2L2,NR3C1,PARP14,PPP1CB,PPP1CC,PPP2CA,PPP2R5A,PPP4R1,PPP6C,PRNP,PSMA1,PTPRC,RAD21,RAF1,RBBP4,RICTOR,RIT1,RNF31,S100A6,SELE,SELL,SPDYA,STAT1,TDP2,TGFB2,TNFSF13B,TUBB3,VCP,APAF1,APOBEC3B,CD53,EIF2AK2,GPX1,GZMA,MCL1,MITCH1,NR3C1,PPP1CC,PRNP,SERINC3,STAT1	59
Cell Death and Survival, DNA Replication, Recombination, and Repair	fragmentation of DNA	3.36E-04		13
Cell Death and Survival	cell death of tumor cell lines	3.43E-04	APAF1,ATM,BAZ1A,BRAT1,CARD8,CCAR1,CCT8,CD47,CDC42,CDKN1C,CFLAR,CNPY2,CYLD,DAP3,DDX3X,DDX58,DYPD,EGLN1,EIF2AK2,EIF2S1,EIF4G2,EPHB4,ERN1,FCER1A,FKBP1A,GLRX,GPX1,IFNAR1,IFRD1,IGFBP7,IPMK,IQGAP2,ITGA4,JAK2,LMO4,MCL1,MTMR6,NFE2L2,NR3C1,OAS3,PARP14,PHIP,PPP2CA,PRNP,PTPRC,RAB32,RAD21,RAF1,RASSF3,RBL2,RFWD2,RICTOR,RIT1,RNF13,RNF31,RNF5,S100A6,SRI,STAT1,TDP2,TGFB2,TMSB10/TMSB4X,TNFSF13B,TUBB3,TXNRD1,VCP,YWHA	67

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Alternately Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell Death and Survival	cell survival	3.95E-04	APAF1, APOBEC3A, ATM, C1QTNF9, CD47, CD74, CD86, CDC42, CDKL3, CDKN1C, CFLAR, CYBB, CYLD, DDX3X, DPYD, DUSP22, EIF2S1, EPHB4, ERN1, FCER1A, GLRX, GLUD1, GPX1, HMGGB1, IFIH1, IGF8P7, IRF9, JAK2, LRRK2, MCL1, MGST1, MTMR1, MTMR6, MX1, NFE2L2, NR3C1, PARP14, PPP1CB, PPP1CC, PPP2CA, PPP2R5A, PPP4R1, PPP6C, PRNP, PSMA1, PTPRC, RAD21, RAF1, RBBP4, RICTOR, RIT1, RNF31, S100A6, SELE, SELL, SPDYA, STAT1, TDP2, TGFBR2, TNFSF13B, TUBB3, VCP	62
Cell Death and Survival	cytolysis	4.21E-04	ANXA1, CD244, CD46, CD47, FCER1A, GZMA, IFNAR1, MICA, NFE2L2, NR3C1, PPP3CB, PPP3R1, PTPRC, TGFBR2	14
Cardiovascular System Development and Function, Cell Death and Survival, Cellular Development, Organ Morphology, Tissue Development, Tissue Morphology	regeneration of cardiomyocytes	4.91E-04	HMGB1, MTPN	2
Cell Death and Survival, Connective Tissue Disorders, Hematological Disease	hemolysis	5.26E-04	ANXA1, CD47, IFNAR1, NFE2L2, NR3C1, PPP3CB, PPP3R1	7

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Alternately Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell Death and Survival	cell death of immune cells	5.41E-04	ANXA1, APAF1, ATM, CD47, CD74, CD86, CDC42, CFLAR, CYBB, CYLD, EIF2AK2, ERN1, FCER1A, GZMA, HMGB1, IFIH1, IFNAR1, IFNGR1, ITGA4, JAK2, KLF13, MCL1, MX1, NFE2L2, NR3C1, PARP14, PPP3CB, PTGER4, PTPRC, RAF1, STAT1, TGFB2, TNFSF13B	33
Cancer, Cell Death and Survival, Tumor Morphology	cell death of cancer cells	8.29E-04	ANXA1, APAF1, ATM, CD47, CD74, CFLAR, EIF2AK2, HMGB1, JAK2, LRRK2, MCL1, NFE2L2, NR3C1, PARP14, PRNP, RAF1, SELL, TNFSF13B	18
Cell Death and Survival	cell death of kidney cell lines	8.85E-04	APOBEC3B, CDC42, CFLAR, DAP3, EIF2AK2, ERN1, JAK2, MCL1, NFE2L2, PPP3R1, PRMT2, PRNP, RAD21, RAF1, RNF13, RNF31, SLK, VCP	18
Cell Death and Survival	cell viability of tumor cell lines	9.22E-04	ATM, CDKL3, CDKN1C, CFLAR, CYBB, DUSP22, EPHB4, GLUD1, GPX1, HMGB1, IGFBP7, MCL1, MTMR1, MTMR6, NF2L2, NR3C1, PARP14, PPP1CC, PPP2CA, PPP2R5A, PPP4R1, PPP6C, PRNP, PSMA1, RAD21, RAF1, RBBP4, RICTOR, RIT1, RNF31, S100A6, TDP2, TGFB2, TNFSF13B, TUBB3, VCP	36
Cell Death and Survival	apoptosis of fibroblast cell lines	9.87E-04	APAF1, ATM, ATP6V1G2, CFLAR, CYLD, DDX3X, EIF2AK2, EIF2S1, EPHX1, IFNAR1, MCL1, NFE2L2, NR3C1, PRNP, PSMD6, RBL2, RNF13, STAT1, TAX1BP1	19
Cell Death and Survival, Connective Tissue Disorders, Hematological Disease	hemolytic anemia	9.89E-04	ANXA1, CD47, IFNAR1, NR3C1, PPP3CB, PPP3R1	6
Cancer, Cell Death and Survival, Tumor Morphology	cell death of tumor cells	1.00E-03	ANXA1, APAF1, ATM, CARD8, CD47, CD74, CFLAR, EIF2AK2, HMGB1, JAK2, LRRK2, MCL1, NFE2L2, NR3C1, PARP14, PPP2CA, PRNP, RAF1, SELL, TGFB2, TNFSF13B	21

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Alternately Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell Death and Survival	cell death of connective tissue cells	1.27E-03	APAF1,ATM,ATP6V1G2,CDC42,CFLAR,CYLD,DDX3X,DDX58,EIF2AK2,EIF2S1,EPHX1,FNTA,GPX1,GZMA,IFNAR1,MCL1,NFE2L2,NR3C1,PRMT2,PRNP,PSMD6,RAF1,RBL2,RECQL,RNF13,SCP2,SLK,STAT1,TAX1BP1,VCP	30
Cell Death and Survival, Cellular Compromise, Neurological Disease, Tissue Morphology	degeneration of nerve ending	1.45E-03	ARNTL,ATM	2
Cell Death and Survival, Respiratory Disease	quantity of apoptotic pneumocytes	1.45E-03	CD36,NFE2L2	2
Cell Death and Survival	cell death of fibroblast cell lines	1.50E-03	APAF1,ATM,ATP6V1G2,CFLAR,CYLD,DDX3X,EIF2AK2,EIF2S1,EPHX1,FNTA,IFNAR1,MCL1,NFE2L2,NR3C1,PRNP,PSMD6,RBL2,RECQL,RNF13,SCP2,STAT1,TAX1BP1,VCP	23
Cell Death and Survival	cell death of thymocytes	1.50E-03	APAF1,ATM,CFLAR,CYLD,GZMA,KLF13,MCL1,NFE2L2,NR3C1,PTPRC	10
Cell Death and Survival	cell death of epithelial cells	1.52E-03	APAF1,APOBEC3B,ATM,CDC42,CFLAR,CTSS,CYLD,DAP3,EIF2AK2,ERN1,HMGB1,IFNGR1,JAK2,MC1R,MCL1,NFE2L2,NR3C1,PPP3R1,PRMT2,PRNP,RAD21,RAF1,RBL2,RNF31,TGFB2	25
Cell Death and Survival	mitochondrial cell death of tumor cell lines	1.57E-03	DDX58,MCL1,SRI	3
Cell Death and Survival	apoptosis of leukocytes	1.61E-03	ANXA1,ATM,CD47,CDC42,CFLAR,CYBB,CYLD,EIF2AK2,FCER1A,GZMA,HMGB1,IFNGR1,JAK2,KLF13,MCL1,NFE2L2,NR3C1,PPP3CB,PTGER4,PTPRC,RAF1,STAT1,TNFSF13B	23

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Alternately Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell Death and Survival	apoptosis of tumor cell lines	1.73E-03	APAF1, ATM, BAZ1A, BRAT1, CARD8, CCAR1, CD47, CDC42, CDKN1C, CFLAR, CYLD, DDX58, EIF2AK2, EIF4G2, EPHB4, ERN1, FCER1A, GLRX, GPX1, IGFBP7, JAK2, LMO4, MCL1, MTMR6, NFE2L2, NR3C1, OAS3, PARP14, PHIP, PPP2CA, PRNP, PTPRC, RAB32, RAD21, RAF1, RASSF3, RBL2, RICTOR, RIT1, RNF13, RNF31, RNF5, S100A6, SRI, STAT1, TDP2, TGFBR2, TMSB10/TMSB4X, TNFSF13B, TXNRP1, VCP, YWHA	52
Cell Death and Survival, Connective Tissue Disorders, Hematological Disease, Immunological Disease	autoimmune hemolytic anemia	1.78E-03	CD47, NR3C1, PPP3CB, PPP3R1	4
Cell Death and Survival	cell viability of cervical cancer cell lines	1.89E-03	ATM, CDKL3, DUSP22, MCL1, MTMR1, MTMR6, PPP1CC, PPP2CA, PPP2R5A, PPP4R1, PPP6C, RAD21, TGFBR2	13
Cell Death and Survival	cell death of colon cancer cell lines	1.97E-03	APAF1, CCAR1, CDC42, CDKN1C, CFLAR, EPHB4, MCL1, RAF1, RASSF3, SRI, STAT1, TGFBR2, TMSB10/TMSB4X, TXNRP1, VCP, YWHA	16
Cell Death and Survival	cell viability of leukocytes	2.26E-03	CD47, CD74, CD86, CYLD, ERN1, FCER1A, HMGB1, JAK2, MCL1, MX1, PARP14, PTPRC, RAF1, STAT1, TNFSF13B	15
Cell Death and Survival	killing of natural killer cells	2.42E-03	CD244, IFNAR1, IFNGR1, STAT1	4
Cell Death and Survival	cell death of myeloid cells	2.46E-03	ANXA1, CFLAR, CYBB, EIF2AK2, FCER1A, HMGB1, IFNAR1, JAK2, MCL1, NFE2L2, NR3C1, RAF1, STAT1	13

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Alternately Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell Death and Survival	cell death of epithelial cell lines	2.68E-03	APOBEC3B, CDC42, CFLAR, DAP3, EIF2AK2, ERN1, JAK2, MCL1, NFE2L2, PPP3R1, PRMT2, PRNP, RAD21, RAF1, RNF31, TGFB2	16
Cell Death and Survival	necrosis of epithelial tissue	2.81E-03	APAF1, APOBEC3B, ATM, CD36, CDC42, CFLAR, CTSS, CYLD, DAP3, EIF2AK2, ERN1, GPX1, HMGB1, IFNGR1, JAK2, MCL1, MCL1, NFE2L2, NR3C1, PPP3R1, PRMT2, PRNP, PSMB8, RAD21, RAF1, RBL2, RNF31, TGFB2	28
Cell Death and Survival	cell viability of blood cells	2.85E-03	CD47, CD74, CD86, CYLD, ERN1, FCER1A, HMGB1, JAK2, MCL1, MX1, PARP14, PTPRC, RAF1, SELE, STAT1, TNFSF13B	16
Cell Death and Survival	cytotoxicity	2.87E-03	CALM1 (includes others), CD244, CD46, CD74, CFLAR, CYBB, FKBP1A, GZMA, HLA-DRB1, IFNAR1, MICA, PTPRC, STAT1, TGFB2	14
Cell Death and Survival, Embryonic Development	cell death of embryonic cell lines	2.97E-03	APOBEC3B, CDC42, CFLAR, DAP3, EIF2AK2, ERN1, IFNAR1, MCL1, NFE2L2, PPP3R1, PRMT2, PRNP, RAD21, RNF31	14
Cancer, Cell Death and Survival, Tumor Morphology	cell death of leukemia cells	3.42E-03	ATM, CD47, JAK2, MCL1, RAF1, SELL, TNFSF13B	7
Cell Death and Survival, Cellular Compromise	cytotoxicity of cells	3.51E-03	CALM1 (includes others), CD244, CD46, CD74, CFLAR, CYBB, GZMA, HLA-DRB1, IFNAR1, MICA, PTPRC, STAT1, TGFB2	13
Cell Death and Survival	killing of lymphocytes	3.74E-03	CD244, CD47, IFNAR1, IFNGR1, STAT1	5

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Alternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell Death and Survival	apoptosis of fibroblasts	3.99E-03	APAF1,ATM, CDC42,CFLAR,DDX58,EIF2AK2,EIF2S1,GZMA,MCL1,PRMT2,RAF1,SLK	12
Cell Death and Survival	cell death of fibroblasts	4.36E-03	APAF1,ATM, CDC42,CFLAR,DDX58,EIF2AK2,EIF2S1,EPHX1,GPX1,GZMA,MCL1,PRMT2,RAF1,SLK	14
Cell Death and Survival, Cell Signaling	activation of caspase	4.56E-03	APAF1,CARD8,JAK2,MTCH1,STAT1,VCP	6
Cancer, Cell Death and Survival, Tumor Morphology	cell viability of cancer cells	4.64E-03	CD74,HMGB1,MCL1,NFE2L2,PARP14,SELL,TNFSF13B	7
Cancer, Cell Death and Survival, Tumor Morphology	cell death of chronic lymphocytic leukemia cells	4.68E-03	ATM,CD47,SELL,TNFSF13B	4
Cell Death and Survival	cytolysis of lymphoblastoid cell lines	4.70E-03	CD244,MICA	2
Cell Death and Survival	loss of B lymphocytes	4.70E-03	CD74,SPPL2A	2
Cell Death and Survival	cell death of T lymphocytes	5.03E-03	APAF1,ATM,CD47,CDC42,CFLAR,CYLD,GZMA,IFNGR1,KLF13,MCL1,NFE2L2,NR3C1,PPP3CB,PTPRC,STAT1,TGFB	16

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cancer, Cell Death and Survival, Tumor Morphology	cell viability of tumor cells	5.07E-03	CD74, HMGB1, LRRK2, MCL1, NFE2L2, PARP14, SELL, TNFSF13B	8
Cell Death and Survival	cell death of mononuclear leukocytes	5.35E-03	APAF1, ATM, CD47, CDC42, CFLAR, CYLD, EIF2AK2, FCER1A, GZMA, IFNGR1, KLF13, MCL1, NFE2L2, NR3C1, PPP3CB, PTPRC, STAT1, TGFB2, TNFSF13B	19
Cell Death and Survival	apoptosis of colon cancer cell lines	5.39E-03	APAF1, CCAR1, CDC42, CDKN1C, CFLAR, EPHB4, MCL1, RASSF3, SRI, STAT1, TMSB10/TMSB4X, VCP, YWHAE	13
Cell Death and Survival	cell death of phagocytes	5.46E-03	ANXA1, CFLAR, CYBB, EIF2AK2, FCER1A, HMGB1, IFNAR1, MCL1, NFE2L2, NR3C1, PTGER4, STAT1	12
Cell Death and Survival	apoptosis of myeloid cells	5.60E-03	ANXA1, CFLAR, CYBB, EIF2AK2, FCER1A, HMGB1, JAK2, MCL1, NFE2L2, RAF1, STAT1	11
Cell Death and Survival	apoptosis of thymocytes	6.47E-03	ATM, CFLAR, CYLD, GZMA, KLF13, NFE2L2, NR3C1, PTPRC	8
Cell Death and Survival	apoptosis of kidney cell lines	6.50E-03	CFLAR, DAP3, EIF2AK2, JAK2, MCL1, NFE2L2, PPP3R1, PRMT2, RAD21, RAF1, RNF13, RNF31, SLK	13
Cell Death and Survival	necroptosis of tumor cell lines	6.94E-03	CYLD, STAT1	2

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell Death and Survival, DNA Replication, Recombination, and Repair	fragmentation of DNA fragment	7.93E-03	APOBEC3B, EIF2AK2, GZMA, MTCH1, PPP1CC	5
Cell Death and Survival	apoptosis of peritoneal macrophages	8.07E-03	CFLAR, MCL1, NFE2L2	3
Cancer, Cell Death and Survival, Tumor Morphology	apoptosis of leukemia cells	8.20E-03	ATM, JAK2, MCL1, RAF1, SELL, TNFSF13B	6
Cell Death and Survival	cell death of lymphocytes	8.22E-03	APAF1, ATM, CD47, CDC42, CFLAR, CYLD, EIF2AK2, GZMA, IFNGR1, KLF13, MCL1, NFE2L2, NR3C1, PPP3CB, PTPRC, STAT1, TGFBR2, TNFSF13B	18
Cancer, Cell Death and Survival, Tumor Morphology	cell viability of chronic lymphocytic leukemia cells	9.34E-03	CD74, SELL, TNFSF13B	3
Cell Death and Survival	cell death of hematopoietic cells	9.40E-03	APAF1, ATM, CFLAR, CYLD, EIF2AK2, GZMA, KLF13, MCL1, NFE2L2, NR3C1, PTPRC, RAF1	12

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell Death and Survival, Cellular Compromise, Neurological Disease, Organismal Injury and Abnormalities, Tissue Morphology	neurodegenerat ion of granule cells	9.58E-03	ATM, PRNP	2
Cell Death and Survival	apoptosis of epithelial cell lines	9.98E-03	CFLAR, DAP3, EIF2AK2, JAK2, MCL1, NFE2L2, PPP3R1, PRMT2, RAD21, RAF1, RNF31, TGFB2	12
Cell Death and Survival	apoptosis of lymphoma cell lines	1.05E-02	CARD8, CFLAR, EIF2AK2, ERN1, FCER1A, IGFBP7, JAK2, MCL1, PTPRC, TNFSF13B	10
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell Trafficking, Inflammatory	activation of leukocytes	6.10E-08	ANXA1, ATM, BLOC1S6, CD244, CD36, CD46, CD47, CD58, CD74, CD86, CLEC7A, CTSS, CYBB, DDX58, ERAP1, FKBP1 A, GZMA, HBP1, HLA-DMA, HLA-DMB, HLA-DQA1, HLA-DRB1, HMGGB1, IFNAR1, JAK2, MGST1, MICA, NBR1, NDFIP1, NFE2L2, PELI1, PPP3CB, PRNP, PSM1B8, PTGER4, PTPR C, RAB10, RAB32, RAB6A, RAB8B, SELE, SELL, STAT1, TGFB2, TNFSF13B	45

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Alternately Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Response Cell-To-Cell Signaling and Interaction, Hematological System Development and Function	activation of blood cells	1.61E-07	ANXA1,ATM,BLOC1S6,CD244,CD36,CD46,CD47,CD58,CD74,CD86,CLEC7A,CTSS,CYBB,DDX58,ERAP1,FKBP1A,GZMA,HBP1,HLA-DMA,HLA-DMB,HLA-DQA1,HLA-DRB1,HMGB1,IFNAR1,JAK2,MGST1,MICA,NBR1,NDFIP1,NFE2L2,PELI1,PLEK,PPP3CB,PRNP,PSMB8,PTGER4,PTPRC,RAB10,RAB32,RAB6A,RAB8B,SELE,SELL,STAT1,TGFB2,TNFSF13B	46
Cell-To-Cell Signaling and Interaction	activation of cells	4.70E-07	ANXA1,ATM,BLOC1S6,CD244,CD36,CD46,CD47,CD58,CD74,CD86,CLEC7A,CTSS,CYBB,CYLD,DDX58,EIF2AK2,ERAP1,ERIN1,FCER1A,FKBP1A,FNTA,GPX1,GZMA,HBP1,HLA-DMA,HLA-DMB,HLA-DQA1,HLA-DRB1,HMGB1,IFNAR1,JAK2,MGST1,MICA,MTCH1,NBR1,NDFIP1,NFE2L2,PELI1,PLEK,PPP2CA,PPP3CB,PRNP,PSMB8,PTGER4,PTPRC,RAB10,RAB32,RAB6A,RAB8B,RICTOR,SELE,SELL,STAT1,TGFB2,TNFSF13B	55
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell Trafficking, Inflammatory Response	activation of antigen presenting cells	5.45E-07	ATM,CD36,CD47,CD74,CD86,CLEC7A,CTSS,CYBB,ERAP1,HBP1,HLA-DMA,HLA-DMB,HLA-DQA1,HMGB1,IFNAR1,JAK2,PELI1,PRNP,PSMB8,PTGER4,RAB10,RAB32,RAB6A,RAB8B,STAT1	25

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Antimicrobial Response, Cell-To-Cell Signaling and Interaction, Connective Tissue Development and Function, Inflammatory Response	antiviral response of fibroblasts	1.08E-05	DDX58, IFNAR1, STAT1	3
Cell-To-Cell Signaling and Interaction, Cellular Movement, Hematological System Development and Function, Immune Cell Trafficking	recruitment of leukocytes	2.61E-05	ANXA1, CD36, CD47, CD74, CLEC7A, DDX58, FCER1A, GLRX, HDC, HMGB1, IFNAR1, ITGA4, IRRK2, NFE2L2, PELI1, P RMT2, RAP1A, ROCK1, SELE, SELL, TGFBR2	21

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Alternately Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction, Tissue Development	adhesion of blood cells	6.76E-05	ANXA1, ANXA7, CD36, CD46, CD47, CD58, CD74, CDC42, GLRX, HMGB1, IFNGR1, ITGA4, JAK2, PAFAH1B1, PTGER4, PTPRC, RICTOR, ROCK1, SELE, SELL, STAT1, TGFBR2	24
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell Trafficking, Tissue Development	adhesion of immune cells	1.31E-04	ANXA1, CD36, CD46, CD47, CD58, CD74, CDC42, GALNT1, GLRX, HMGB1, IFNGR1, ITGA4, JAK2, PAFAH1B1, PTGER4, PTPRC, RICTOR, ROCK1, SELE, SELL, STAT1, TGFBR2	22
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell	activation of lymphocytes	1.39E-04	ANXA1, BLOC1S6, CD244, CD46, CD47, CD58, CD74, CD86, CLEC7A, DDX58, GZMA, HLA-DRB1, HMGB1, IFNAR1, MGST1, MICA, NBR1, NDFIP1, NFE2L2, PELI1, PPP3CB, PRNP, PTPRC, STAT1, TGFBR2, TNFSF13B	26

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Trafficking, Inflammatory Response				
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell Trafficking, Tissue Development	adhesion of mononuclear leukocytes	2.18E-04	ANXA1,CD47,CD58,HMGB1,IFNGR1,ITGA4,JAK2,RICTOR,ROCK1,SELE,SELL,TGFBR2	12
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell	activation of T lymphocytes	2.25E-04	ANXA1,CD244,CD46,CD47,CD58,CD74,CD86,CLEC7A,DDX58,GZMA,HLA-DRB1,IFNAR1,MGST1,NBR1,NDFIP1,NFE2L2,PPP3CB,PRNP,PTPRC,STAT1,TGFBR2	21

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Trafficking, Inflammatory Response				
Cell-To-Cell Signaling and Interaction, Cell-mediated	adhesion of T lymphocytes	3.06E-04	ANXA1,CD47,CD58,IFNGR1,ITGA4,AK2,RICTOR,SELE,SELL	9
Immune Response, Cellular Movement, Hematological System				
Development and Function, Immune Cell				
Trafficking, Tissue Development				
Cell-To-Cell Signaling and Interaction, Inflammatory Response	response of phagocytes	3.84E-04	ABCA7,ANXA1,CD36,CD47,CLEC7A,DDX58,ERN1,FCER1A,GLRX,HMGB1,IFNAR1,ITGA4,NR3C1,ZEB2	14

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell Trafficking, Tissue Development	adhesion of lymphocytes	4.20E-04	ANXA1,CD47,CD58,IFNGR1,ITGA4,IAK2,RICTOR,ROCK1,SELE,SELL	10
Cell-To-Cell Signaling and Interaction, Cellular Function and Maintenance, Hematological System Development and Function, Inflammatory Response	phagocytosis of granulocytes	4.51E-04	ANXA1,CD36,CD47,GLRX,HMGB1,IFNAR1	6

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction, Connective Tissue Development and Function	response of fibroblasts	4.52E-04	CD36,DDX58,IFNAR1,STAT1	4
Cell-To-Cell Signaling and Interaction, Cellular Function and Maintenance, Hematological System Development and Function, Inflammatory Response	phagocytosis of bone marrow-derived neutrophils	4.91E-04	CD47,HMGB1	2

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cardiovascular System Development and Function, Cell-To-Cell Signaling and Interaction, Tissue Development	adhesion of endothelial cells	5.03E-04	ANXA7,CD36,CDC42,HMGB1,IGFBP7,ITGA4,RICTOR,SELE,SELL,TGFBR2,TMSB10/TMSB4X	11
Cell-To-Cell Signaling and Interaction	response of myeloid cells	5.49E-04	ABCA7,ANXA1,CD36,CD47,DDX58,ERN1,FCER1A,GLRX,HMGB1,IFNAR1,ITGA4,NR3C1,PTPRC	13
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell Trafficking, Tissue Development	detachment of leukocytes	8.24E-04	ANXA1,PTPRC,SELL	3
Cell-To-Cell Signaling and Interaction, Inflammatory Response	immune response of leukocytes	8.55E-04	ABCA7,ANXA1,CD36,CD47,CD86,CTSS,DDX58,ERN1,FCER1A,GLRX,HMGB1,IFNAR1,IFNGR1,ITGA4,NR3C1,PTPRC,TGFBR2	17

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cardiovascular System Development and Function, Cell-To-Cell Signaling and Interaction, Tissue Development	adhesion of vascular endothelial cells	9.38E-04	ANXA7,CD36,HMGB1,IGFBP7,ITGA4,RICTOR,SELE,TMSB10/TMSB4X	8
Cell-To-Cell Signaling and Interaction, Inflammatory Response	immune response of phagocytes	1.30E-03	ABCA7,ANXA1,CD36,CD47,DDX58,ERN1,FCER1A,GLRX,HMGB1,IFNAR1,ITGA4,NR3C1	12
Cell-To-Cell Signaling and Interaction	response of granulocytes	1.33E-03	ANXA1,CD36,CD47,FCER1A,GLRX,HMGB1,IFNAR1,ITGA4	8
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Inflammatory Response	immune response of neutrophils	1.37E-03	CD36,CD47,FCER1A,GLRX,HMGB1,IFNAR1,ITGA4	7

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction	response of antigen presenting cells	1.42E-03	ABCA7, ANXA1, CD36, CD47, CLEC7A, CTSS, DDX58, ERN1, HMGB1, IFNAR1, NR3C1	11
Cell-To-Cell Signaling and Interaction, Cellular Movement, Hematological System Development and Function, Immune Cell Trafficking	recruitment of mononuclear leukocytes	1.80E-03	CD47, DDX58, FCER1A, HDC, HMGB1, ITGA4, PELI1, SELE, SELL	9
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function	immune response of antigen presenting cells	2.03E-03	ABCA7, ANXA1, CD36, CD47, CTSS, DDX58, ERN1, HMGB1, IFNAR1, NR3C1	10
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function	binding of B-lymphocyte derived cell lines	2.05E-03	CD47, CRKL, ITGA4	3

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell Cycle, Cell-To-Cell Signaling and Interaction, Cellular Growth and Proliferation	contact growth inhibition of leukocytes	2.05E-03	HMGB1, IKZF1, PTPRC	3
Cell-To-Cell Signaling and Interaction, Cellular Function and Maintenance, Hematological System	phagocytosis of neutrophils	2.53E-03	CD36,CD47,GLRX,HMGB1,IFNAR1	5
Development and Function, Inflammatory Response				
Cell-To-Cell Signaling and Interaction, Hematological System	cell-cell adhesion of leukocytes	2.80E-03	ITGA4,PTPRC,ROCK1,SELE	4
Development and Function, Immune Cell Trafficking, Tissue Development				

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cardiovascular System Development and Function, Cell-To-Cell Signaling and Interaction, Tissue Development	adhesion of HCAEC cells	2.86E-03	SELE,SELL	2
Cell-To-Cell Signaling and Interaction, Cellular Compromise, Tissue Development, Tumor Morphology	adhesion of acute myeloid leukemia blast cells	2.86E-03	SELE,SELL	2
Cell-To-Cell Signaling and Interaction, Nervous System Development and Function	afterhyperpolarization of central nervous system cells	2.86E-03	ATP2B4,LMO4	2

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction, Cellular Movement, Hematological System Development and Function, Immune Cell Trafficking, Tissue Development	detachment of phagocytes	2.86E-03	ANXA1,PTPRC	2
Cell-To-Cell Signaling and Interaction, Cell-mediated Immune Response, Cellular Movement, Hematological System Development and Function, Immune Cell Trafficking	recruitment of CD8+ T lymphocyte	2.86E-03	DDX58,PELI1	2

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell Cycle, Cell-To-Cell Signaling and Interaction, Cellular Growth and Proliferation	contact growth inhibition	3.09E-03	CDC42, GBP2, HMGB1, IKZF1, ING4, JAK2, PTPRC, RAF1, RBL2, STAT1	10
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell Trafficking, Infectious Disease, Tissue Development	fusion of leukocytes	3.21E-03	CD36, CD46, CD47, STAT1	4
Cell-To-Cell Signaling and Interaction, Inflammatory Response	response of macrophages	3.89E-03	ABCA7, ANXA1, CD36, CD47, CLEC7A, DDX58, ERN1, HMGB1, NR3C1	9

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction, Cellular Function and Maintenance, Inflammatory Response	phagocytosis of cells	4.10E-03	ABCA7, ANXA1, CD302, CD36, CD47, CDC42, CLEC7A, CLTC, DNTTIP1, GLRX, HMGB1, IFNAR1, LY75, NR3C1	14
Cell-To-Cell Signaling and Interaction	binding of blood cells	4.16E-03	CD47, CD58, CD86, HLA-DMA, HMGB1, IFNGR1, ITGA4, JAK2, NFE2L2, PTPRC, RAP1B, SELE, SELL	13
Cell-To-Cell Signaling and Interaction, Hematological System	binding of T lymphocytes	4.25E-03	CD47, CD58, CD86, HLA-DMA, IFNGR1, ITGA4	6
Development and Function, Tissue Development				

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell Trafficking, Inflammatory Response, Tissue Development	adhesion of monocytes	4.49E-03	HMGB1, ROCK1, SELE, SELL, TGFBR2	5
Cell-To-Cell Signaling and Interaction, Cell-mediated Immune Response, Cellular Movement, Hematological System Development and Function, Immune Cell Trafficking	recruitment of T lymphocytes	4.56E-03	CD47, DDX58, FCER1A, HDC, PELL1, SELE	6

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction, Nervous System Development and Function	afterhyperpolarization of neurons	4.70E-03	ATP2B4, LMO4	2
Cell Cycle, Cell-To-Cell Signaling and Interaction, Cellular Growth and Proliferation	contact growth inhibition of melanoma cell lines	4.70E-03	RAF1, STAT1	2
Cell-To-Cell Signaling and Interaction, Cellular Growth and Proliferation, Hematological System Development and Function	suppression of effector T lymphocytes	4.70E-03	CD46, CD86	2

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function	binding of mononuclear leukocytes	5.07E-03	CD47,CD58,CD86,HLA-DMA,IFNGR1,ITGA4,SELE,SELL	8
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function	binding of lymphocytes	5.22E-03	CD47,CD58,CD86,HLA-DMA,IFNGR1,ITGA4,SELL	7
Cell-To-Cell Signaling and Interaction, Cellular Movement, Hematological System Development and Function, Immune Cell Trafficking	recruitment of lymphocytes	5.52E-03	CD47,DDX58,FCER1A,HDC,PELI1,SELE,SELL	7

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell Trafficking, Inflammatory Response, Tissue Development	adhesion of phagocytes	5.85E-03	ANXA1, GLRX, HMGB1, ITGA4, PAFAH1B1, ROCK1, SELE, SELL, TGFBR2	9
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Hematopoiesis	binding of hematopoietic progenitor cells	5.85E-03	CD47, ITGA4, RAP1B	3
Cell-To-Cell Signaling and Interaction	binding of leukemia cell lines	6.81E-03	CD36, CD47, ITGA4, JAK2, SELL	5
Cell-To-Cell Signaling and Interaction	binding of bone marrow cell lines	6.90E-03	CRKL, ITGA4, RAF1	3

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction, Cell-mediated Immune Response, Cellular Movement, Hematological System Development and Function, Immune Cell Trafficking, Tissue Development	adhesion of Th1 cells	6.94E-03	ITGA4, SELE	2
Antigen Presentation, Cell-To-Cell Signaling and Interaction, Inflammatory Response	antigen presentation of antigen presenting cells	6.94E-03	CTSS, IFNAR1	2

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell Trafficking, Tissue Development	detachment of myeloid cells	6.94E-03	ANXA1,PTPRC	2
Cell-To-Cell Signaling and Interaction, Inflammatory Response	response of mast cells	6.94E-03	FCER1A,ZEB2	2
Cell-To-Cell Signaling and Interaction, Inflammatory Response	immune response of macrophages	7.11E-03	ABCA7,ANXA1,CD36,CD47,DDX58,ERN1,HMGB1,NR3C1	8
Cell-To-Cell Signaling and Interaction	recognition of cells	7.26E-03	CD36,CD47,CLEC7A,MICA	4

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell Trafficking, Inflammatory Response	activation of phagocytes	7.34E-03	ANXA1,ATM,CD36,CD47,CD86,CLEC7A,CYBB,FKBP1A,GZMA,HMGB1,IFNAR1,JAK2,PELI1,PRNP,PTGER4,SELE,SELL,STAT1	18
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Humoral Immune Response	binding of B lymphocytes	8.07E-03	CD47,CD86,ITGA4	3

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cardiovascular System Development and Function, Cell-To-Cell Signaling and Interaction, Tissue Development	adhesion of postcapillary venule	9.58E-03	CD74,SELL	2
	contact growth inhibition of lymphocytes	9.58E-03	IKZF1,PTPRC	2
	phagocytosis of blood cells	1.06E-02	ABCA7,ANXA1,CD36,CD47,CDC42,GLRX,HMGB1,IFNAR1	8

TABLE 6. Functions, Associated with the Top 2 Molecular and Cellular Functions Over-Represented in the 412 Differentially Aternatively Spliced Genes - Cell Death and Survival, and Cell-to-Cell Signaling				
Categories	Diseases or Functions Annotation	p-Value	Molecules	# Molecules
Cell-To-Cell Signaling and Interaction, Cellular Function and Maintenance, Inflammatory Response	phagocytosis of phagocytes	1.14E-02	ABCA7, ANXA1, CD36, CD47, GLRX, HMGB1, IFNAR1	7
	fusion of cells	1.15E-02	ANXA1, CD36, CD46, CD47, IFRD1, ROCK1, STAT1, UBE2B	8

TABLE 1. Differentiated Exon Usage in the 5 Groups ($p < 0.005$, $|FC| > 1.2$)

Table 1A: Exon Usage Upregulated in Cardioembolic Ischemic Stroke (CE IS)				
Marker ID	Gene Symbol	Entrez GeneID	Ensembl	UniProtKB
chr17.73000302-73002233>CDR2L	CDR2L	30850	ENSG00000109089	Q86X02
chr8.104406853-104407319>shuskeebu	shuskeebu	"NoInfo"	"NoInfo"	"NoInfo"
chr3.48456585-48456756>PLXNB1	PLXNB1	5364	ENSG00000164050	Q43157
chr1.86861716-86861978>ODF2L	ODF2L	57489	ENSG00000122417	Q9UL1
chr19.58427747-		147687 and		
58427959>ZNF417 and ZNF814	ZNF417 and ZNF814	730051	ENSG00000173480 and ENSG00000204514	Q8TAU3 and B7Z6K7
chr19.58427747-		147687 and		
58427960>ZNF417 and ZNF814	ZNF417 and ZNF814	730051	ENSG00000173480 and ENSG00000204514	Q8TAU3 and B7Z6K7
chr22.19115606-19115962>skatee	skatee	"NoInfo"	"NoInfo"	"NoInfo"
chr10.49253461-49254183>BMS1P7	BMS1P7	100133265	ENSG00000243899	
chr14.70242552-70243105>SLC10A1	SLC10A1	6554	ENSG00000100652	Q14973
chr7.142630429-142630905>TRPV5	TRPV5	56302	ENSG00000127412	Q9NQA5
chr10.38299602-38299711>ZNF33A	ZNF33A	7581	ENSG00000189180	Q06730
chr10.38299604-38299711>ZNF33A	ZNF33A	7581	ENSG00000189180	Q06730
chr2.119988299-119988610>STEAP3	STEAP3	55240	ENSG00000115107	Q658P3
chr2.179463448-179463831>CCDC141 and TTN	CCDC141 and TTN	285025 and 7273	ENSG00000163492 and ENSG00000155657	Q6ZP82 and Q8WZ42
chr2.25258142-25260098>LOC729723	LOC729723	"NoInfo"	"NoInfo"	"NoInfo"
chr17.34856670-34856799>MYO19	MYO19	80179	ENSG00000141140	Q96H55
chr7.158334118-158334468>PTPRN2	PTPRN2	5799	ENSG00000155093	Q92932
chr3.188326949-188327339>LPP	LPP	4026	ENSG00000145012	Q93052
chr19.18959976-18960255>UPF1	UPF1	5976	ENSG000000005007	Q92900
chr6.37225553-37225749>TBC1D22B	TBC1D22B	55633	ENSG000000065491	Q9NU19
chr20.43995515-43996064>SYS1-DBNDD2	SYS1-DBNDD2	767557	ENSG00000254806	H3BUS1
chr3.49448633-49449166>myforbo	myforbo	"NoInfo"	"NoInfo"	"NoInfo"
chr4.15570247-15570813>klawgu	klawgu	"NoInfo"	"NoInfo"	"NoInfo"

TABLE 1. Differentiated Exon Usage in the 5 Groups (p < 0.005, |FC| > 1.2)

Table 1B: Exon Usage Upregulated in Large Vessel Ischemic Stroke (LV IS)				
Marker ID	Gene Symbol	Entrez GeneID	Ensembl	UniProtKB
chr6.37225553-37225749>TBC1D22B	TBC1D22B	55633	ENSG000000065491	Q9NU19
chr20.43995515-43996064>SYS1-DBNDD2	SYS1-DBNDD2	767557	ENSG000000254806	H3BUS1
chr3.49448633-49449166>myforbo	myforbo	"NoInfo"	"NoInfo"	"NoInfo"
chr4.15570247-15570813>klawgu	klawgu	"NoInfo"	"NoInfo"	"NoInfo"
chr14.53248502-53248629>GNPNAT1	GNPNAT1	64841	ENSG00000100522	Q96EK6
chr22.29141852-29141989>HSCB	HSCB	150274	ENSG00000100209	Q8IWL3
chr16.72146312-72146549>DHX38	DHX38	9785	ENSG00000140829	Q92620
chr5.176715528-176715926>NSD1	NSD1	64324	ENSG00000165671	Q96L73
chr6.100023529-100023947>RPS3P5	RPS3P5	100131956	ENSG000000219755	"NoInfo"
chr13.103506107-103506222>BIVMandERCC5	BIVM and ERCC5	54841 and 2073	ENSG00000134897 and ENSG00000134899	Q86UB2 and P28715
chr7.2282560-2282683>NUDT1	NUDT1	4521	ENSG00000106268	P36639
chr12.54645834-54646011>CBX5	CBX5	23468	ENSG000000094916	P45973
chr20.33056659-33057236>vytaw	vytaw	"NoInfo"	"NoInfo"	"NoInfo"
chr5.162902464-162902678>HMMR	HMMR	3161	ENSG00000072571	O75330
chr11.62389338-62389648>B3GAT3	B3GAT3	26229	ENSG00000149541	O94766
chr15.101847418-101849508>PCSK6	PCSK6	5046	ENSG00000140479	P29122
chr5.61688639-61688817>DIMIT1L	DIMIT1L (DIMIT1)	27292	ENSG000000086189	Q9UNQ2
chr12.56334947-56335109>DGKA	DGKA	1606	ENSG000000065357	P23743
chr10.46918169- 46918362>FAM35B and RHEBP1	FAM35B(FAM35BP) and RHEBP1	414241 and 6008	ENSG00000165874 and ENSG00000229927	"NoInfo"
chr2.20756227-20757428>dawgorbu	dawgorbu	"NoInfo"	"NoInfo"	"NoInfo"
chrX.152226503-152227128>PNMIA3	PNMIA3	29944	ENSG00000183837	Q9UL41
chr22.18613610-18614498>PEX26 and TUBA8	PEX26 and TUBA8	55670 and 51807	ENSG00000215193 and ENSG00000183785	Q7Z412 and Q9NY65
chr6.111619174-111619773>sljey	sljey	"NoInfo"	"NoInfo"	"NoInfo"
chr17.43002077-43003867>KIF18B	KIF18B	146909	ENSG00000186185	Q86Y91

TABLE 1. Differentiated Exon Usage in the 5 Groups ($p < 0.005$, $|FC| > 1.2$)

chr8.90798887-90799401>RIPK2	RIPK2	8767	ENSG00000104312	O43353
chr1.214836934-214837426>CENPF	CENPF	1063	ENSG00000117724	P49454
chr3.8606070-8609805>LMCD1	LMCD1	29995	ENSG00000071282	Q9NZU5
chr20.52560545-52561535>BCAS1	BCAS1	8537	ENSG000000064787	O75363
chr2.173420100-173420447>PDK1	PDK1	5163	ENSG00000152256	Q15118
chr15.81584265-81585378>IL16	IL16	3603	ENSG00000172349	Q14005
chr9.131486273-131486409>ZDHHC12	ZDHHC12	84885	ENSG00000160446	Q96GR4
chr16.4475881-4476093>DNAJA3	DNAJA3	9093	ENSG00000103423	Q96EY1

Table 1C: Exon Usage Upregulated in Lacunar Ischemic Stroke (L IS)

Marker ID	Gene Symbol	Entrez GeneID	Ensembl	UniProtKB
chr11.1.119039480-119040011>NLRX1	NLRX1	79671	ENSG00000160703	Q86UT6
chr15.52970203-52970319>KIAA1370	KIAA1370 (FAM214A)	56204	ENSG00000047346	Q32MH5
chr11.62475067-62475387>GNG3	GNG3	2785	ENSG00000162188	P63215
chr12.94914730-94915694>LOC400061	LOC400061	400061	ENSG00000258357	"NoInfo"
chr16.15013757-15013940>zoner	zoner	"NoInfo"	"NoInfo"	"NoInfo"
chr2.29258330-29258510>FAM179A	FAM179A	165186	ENSG00000189350	Q6ZUX3
chr18.33077683-33077895>INO80C	INO80C	125476	ENSG00000153391	Q6PI98
chr2.160143094-160143317>WDSUB1	WDSUB1	151525	ENSG00000196151	Q8N9V3
chr22.44514918-44515020>PARVB	PARVB	29780	ENSG00000188677	Q9HB11
chr5.156821041-156822687>ADAM19	ADAM19	8728	ENSG00000135074	Q9H013
chr6.146285293-146285559>SHPRH	SHPRH	257218	ENSG00000146414	Q149N8
chr6.146285293-146285525>SHPRH	SHPRH	257218	ENSG00000146414	Q149N8
chr22.24316496-24316679>GSTTP1andDDT	GSTTP1 and DDT	25774 and 1652	ENSG00000241850 and ENSG00000099977	"NoInfo" and P30046
chr12.2966630-2968829>FOXMI	FOXMI	2305	ENSG0000011206	Q08050
chr7.99674926-99675056>ZNF3	ZNF3	7551	ENSG00000166526	P17036
chr6.30610545-30612432>C6orf134	C6orf134 (ATAT1)	79969	ENSG00000137343	Q55Q10
chr19.35173682-35173954>ZNF302	ZNF302	55900	ENSG00000089335	Q9NR11

TABLE 1. Differentiated Exon Usage in the 5 Groups ($p < 0.005$, $|FC| > 1.2$)

Marker ID	Gene Symbol	Entrez GeneID	Ensembl	UniProtKB
chr21.47706315-47706712>C21orf57	C21orf57 (YBEY)	54059	ENSG000000182362	P58557
chr12.111065735-111066029>TCTN1	TCTN1	79600	ENSG000000204852	Q2MV58
chrX.40495835-40495964>CXorf38	CXorf38	159013	ENSG000000185753	Q8TB03
chr9.46687439-46688197>KGFLP1	KGFLP1	387628	ENSG000000227449	Q2TVT4
chr2.101627502-101628002>TBC1D8	TBC1D8	11138	ENSG000000204634	O95759
chr1.160580214-160580588>SLAMF1	SLAMF1	6504	ENSG000000117090	Q13291
chr8.10340434-10340741>LOC346702	LOC346702	"NoInfo"	"NoInfo"	"NoInfo"
chr6.168370462-168372588>MLLT4	MLLT4	4301	ENSG000000130396	P55196
chr1.155691308-155691471>DAP3	DAP3	7818	ENSG000000132676	P5139
chr12.123262038-123262230>CCDC62	CCDC62	84660	ENSG000000130783	Q6P9F0
chr14.96795821-96795971>ATG2B	ATG2B	55102	ENSG000000066739	Q96BY7
chr20.32079185-32079982>spawvor	spawvor	"NoInfo"	"NoInfo"	"NoInfo"
chr6.163984476-163984751>QKI	QKI	9444	ENSG000000112531	Q96PU8
chr1.246729640-246730091>CNST	CNST	163882	ENSG000000162852	Q6PJW8

Table 1D: Exon Usage Upregulated in Intracerebral Hemorrhage (ICH)				
Marker ID	Gene Symbol	Entrez GeneID	Ensembl	UniProtKB
chr19.44128266-44128394>CADM4	CADM4	199731	ENSG000000105767	Q8NfZ8
chr5.139929370-139930496>APBB3andSRA1	APBB3 and SRA1	10307 and 10011	ENSG000000113108 and ENSG000000213523	O95704 and Q9HD15
chr1.85127881-85128058>SSX2IP	SSX2IP	117178	ENSG000000117155	Q9Y2D8
chr22.31733654-31734031>sneypoy	sneypoy	"NoInfo"	"NoInfo"	"NoInfo"
chr17.40280569-40280818>RAB5C	RAB5C	5878	ENSG000000108774	P51148
chr3.23929058-23929280>UBE2E1	UBE2E1	7324	ENSG000000170142	P51965
chr7.149598-152547>kehera	kehera	"NoInfo"	"NoInfo"	"NoInfo"
chr3.122283274-122283460>DTX3L	DTX3L	151636	ENSG000000163840 ENSG000000119686 and ENSG000000119685 and	Q8TDB6
chr14.76107075-76107403>FLVCR2andTTLL5andC14orf179	FLVCR2 and TTLL5 and C14orf179 (IFT43)	55640 and 23093 and 112752	ENSG000000119650	Q9UPI3 and Q6EMB2 and Q96FT9

TABLE 1. Differentiated Exon Usage in the 5 Groups ($p < 0.005$, $|FC| > 1.2$)

chr1.235956803-235956912>LYST	LYST	1130	ENSG000000143669	Q99698
chr2.198175302-198175503>ANKRD44	ANKRD44	91526	ENSG000000065413	Q8N8A2
chr22.20093700-20093800>DGCR8	DGCR8	54487	ENSG000000128191	Q8WYQ5
chr1.112991564-112991794>CTTNBP2NL	CTTNBP2NL	55917	ENSG000000143079	Q9P2B4
chr1.19470474-19470585>UBR4	UBR4	23352	ENSG000000127481	Q5T4S7
chr5.134343647-			ENSG000000132570 and	
134343829>PCBD2 and CATSPER3	PCBD2 and CATSPER3	84105 and 347732	ENSG000000152705	Q9H0N5 and Q86XQ3
chr19.49314066-49314178>BCAT2	BCAT2	587	ENSG000000105552	O15382
chr2.118864235-118864479>INSIG2	INSIG2	51141	ENSG000000125629	Q9Y5U4
chr18.48443613-48443878>ME2	ME2	4200	ENSG000000082212	P23368
chr22.45254869-45255776>PRR5-ARHGAP8	PRR5-ARHGAP8	553158	ENSG000000248405	B1AHC4
chr1.27431807-27432578>SLC9A1	SLC9A1	6548	ENSG000000090020	P19634
chr8.133984843-133984986>TG	TG	7038	ENSG000000042832	P01266
chr6.41751200-			ENSG000000124593 and	
41751976>PRICKLE4 and TOMM6	PRICKLE4 and TOMM6	29964 and 100188893	ENSG000000214736	Q2TBC4 and Q96B49
chr17.57728564-57728677>CLTC	CLTC	1213	ENSG000000141367	Q00610
chr3.150280329-150280447>EIF2A	EIF2A	83939	ENSG000000144895	Q9BY44
chr2.242282407-242282508>SEPT2	SEPT2	4735	ENSG000000168385	Q15019
chr21.40619627-40619758>BRWD1	BRWD1	54014	ENSG000000185658	Q9NS16
chr1.26799700-26800018>HMG2	HMG2	3151	ENSG000000198830	P05204
chr5.140895496-140896575>DIAPH1	DIAPH1	1729	ENSG000000131504	O60610
chr5.140895875-140896575>DIAPH1	DIAPH1	1729	ENSG000000131504	O60610
chr1.180049625-180049796>CEP350	CEP350	9857	ENSG000000135837	Q5VT06
chr1.180049652-180049796>CEP350	CEP350	9857	ENSG000000135837	Q5VT06
chr5.70531277-70532281>goychyby	goychyby	"NoInfo"	"NoInfo"	"NoInfo"
chr13.100543572-100543866>CLYBL	CLYBL	171425	ENSG000000125246	Q8N0X4
chr19.36515246-36515534>CLIP3	CLIP3	25999	ENSG000000105270	Q96DZ5
chr6.144289727-			ENSG000000118495 and	
144290115>PLAGL1 and HYMAI	PLAGL1 and HYMAI	5325 and 57061	"NoInfo"	Q9UM63 and "NoInfo"

TABLE 1. Differentiated Exon Usage in the 5 Groups ($p < 0.005$, $|FC| > 1.2$)

			"NoInfo"	"NoInfo"	"NoInfo"
chr21.147608408-47608855>klorley	klorley				"NoInfo"
chr9.17135038-17135423>CNTLN	CNTLN		54875	ENSG000000044459	Q9NXG0
chr1.114499947-114500540>wawleybo	wawleybo		"NoInfo"	"NoInfo"	"NoInfo"
chr17.18486655-18486837>CCDC144B	CCDC144B		284047	ENSG000000154874	Q3MJ40
chr4.40800804-40800921>NSUN7	NSUN7		79730	ENSG000000179299	Q8NE18
chr3.39162488-39162680>TTC21A	TTC21A		199223	ENSG000000168026	Q8NDW8
chr1.161196029-161196394>TOMM40L	TOMM40L		84134	ENSG000000158882	Q969M1
chr7.45083306-45083697>CCM2	CCM2		83605	ENSG000000136280	Q9BSQ5
chr19.13009896-13010199>SYCE2	SYCE2		256126	ENSG000000161860	Q6PIF2
chr3.20019802-20020396>RAB5A	RAB5A		5868	ENSG000000144566	P20339
chr6.122792844-122793050>SERINC1	SERINC1		57515	ENSG000000111897	Q9NRX5
chr2.231663444-231663879>CAB39	CAB39		51719	ENSG000000135932	Q9Y376
chr1.145790974-145791170>GPR89A	GPR89A		653519	ENSG000000117262	B7ZQA6
chr4.175223190-175223337>KIAA1712	KIAA1712 (CEP44)		80817	ENSG000000164118	Q9C0F1
chr2.182339687-182340015>ITGA4	ITGA4		3676	ENSG000000115232	P13612
chr16.18799866-18800440>ARL6IP1 and RPS15A	ARL6IP1 and RPS15A		23204 and 6210	ENSG000000170540 and ENSG000000134419	Q15041 and P62244
chr6.3021094-3022352>teyybo	teyybo		"NoInfo"	"NoInfo"	"NoInfo"
chr16.22277711-22277845>EEF2K	EEF2K		29904	ENSG000000103319	O00418
chr11.7479027-7479174>veemee	veemee		"NoInfo"	"NoInfo"	"NoInfo"
chrX.77303661-77305892>ATP7A	ATP7A		538	ENSG000000165240	Q04656
chr1.78207302-78207433>USP33	USP33		23032	ENSG000000077254	Q8TEY7
chrX.76776266-76776394>ATRX	ATRX		546	ENSG000000085224	P46100
chr12.6761437-6761584>ING4	ING4		51147	ENSG000000111653	Q9UNL4
chr17.77079383-77079672>ENGASE	ENGASE		64772	ENSG000000167280	Q8NFI3
chr11.11189680-111893374>DIXDC1	DIXDC1		85458	ENSG000000150764	Q155Q3
chr11.11189680-111893310>DIXDC1	DIXDC1		85458	ENSG000000150764	Q155Q3
chr4.157731989-157732169>PDGFC	PDGFC		56034	ENSG000000145431	Q9NRA1

TABLE 1. Differentiated Exon Usage in the 5 Groups ($p < 0.005$, $|FC| > 1.2$)

chr20.18449588-18449705>POLR3F	POLR3F	10621	ENSG000000132664	Q9H1D9
chr11.47738539-47739064>FNBP4	FNBP4	23360	ENSG000000109920	Q8N3X1
chr16.30593851-30595166>syrrar	syrrar	"NoInfo"	"NoInfo"	"NoInfo"
chr13.41593364-41593568>ELF1	ELF1	1997	ENSG000000120690	P32519
chr22.51221467-51221714>RABL2B	RABL2B	11158	ENSG000000079974	Q9UNT1
chr9.33264164-33264493>CHMP5	CHMP5	51510	ENSG000000086065	Q9NZZ3
chr1.154928545-154928780>SHC1andPYGO2andPBXIP1	SHC1 and PYGO2 and PBXIP1	6464 and 90780 and	ENSG000000160691 and	P29353 and Q9BRQ0 and
chr19.1953385-1953505>C19orf34	C19orf34 (CSNK1G2-AS1)	57325	ENSG000000163346	Q96AQ6
chr2.113175261-113175491>RGPD8	RGPD8	255193	ENSG000000180846	Q8NCQ2
chr1.145509166-145509612>RBM8A.1	RBM8A.1	727851	ENSG000000169629	O14715
chr1.89271574-89271700>PKN2	PKN2	"NoInfo"	"NoInfo"	"NoInfo"
chr10.99433338-99433902>DHGPSlandPI4K2A	DHGPSL (HOGA1) and PI4K2A	5586	ENSG000000065243	Q16513
chr7.74166365-74166897>GTF2I	GTF2I	112817 and 55361	ENSG000000241935 and	Q86XE5 and Q9BTU6
chr18.54318248-54318824>TXNL1	TXNL1	2969	ENSG000000077809	P78347
chr12.58345541-58345678>XRCC6BP1	XRCC6BP1	9352	ENSG000000091164	O43396
chr7.76870183-76870364>CCDC146	CCDC146	91419	ENSG000000166896	Q9Y6H3
chr3.52385978-52386119>DNAH1	DNAH1	57639	ENSG000000135205	Q8IYE0
chr12.96258857-96259166>SNRPF	SNRPF	25981	ENSG000000114841	Q9P2D7
chr1.63269390-63269533>ATG4C	ATG4C	6636	ENSG000000139343	P62306
chr2.172848099-172848599>HAT1	HAT1	84938	ENSG000000125703	Q96DT6
chr18.67508480-67516323>DOK6	DOK6	8520	ENSG000000128708	O14929
chr8.30948350-30948458>WRN	WRN	220164	ENSG000000206052	Q6PKX4
chr2.208446079-208446884>FAM119A	FAM119A (METTL21A)	7486	ENSG000000165392	Q14191
chr7.5938415-5938550>CCZ1	CCZ1	151194	ENSG000000144401	Q8WXB1
chr19.44619641-44619995>ZNF225	ZNF225	51622	ENSG000000122674	P86791
chr1.243652316-243652442>SDCCAG8	SDCCAG8	7768	ENSG000000256294	Q9UK10
		10805	ENSG000000054282	Q86SQ7

TABLE 1. Differentiated Exon Usage in the 5 Groups ($p < 0.005$, $|FC| > 1.2$)

chr4.122723829-122723983>EXOSC9	EXOSC9	5393	ENSG00000123737	Q06265
chr4.122723829-122723948>EXOSC9	EXOSC9	5393	ENSG00000123737	Q06265
chr1.46805848-46806591>NSUN4andFAAH	NSUN4 and FAAH	387338 and 2166	ENSG00000117481 and ENSG00000117480	Q96CB9 and O00519
chr10.51592090-51592619>LOC100287554	LOC100287554	"NoInfo"	"NoInfo"	"NoInfo"
chrX.138864706-138864887>ATP11C	ATP11C	286410	ENSG00000101974	Q8NB49
chr14.50246313-50246524>KLHDC2	KLHDC2	23588	ENSG00000165516	Q9Y2U9
chr7.22980878-22987334>FAM126A	FAM126A	84668	ENSG00000122591	Q9BY13
chr1.150778337-150778492>CTSK	CTSK	1513	ENSG00000143387	P43235
chr12.48094974-48095387>RPAP3	RPAP3	79657	ENSG000000005175	Q9H6T3
chr15.38619054-38620016>koyzawbu	koyzawbu	"NoInfo"	"NoInfo"	"NoInfo"
chr11.836251-836525>CD151	CD151	977	ENSG00000177697	P48509
chr17.27581220-27581513>CRYBA1	CRYBA1	1411	ENSG00000108255	P05813
chr14.105236090-105236707>AKT1	AKT1	207	ENSG00000142208	P31749
chr10.69828759-69829524>HERC4	HERC4	26091	ENSG00000148634	Q5GLZ8
chr22.50320903-50321181>CRELD2	CRELD2	79174	ENSG00000184164	Q6UXH1
chr12.10561988-10562183>KLRK4andKLRK1	KLRK4 and KLRK1	8302 and 22914	ENSG00000183542 and ENSG00000213809	O43908 and P26718
chr8.104455023-104455428>DCAF13	DCAF13	25879	ENSG00000164934	Q9NV06
chr12.40441853-40442012>SLC2A13	SLC2A13	114134	ENSG00000151229	Q96QE2
chrX.16870674-16871149>RBBP7	RBBP7	5931	ENSG00000102054	Q16576
chr12.54789679-54790160>ITGA5	ITGA5	3678	ENSG00000161638	P08648
chr1.150939858-150940190>LASS2	LASS2 (CERS2)	29956	ENSG00000143418	Q96G23
chr13.113864293-113864812>PCID2	PCID2	55795	ENSG00000126226	Q5JVF3
chr15.80191177-80191467>ST20andMTHFS	ST20 and MTHFS	400410 and 10588	ENSG00000180953 and ENSG00000136371	Q9HBF5 and P49914
chr5.145493406-145493874>LARS	LARS	51520	ENSG00000133706	Q9P2J5
chr16.3493611-3493837>ZNF174andNAT15andCLUAP1	ZNF174 and NAT15 (NAA60) and CLUAP1	7727 and 79903 and 23059	ENSG00000103343 and ENSG00000122390 and	Q15697 and Q9H7X0 and Q96AJ1

TABLE 1. Differentiated Exon Usage in the 5 Groups ($p < 0.005$, $|FC| > 1.2$)

chr6.79664949-79665569>PHIPandTRNAF13P	PHIP and TRNAF13P		ENSG000000103351	Q8WWQ0 and "NoInfo"
chr17.62745780-62746126>LOC146880	LOC146880		ENSG000000146247 and "NoInfo"	
chr17.61473104-61473289>TANC2	TANC2	55023 and 100189446	ENSG000000215769	"NoInfo"
chr15.59102429-59102587>FAM63B	FAM63B	146880	ENSG000000170921	Q9HCD6
chr10.11272033-11272456>CELF2	CELF2	26115	ENSG000000128923	Q8NBR6
chr20.34487292-34487561>PHF20	PHF20	54629	ENSG000000048740	Q95319
chr8.74858684-74859055>TCEB1	TCEB1	10659	ENSG000000025293	Q9BV10
chr2.17953901-17954051>GEN1	GEN1	51230	ENSG000000154582	Q15369
chr14.88431849-88431973>GALC	GALC	6921	ENSG000000178295	Q17RS7
chr19.1877203-1877424>FAM108A1	FAM108A1 (ABHD17A)	348654	ENSG000000054983	P54803
chr17.18087711-18088067>jeeroy	jeeroy	2581	ENSG000000129968	Q96GS6
chr1.168262382-		81926	"NoInfo"	"NoInfo"
168262516>SFT2D2andTBX19	SFT2D2 and TBX19	"NoInfo"	ENSG000000213064 and	
chr6.158088239-158089557>fyjaw	fyjaw	375035 and 9095	ENSG000000143178	O95562 and O60806
chr15.30711214-30711348>rukuru	rukuru	"NoInfo"	"NoInfo"	"NoInfo"
chr8.24256387-24256553>ADAMDEC1	ADAMDEC1	"NoInfo"	"NoInfo"	"NoInfo"
chr15.57545460-57545666>stoyguby	stoyguby	27299	ENSG000000134028	O15204
chr10.75230828-75230967>PPP3CB	PPP3CB	"NoInfo"	"NoInfo"	"NoInfo"
chr20.43808628-43808775>rotora	rotora	5532	ENSG000000107758	P16298
chr1.46467098-46468407>MAST2	MAST2	"NoInfo"	"NoInfo"	"NoInfo"
chr7.2635311-2636062>dochuby	dochuby	23139	ENSG000000086015	Q6P0Q8
chr19.11411543-11411912>tojaw	tojaw	"NoInfo"	"NoInfo"	"NoInfo"
chrX.153744234-153744566>FAM3A	FAM3A	"NoInfo"	"NoInfo"	"NoInfo"
chr2.73957016-73957156>TPRKB	TPRKB	60343	ENSG000000071889	P98173
chr2.234112772-234113219>INPP5D	INPP5D	51002	ENSG000000144034	Q9Y3C4
chr6.41036580-		3635	ENSG000000168918	Q92835
41036692>C6orf130andUNC5CL			ENSG000000124596 and	
	C6orf130 (OARD1) and UNC5CL	221443 and 222643	ENSG000000124602	Q9Y530 and Q8IV45

TABLE 1. Differentiated Exon Usage in the 5 Groups ($p < 0.005$, $|FC| > 1.2$)

chr15.75165540-75165688>SCAMP2	SCAMP2	10066	ENSG00000140497	O15127
chrX.74282163-74282417>ABC87	ABC87	22	ENSG00000131269	O75027
chr2.88336462-88336570>KRCC1	KRCC1	51315	ENSG00000172086	Q9NP17
chrX.2839944-2840065>ARSD	ARSD	414	ENSG00000006756	P51689
chr11.89933252-89935719>CHORDC1	CHORDC1	26973	ENSG00000110172	Q9UHD1
chr8.62438536-62438671>ASPH	ASPH	444	ENSG00000198363	Q12797
chr3.69028819-69028938>C3orf64	C3orf64 (EOGT)	285203	ENSG00000163378	Q5NDL2
chr5.35053745-35054334>fugey	fugey	"NoInfo"	"NoInfo"	"NoInfo"
chr9.35737655-35737936>GBA2	GBA2	57704	ENSG00000070610	Q9HCG7
chr15.94774950-94775234>MCTP2	MCTP2	55784	ENSG00000140563	Q6DN12
chr3.52561845-52561947>NT5DC2	NT5DC2	64943	ENSG00000168268	Q9H857
chr1.85039599-85040103>CTBSandNG5	CTBS and GNG5	1486 and 2787	ENSG00000117151 and ENSG00000174021	Q01459 and P63218
chr10.99195666-99196308>EXOSC1	EXOSC1	51013	ENSG00000171311	Q9Y3B2
chr20.23401942-23402097>NAPB	NAPB	63908	ENSG00000125814	Q9H115
chr17.36351796-36351996>TBC1D3	TBC1D3	729873	ENSG00000197681	Q8IZP1
chrX.118985730-118985836>UPF3B	UPF3B	65109	ENSG00000125351	Q9BZ17
chr15.66811217-66811416>ZWILCH	ZWILCH	55055	ENSG00000174442	Q9H900
chr15.66811217-66811467>ZWILCH	ZWILCH	55055	ENSG00000174442	Q9H900
chr11.125490667- 125490901>STT3AandCHEK1	STT3A and CHEK1	3703 and 1111	ENSG00000134910 and ENSG00000149554	P46977 and O14757
chr3.15778540-15778740>ANKRD28	ANKRD28	23243	ENSG00000206560	O15084
chr19.9720432-9722012>ZNF562andZNF561	ZNF562 and ZNF561	54811 and 93134	ENSG00000171469	Q6V9R5 and Q8N587
chr3.167452594-167452717>PDCD10	PDCD10	11235	ENSG00000114209	Q9BUL8
chr1.10509776-10510379>APITD1andCORT	APITD1 and CORT	378708 and 1325	ENSG00000175279 and ENSG00000241563	Q8N2Z9 and O00230
chr6.34360041-34360260>RPS10andNUDT3	RPS10 and NUDT3	6204 and 11165	ENSG00000124614 and ENSG00000272325	P46783 and Q95989

TABLE 1. Differentiated Exon Usage in the 5 Groups ($p < 0.005$, $|FC| > 1.2$)

TABLE 1. Differentiated Exon Usage in the 5 Groups (p < 0.005, FC >1.2)				
	NCRNA00085 (SPACA6P)	147650 "NoInfo"	ENSG000000182310 "NoInfo"	NoData "NoInfo"
chr19.52207575-52207733>NCRNA00085	saroro	653635	ENSG000000227232	NoData
chr11.62105383-62105784>saroro	WASH7P	5052	ENSG000000117450	Q06830
chr1.17056-17742>WASH7P	PRDX1	10806	ENSG000000054282	Q86SQ7
chr1.45987501-45987609>PRDX1	SDCCAG8	729540	ENSG000000183054	Q99666
chr1.243419358-243419542>SDCCAG8	RGPDP6	84220	ENSG00000015568	Q99666
chr2.111302237-111302383>RGPDP6	RGPDP5	84071	ENSG000000118690	Q8NEN0
chr2.110584278-110584424>RGPDP5	ARMC2	10914	ENSG000000090060	P51003
chr6.109248281-109249436>ARMC2	PAPOLA	147687 and 730051	ENSG000000173480 and ENSG000000204514	Q8TAU3 and B7Z6K7
chr14.96997812-96999040>PAPOLA		147687 and 730051	ENSG000000204514	Q8TAU3 and B7Z6K7
chr19.58423428- 58423554>ZNF417andZNF814	ZNF417 and ZNF814	8776	ENSG000000063601	Q13613
chr19.58423428- 58423557>ZNF417andZNF814	ZNF417 and ZNF814	5802	ENSG000000105426	Q13332
chrX.149924161-149924396>MTMR1	MTMR1	7011	ENSG000000129566	Q99973
chr19.5208248-5208402>PTPRS	PTPRS	128637	ENSG000000125875	Q96BZ9
chr14.20872770-20872931>TEP1	TEP1	2958	ENSG000000140307	P52657
chr20.416929-419485>TBC1D20	TBC1D20	8905	ENSG000000182287	P56377
chr15.59943710-59944525>GTF2A2	GTF2A2	8925	ENSG000000103657	Q15751
chrX.15862547-15863639>AP1S2	AP1S2	9522	ENSG000000085365	O15126
chr15.64017491-64017712>HERC1	HERC1	10055	ENSG000000142230	Q9UBEO
chr5.77656415-77656552>SCAMP1	SCAMP1	10055	ENSG000000142230	Q9UBEO
chr19.47646729-47646862>SAE1	SAE1	"NoInfo"	"NoInfo"	"NoInfo"
chr19.47646751-47646862>SAE1	SAE1	89796	ENSG000000134369	Q8NEY1
chr3.81552424-81552865>chordybo	chordybo	220002	ENSG000000162144	Q8NBI2
chr1.201780731-201780885>NAV1	NAV1		ENSG000000132286 and ENSG000000179532	Q9Y5J6 and Q96M86
chr11.61129205-61129720>CYBASC3	CYBASC3 (CYB561A3)			
chr11.6523983-6524156>FXC1andDNHD1	FXC1 (TIMM10B) and DNHD1	26515 and 144132		
chr19.8441789-8441951>lyta	lyta	"NoInfo"	"NoInfo"	"NoInfo"

TABLE 1. Differentiated Exon Usage in the 5 Groups ($p < 0.005$, $ FC > 1.2$)				
chr6.153291674-153292549>FBXO5	FBXO5	26271	ENSG000000112029	Q9UKT4
chr6.153291660-153292549>FBXO5	FBXO5	26271	ENSG000000112029	Q9UKT4
chr6.153291654-153292549>FBXO5	FBXO5	26271	ENSG000000112029	Q9UKT4
chr7.29549802-29552165>klerky	klerky	"NoInfo"	"NoInfo"	"NoInfo"
chr22.41175013-41175129>SLC25A17	SLC25A17	10478	ENSG000000100372	O43808
chr4.76874494-76874938>sporsmorby	sporsmorby	"NoInfo"	"NoInfo"	"NoInfo"
chr5.39274505-39274630>FYB	FYB	2533	ENSG000000082074	O15117
chr10.32324818-32324922>KIF5B	KIF5B	3799	ENSG000000170759	P33176
chr14.52957557-52957723>TXNDC16	TXNDC16	57544	ENSG000000087301	Q9P2K2
chr14.88452833-88452946>GALC	GALC	2581	ENSG000000054983	P54803
chr20.30720816-30720929>TM9SF4	TM9SF4	9777	ENSG000000101337	Q92544
chr19.54610118-54610266>NDUFA3	NDUFA3	4696	ENSG000000170906	O95167
chr10.92500578-92502285>HTR7	HTR7	3363	ENSG000000148680	P34969
chr3.25637911-25639423>RARB	RARB	5915	ENSG000000077092	P10826
chr5.14381239-14381361>TRIO	TRIO	7204	ENSG000000038382	O75962
chr2.243168539-243168819>samemo	samemo	"NoInfo"	"NoInfo"	"NoInfo"
chr3.137963865-137964523>vusmyby	vusmyby	"NoInfo"	"NoInfo"	"NoInfo"
chr3.137963930-137964523>ARM/C8	ARM/C8	25852	ENSG000000114098	Q8IUR7
chr3.137963930-137964524>ARM/C8	ARM/C8	25852	ENSG000000114098	Q8IUR7
chr14.100743755-100744113>YY1	YY1	7528	ENSG000000100811	P25490
Table 1E – Exon Usage Upregulated in Subjects Who Have Not Experienced Ischemic Stroke/ICH				
Marker ID	Gene Symbol	Entrez GeneID	Ensembl	UniProtKB
chr20.32880178-32880359>AHCY	AHCY	191	ENSG000000101444	P23526
chr2.242611606-242612016>ATG4B	ATG4B	23192	ENSG000000168397	Q9Y4P1
chr9.96866557-96866667>PTPDC1	PTPDC1	138639	ENSG000000158079	A2A3K4
chr17.42982993-42984756>GFAP	GFAP	2670	ENSG000000131095	P14136
chr22.41252435-41253036>ST13	ST13	6767	ENSG000000100380	P50502
chr1.53416427-53416558>SCP2	SCP2	6342	ENSG000000116171	P22307

TABLE 1. Differentiated Exon Usage in the 5 Groups ($p < 0.005$, $ FC > 1.2$)				
chr6.32806430-32806547>TAP2andHLA-DOB	TAP2 and HLA-DOB	6891 and 3112	ENSG00000204267 and	Q03519 and P13765
chr14.19683027-19683434>DUXAP10	DUXAP10	503639	ENSG00000241106	"NoInfo"
chr9.95018962-95019082>IARS	IARS	3376	ENSG00000257227	P41252
chr19.39138368-39138547>ACTN4	ACTN4	81	ENSG00000196305	O43707
chr9.140473077-140473340>WDR85	WDR85 (DPH7)	92715	ENSG00000148399	Q9BTV6
chrX.48367956-48368344>PORCN	PORCN	64840	ENSG00000102312	Q9H237
chr2.101606718-101606908>NPAS2	NPAS2	4862	ENSG00000170485	Q99743
chr7.101475858-101476865>snorkar	snorkar	"NoInfo"	"NoInfo"	"NoInfo"
chr19.45543176-45543569>SFRS16	SFRS16 (CLASRP)	11129	ENSG00000104859	Q8N2M8
chr18.28642978-28643439>DSC2	DSC2	1824	ENSG00000134755	Q02487
chr22.36892014-36892255>FOXRED2andTXN2	FOXRED2 and TXN2	80020 and 25828	ENSG00000100350 and	Q8WFF2 and Q99757
chr18.43417478-43417850>SIGLEC15	SIGLEC15	284266	ENSG00000100348	Q8WFF2 and Q99757
			ENSG00000197046	Q6ZMC9

TABLE 7. Differential Exon Usage in the 5 Groups (p < 0.005, FC > 1.2). FC-Fold Change									
Upregulated in CE IS									
Marker ID	Gene Symbol	CE Stroke vs. Controls		CE Stroke vs. ICH		CE Stroke vs. LV		CE Stroke vs. Lacunar	
		p-value	FC	p-value	FC	p-value	FC	p-value	FC
chr1.86861716-86861978>ODF2L	ODF2L	4.89E-04	32.54	8.33E-02	1.68	4.39E-04	52.79	4.15E-04	77.95
chr10.38299602-38299711>ZNF33A	ZNF33A	1.34E-03	8.75	4.81E-04	>500	3.54E-03	4.52	4.80E-04	Not Estimable
chr10.38299604-38299711>ZNF33A	ZNF33A	1.34E-03	8.75	4.81E-04	>500	3.54E-03	4.52	4.80E-04	Not Estimable
chr10.49253461-49254183>BMS1P7	BMS1P7	3.00E-04	11.83	1.29E-04	>500	2.16E-03	3.62	5.90E-04	6.62
chr14.70242552-70243105>SLC10A1	SLC10A1	3.87E-04	Not Estimable	1.52E-02	2.52	4.05E-03	3.93	7.65E-03	3.10
chr17.34856670-34856799>MYO19	MYO19	6.48E-04	7.89	2.45E-03	3.85	1.19E-03	5.32	4.55E-04	11.01
chr17.73000302-73002233>CDR2L	CDR2L	1.76E-05	10.40	1.03E-05	19.45	1.19E-05	15.70	2.54E-05	7.93
chr19.18959976-18960255>UPF1	UPF1	6.28E-04	4.27	8.00E-05	21.25	4.87E-05	Not Estimable	9.17E-05	16.73
chr19.58427747-58427959>ZNF417 and ZNF814	ZNF417 and ZNF814	4.40E-04	4.45	3.91E-02	1.64	5.11E-05	31.22	4.31E-05	62.20
chr19.58427747-58427960>ZNF417 and ZNF814	ZNF417 and ZNF814	4.40E-04	4.45	3.91E-02	1.64	5.11E-05	31.22	4.31E-05	62.20
chr2.119988299-119988610>STEAP3	STEAP3	4.66E-04	199.47	1.78E-03	6.53	4.46E-04	>500	5.08E-04	68.51
chr2.179463448-179463831>CCDC141 and TTN	CCDC141 and TTN	4.17E-06	56.83	5.56E-05	4.49	3.38E-06	>500	3.38E-06	>500
chr2.25258142-25260098>LOC729723	LOC729723	1.67E-03	4.92	4.83E-04	13.26	6.86E-04	8.95	5.62E-04	10.97
chr20.43995515-43996064>SYS1-DBNDD2	SYS1-DBNDD2	1.17E-02	9.29	9.88E-02	2.21	2.68E-02	-1.76	3.16E-02	3.81
chr22.19115606-19115962>skatee	skatee	1.69E-02	1.83	6.02E-04	3.72	5.45E-05	16.63	2.53E-04	5.12
chr3.188326949-188327339>LPP	LPP	1.18E-03	9.73	6.73E-04	24.42	5.40E-04	61.39	4.89E-04	196.57
chr3.48456585-48456756>PLXNB1	PLXNB1	1.81E-05	Not Estimable	3.29E-04	4.01	1.81E-05	>500	7.19E-04	3.20
chr3.49448633-49449166>myforbo	myforbo	3.99E-04	5.56	2.06E-04	8.39	8.58E-02	1.50	1.01E-04	19.14
chr4.15570247-15570813>klawgu	klawgu	3.67E-04	7.05	8.78E-03	2.30	6.85E-02	1.58	5.41E-04	5.61
chr6.37225553-37225749>TBC1D22B	TBC1D22B	2.24E-01	1.22	2.12E-02	1.59	1.12E-01	-1.24	7.61E-04	2.56
chr7.142630429-142630905>TRPV5	TRPV5	1.01E-03	4.98	4.08E-03	2.99	1.34E-04	>500	1.68E-04	42.44
chr7.158334118-158334468>PTPRN2	PTPRN2	1.50E-04	Not Estimable	2.64E-04	17.40	3.29E-03	3.27	2.01E-04	33.34
chr8.104406853-104407319>shuskeebu	shuskeebu	9.62E-05	18.92	4.82E-03	2.47	2.53E-04	7.00	1.48E-03	3.32
Upregulated in LV IS									
Marker ID	Gene Symbol	CE Stroke vs. LV		Controls vs. LV		ICH vs. LV		LV vs. Lacunar	
		p-value	FC	p-value	FC	p-value	FC	p-value	FC
chr1.214836934-214837426>CENPF	CENPF	5.00E-04	-3.69	5.93E-02	-1.51	1.21E-03	-2.91	1.98E-04	5.17
chr10.46918169-46918362>FAM35B and RHEBP1	FAM35B and RHEBP1	1.26E-02	-2.69	2.31E-03	-5.33	4.16E-04	<-500	7.30E-04	16.07
chr11.62389338-62389648>B3GAT3	B3GAT3	2.98E-04	-184.49	1.74E-03	-5.23	1.16E-02	-2.57	3.51E-03	3.78
chr12.54645834-54646011>CBX5	CBX5	4.19E-04	-9.67	1.51E-04	<-500	1.53E-04	<-500	7.79E-04	6.06
chr12.56334947-56335109>DGKA	DGKA	3.08E-04	-2.03	3.68E-04	-3.73	4.70E-04	-19.19	9.49E-04	7.91

TABLE 7. Differential Exon Usage in the 5 Groups (p < 0.005, FC > |1.2|). FC-Fold Change

TABLE 7. Differential Exon Usage in the 5 Groups (p < 0.005, FC > 1.2). FC-Fold Change									
		02	03	04	04				
chr13.103506107-103506222>BIVMandERCC5	BIVM and ERCC5	3.55E- 8.46	1.47E- -18.25	7.87E- -119.86	1.72E- 15.06				
chr14.53248502-53248629>GNPNAT1	GNPNAT1	07	07	08	07				
		3.32E- -3.53	2.07E- <-500	4.12E- -13.92	4.11E- 1.85				
		03	04	04	02				
chr15.101847418-101849508>PCSK6	PCSK6	2.64E- -9.47	1.70E- -3.93	1.94E- -2.29	1.42E- 18.68				
		05	04	03	05				
chr15.81584265-81585378>IL16	IL16	4.03E- -7.21	1.56E- -2.08	1.94E- -3.49	1.93E- 14.76				
		04	02	03	04				
chr16.4475881-4476093>DNAJA3	DNAJA3	4.39E- -9.19	2.89E- -1.28	2.48E- -1.98	3.13E- 3.32				
		04	01	02	03				
chr16.72146312-72146549>DHX38	DHX38	3.43E- <-500	3.58E- -207.50	6.13E- -15.82	3.43E- >500				
		04	04	04	04				
chr17.43002077-43003867>KIF18B	KIF18B	7.66E- -4.84	4.20E- -6.67	3.80E- -1.75	2.95E- 3.02				
		04	04	02	03				
chr2.173420100-173420447>PDK1	PDK1	5.32E- -8.27	6.79E- -2.69	2.85E- -3.49	3.74E- 11.68				
		04	03	03	04				
chr2.20756227-20757428>dawgorbu	dawgorbu	5.41E- -3.87	2.90E- Not	2.42E- -5.27	1.12E- 8.19				
		04	05 Estimable	04	04				
chr20.33056659-33057236>vytaw	vytaw	3.05E- -11.22	2.33E- -3.50	7.30E- -5.73	1.25E- Not				
		04	03	04	04 Estimable				
chr20.43995515-43996064>SYS1-DBNDD2	SYS1-DBNDD2	2.68E- -1.76	8.54E- -16.38	7.51E- -3.90	2.23E- 6.72				
		02	05	04	04				
chr20.52560545-52561535>BCAS1	BCAS1	1.65E- -247.51	3.31E- -3.31	6.66E- -6.90	3.85E- 11.11				
		04	03	04	04				
chr22.18613610-18614498>PEX26andTUBA8	PEX26 and TUBA8	1.36E- -2.14	3.42E- -8.12	9.20E- -4.61	7.57E- 1.57				
		02	04	04	02				
chr22.29141852-29141989>HSCB	HSCB	4.31E- -3.84	9.81E- -2.87	4.12E- -167.51	2.88E- 4.61				
		03	03	04	03				
chr3.49448633-49449166>myforbo	myforbo	8.58E- 1.50	1.68E- -3.71	8.50E- -5.60	3.98E- 12.77				
		02	02	03	03				
chr3.8606070-8609805>LMCD1	LMCD1	6.35E- -3.28	2.63E- -4.75	1.48E- -6.74	3.77E- Not				
		03	03	03	04 Estimable				
chr4.15570247-15570813>klawgu	klawgu	6.85E- 1.58	1.98E- -4.45	3.12E- -1.45	2.90E- 3.54				
		02	02	01	02				
chr5.162902464-162902678>HMMR	HMMR	2.07E- <-500	1.05E- -5.96	1.57E- -4.80	4.74E- 3.13				
		04	03	03	03				
chr5.176715528-176715926>NSD1	NSD1	3.78E- -8.90	1.22E- Not	1.01E- -4.81	3.10E- 10.77				
		04	04 Estimable	03	04				
chr5.61688639-61688817>DIMIT1L	DIMIT1L	1.15E- -4.55	2.66E- -12.85	5.61E- -2.70	1.79E- 26.01				
		03	04	03	04				
chr6.100023529-100023947>RPS3P5	RPS3P5	6.84E- -7.70	2.96E- -17.42	1.92E- -4.63	4.47E- 10.72				
		05	05	04	05				
chr6.111619174-111619773>slyjey	slyjey	6.80E- -6.99	4.07E- -3.47	1.65E- -1.74	2.30E- 19.83				
		05	04	02	05				
chr6.37225553-37225749>TBC1D22B	TBC1D22B	1.12E- -1.24	9.78E- -1.52	6.80E- -1.98	2.94E- 3.18				
		01	03	04	05				
chr7.2282560-2282683>NUDT1	NUDT1	5.87E- -3.95	3.45E- Not	3.70E- -150.96	1.65E- 7.00				
		04	05 Estimable	05	04				
chr8.90798887-90799401>RIPK2	RIPK2	1.00E- -18.86	1.65E- -10.01	3.30E- -1.74	4.32E- 5.31				
		04	04	02	04				
chr9.131486273-131486409>ZDHHC12	ZDHHC12	1.41E- -6.54	2.13E- -5.43	5.90E- -11.68	8.83E- 8.53				
		05	05	06	06				
chrX.152226503-152227128>PNMA3	PNMA3	3.13E- -4.43	4.20E- -126.98	5.52E- -26.32	1.74E- 6.14				
		03	04	04	03				
Upregulated in Lacunar IS									
Marker ID	Gene Symbol	CE Stroke vs. Lacunar		Controls vs. Lacunar		ICH vs. Lacunar		LV vs. Lacunar	
		p-value	FC	p-value	FC	p-value	FC	p-value	FC
chr1.155691308-155691471>DAP3	DAP3	1.44E- -5.83		1.51E- -2.40		4.78E- -18.04		9.64E- -7.72	
		03		02		04		04	
chr1.160580214-160580588>SLAMF1	SLAMF1	9.00E- -50.28		6.08E- -4.99		8.40E- -75.82		1.30E- -17.92	
		05		04		05		04	
chr1.246729640-246730091>CNST	CNST	1.49E- <-500		1.49E- <-500		5.30E- -7.83		1.12E- -2.35	
		04		04		04		02	

TABLE 7. Differential Exon Usage in the 5 Groups (p < 0.005, FC > 1.2). FC-Fold Change									
chr11.119039480-119040011>NLRX1	NLRX1	2.47E- 03	-4.13	8.08E- 04	-7.84	5.40E- 04	-11.67	3.97E- 04	-18.66
chr11.62475067-62475387>GNG3	GNG3	2.61E- 02	-2.07	2.51E- 04	<-500	8.27E- 03	-2.76	6.18E- 04	-10.50
chr12.111065735-111066029>TCTN1	TCTN1	2.36E- 04	<-500	5.53E- 04	-11.15	2.41E- 04	-407.21	2.36E- 04	<-500
chr12.123262038-123262230>CCDC62	CCDC62	7.34E- 03	-3.02	6.85E- 04	-12.40	1.61E- 03	-5.83	4.55E- 04	-27.30
chr12.2966630-2968829>FOXM1	FOXM1	4.11E- 04	-4.71	9.88E- 04	-3.47	2.51E- 03	-2.72	1.60E- 04	-7.77
chr12.94914730-94915694>LOC400061	LOC400061	8.26E- 04	-2.46	2.57E- 01	-1.20	1.49E- 05	-9.38	4.11E- 06	Not Estimable
chr14.96795821-96795971>ATG2B	ATG2B	1.42E- 04	-4.39	5.92E- 04	-2.96	1.69E- 02	-1.70	6.23E- 05	-6.19
chr15.52970203-52970319>KIAA1370	KIAA1370	7.48E- 02	-1.68	2.15E- 02	-2.19	2.45E- 03	-4.32	2.70E- 04	<-500
chr16.15013757-15013940>zoner	zoner	8.81E- 03	-2.19	3.72E- 02	-1.70	2.46E- 03	-2.90	5.61E- 05	Not Estimable
chr18.33077683-33077895>INO80C	INO80C	1.26E- 03	-4.39	3.20E- 04	-10.51	6.38E- 02	-1.64	2.82E- 03	-3.28
chr19.35173682-35173954>ZNF302	ZNF302	5.42E- 04	-24.66	7.08E- 04	-14.32	4.23E- 04	-74.20	4.45E- 04	-52.73
chr2.101627502-101628002>TBC1D8	TBC1D8	2.60E- 04	-13.65	1.09E- 03	-4.69	1.25E- 04	<-500	3.07E- 04	-11.16
chr2.160143094-160143317>WDSUB1	WDSUB1	1.02E- 03	-8.14	3.24E- 04	Not Estimable	6.23E- 03	-3.18	2.45E- 03	-4.63
chr2.29258330-29258510>FAM179A	FAM179A	2.28E- 05	<-500	7.40E- 05	-9.36	5.57E- 05	-12.23	4.93E- 03	-2.20
chr20.32079185-32079982>spawvor	spawvor	1.44E- 05	Not Estimable	1.47E- 04	-5.01	3.41E- 04	-3.73	6.92E- 05	-7.31
chr21.47706315-47706712>C21orf57	C21orf57	3.23E- 05	-21.91	9.74E- 05	-7.03	1.42E- 04	-5.74	1.96E- 05	-2028.81
chr22.24316496-24316679>GSTTP1 and DDT	GSTTP1 and DDT	4.42E- 03	-3.29	7.91E- 04	-7.77	9.06E- 02	-1.60	4.00E- 04	-17.20
chr22.44514918-44515020>PARVB	PARVB	3.20E- 03	-3.27	6.91E- 04	-6.35	4.81E- 02	-1.74	2.99E- 04	-13.44
chr5.156821041-156822687>ADAM19	ADAM19	3.01E- 04	-16.01	2.15E- 02	-2.06	1.13E- 03	-5.14	2.42E- 03	-3.71
chr6.146285293-146285525>SHPRH	SHPRH	8.44E- 04	-4.84	3.55E- 04	-8.05	4.01E- 02	-1.75	2.61E- 04	-10.55
chr6.146285293-146285559>SHPRH	SHPRH	8.44E- 04	-4.84	3.55E- 04	-8.05	4.01E- 02	-1.75	2.61E- 04	-10.55
chr6.163984476-163984751>QKI	QKI	3.99E- 07	-5.23	6.22E- 08	-15.32	7.43E- 07	-4.34	2.09E- 07	-6.72
chr6.168370462-168372588>MLLT4	MLLT4	7.37E- 03	-2.24	9.05E- 04	-3.79	2.40E- 03	-2.86	4.22E- 04	-5.10
chr6.30610545-30612432>C6orf134	C6orf134	3.16E- 04	-5.69	1.56E- 04	-8.92	5.98E- 04	-4.30	1.39E- 02	-1.97
chr7.99674926-99675056>ZNF3	ZNF3	6.70E- 04	-6.08	4.74E- 04	-7.65	9.91E- 03	-2.37	2.97E- 04	-11.79
chr8.10340434-10340741>LOC346702	LOC346702	5.43E- 05	-6.06	1.95E- 05	-12.38	7.60E- 06	<-500	1.33E- 05	-20.57
chr9.46687439-46688197>KGFLP1	KGFLP1	1.22E- 05	<-500	1.22E- 05	<-500	1.22E- 05	<-500	3.46E- 05	-10.97
chrX.40495835-40495964>CXorf38	CXorf38	1.50E- 03	-7.97	4.89E- 04	Not Estimable	5.85E- 04	-49.12	5.41E- 04	-86.98
Upregulated in ICH									
Marker ID	Gene Symbol	CE Stroke vs. ICH		Controls vs. ICH		ICH vs. LV		ICH vs. Lacunar	
		p-value	FC	p-value	FC	p-value	FC	p-value	FC
chr1.10509776-10510379>APITD1 and CORT	APITD1 and CORT	7.04E- 04	-4.22	4.26E- 04	-5.20	1.17E- 04	13.61	8.89E- 05	20.93
chr1.112991564-112991794>CTTNBP2NL	CTTNBP2NL	2.49E- 02	-1.96	7.67E- 03	-2.53	4.28E- 04	8.64	3.22E- 03	3.21

TABLE 7. Differential Exon Usage in the 5 Groups (p < 0.005, FC > |1.2|). FC-Fold Change

chr1.114499947-114500540>wawleybo	wawleybo	1.41E- 01	-1.44	1.46E- 03	-4.21	3.22E- 04	11.02	8.68E- 04	5.33
chr1.145509166-145509612>RBM8A.1	RBM8A.1	1.52E- 03	-4.05	2.57E- 03	-3.37	4.91E- 04	7.24	3.48E- 04	9.57
chr1.145790974-145791170>GPR89A	GPR89A	2.08E- 04	-9.88	1.17E- 02	-2.13	3.99E- 02	1.71	1.49E- 03	3.53
chr1.150778337-150778492>CTSK	CTSK	6.96E- 06	-2.75	1.17E- 06	-3.85	5.52E- 03	1.44	1.17E- 04	1.96
chr1.150939858-150940190>LASS2	LASS2	3.59E- 05	-8.01	6.54E- 05	-5.76	9.12E- 04	2.65	1.47E- 04	4.20
chr1.154928545-154928780>SHC1andPYGO2andPBXIP1	SHC1 and PYGO2 and PBXIP1	3.65E- 04	Not Estimable	1.55E- 03	-6.39	4.42E- 03	3.72	1.44E- 02	2.53
chr1.161196029-161196394>TOMM40L	TOMM40L	1.18E- 02	-2.53	9.42E- 04	-7.43	2.63E- 04	>500	6.66E- 04	10.15
chr1.168262382-168262516>SFT2D2andTBX19	SFT2D2 and TBX19	1.10E- 03	-3.16	5.90E- 03	-2.19	4.08E- 04	4.29	1.13E- 04	8.20
chr1.17056-17742>WASH7P	WASH7P	7.18E- 04	-10.55	1.11E- 03	-7.10	4.84E- 04	18.86	2.00E- 03	4.94
chr1.180049625-180049796>CEP350	CEP350	1.98E- 02	-1.72	9.32E- 04	-2.93	2.29E- 04	4.37	2.51E- 03	2.39
chr1.180049652-180049796>CEP350	CEP350	1.98E- 02	-1.72	9.32E- 04	-2.93	2.29E- 04	4.37	2.51E- 03	2.39
chr1.19470474-19470585>UBR4	UBR4	4.12E- 04	-2.86	8.91E- 03	-1.76	2.07E- 05	8.19	1.23E- 04	3.84
chr1.201780731-201780885>NAV1	NAV1	6.28E- 05	-6.82	1.22E- 04	-4.98	4.14E- 05	8.94	1.12E- 01	1.36
chr1.235956803-235956912>LYST	LYST	4.09E- 04	-7.06	9.57E- 05	Not Estimable	1.31E- 01	1.44	1.86E- 03	3.52
chr1.243419358-243419542>SDCCAG8	SDCCAG8	3.06E- 04	-87.36	2.16E- 03	-4.61	1.69E- 02	2.32	7.16E- 03	2.94
chr1.243652316-243652442>SDCCAG8	SDCCAG8	1.83E- 03	-2.98	1.58E- 04	-8.34	6.05E- 03	2.28	6.33E- 04	4.10
chr1.26799700-26800018>HMG2	HMG2	1.04E- 03	-2.73	3.52E- 05	-10.65	7.29E- 05	6.45	1.74E- 04	4.42
chr1.27431807-27432578>SLC9A1	SLC9A1	4.90E- 02	-1.58	3.25E- 04	-4.86	1.19E- 02	1.96	3.45E- 03	2.47
chr1.45987501-45987609>PRDX1	PRDX1	3.62E- 06	<-500	1.49E- 05	-8.59	9.31E- 05	3.89	4.92E- 05	4.78
chr1.46467098-46468407>MAST2	MAST2	3.48E- 04	-3.59	1.16E- 04	-5.26	5.31E- 05	8.00	1.14E- 02	1.83
chr1.46805848-46806591>NSUN4andFAAH	NSUN4 and FAAH	6.05E- 05	<-500	1.71E- 04	-10.12	1.51E- 02	1.99	6.05E- 05	>500
chr1.63269390-63269533>ATG4C	ATG4C	3.01E- 05	-7.06	1.05E- 05	-18.05	6.94E- 05	4.82	1.23E- 05	14.55
chr1.78207302-78207433>USP33	USP33	1.91E- 03	-3.35	4.75E- 03	-2.62	1.69E- 02	2.01	4.67E- 04	5.92
chr1.85039599-85040103>CTBSandGNG5	CTBS and GNG5	1.53E- 03	-6.62	2.47E- 03	-4.94	4.75E- 04	42.06	5.65E- 04	23.30
chr1.85127881-85128058>SSX2IP	SSX2IP	1.86E- 01	-1.31	6.50E- 04	-3.62	1.03E- 02	1.98	1.57E- 04	6.44
chr1.89271574-89271700>PKN2	PKN2	6.12E- 04	-6.28	1.13E- 02	-2.29	1.87E- 04	23.55	1.20E- 03	4.46
chr10.11272033-11272456>CELF2	CELF2	6.92E- 04	-2.68	1.36E- 04	-3.96	1.47E- 05	13.37	6.22E- 05	5.22
chr10.32324818-32324922>KIF5B	KIF5B	2.07E- 03	-2.30	1.93E- 01	-1.26	2.91E- 04	3.49	8.95E- 03	1.84
chr10.51592090-51592619>LOC100287554	LOC100287554	9.51E- 03	-2.27	4.56E- 04	-6.21	1.87E- 03	3.42	9.11E- 04	4.43
chr10.69828759-69829524>HERC4	HERC4	9.83E- 04	-5.89	1.21E- 02	-2.38	5.78E- 04	8.60	1.86E- 04	>500
chr10.75230828-75230967>PPP3CB	PPP3CB	8.45E- 04	-4.23	4.34E- 03	-2.61	2.62E- 04	7.78	4.88E- 02	1.65
chr10.92500578-92502285>HTR7	HTR7	8.97E- 05	-3.59	5.98E- 02	-1.38	3.65E- 04	2.65	4.87E- 03	1.82
chr10.99195666-99196308>EXOSC1	EXOSC1	2.77E- 05	-36.28	1.45E- 02	-2.32	5.19E- 04	10.77	2.56E- 03	3.92

TABLE 7. Differential Exon Usage in the 5 Groups (p < 0.005, FC > |1.2|). FC-Fold Change

		04	02	04	03
chr10.99433338-99433902>DHDPsL and PI4K2A	DHDPsL and PI4K2A	9.07E-29.65	7.99E-46.47	2.70E-7.33	1.53E-11.94
chr11.111889680-111893310>DIXDC1	DIXDC1	1.93E-8.50	6.36E-2.33	1.87E-1.90	3.94E-5.46
chr11.111889680-111893374>DIXDC1	DIXDC1	1.93E-8.50	6.36E-2.33	1.87E-1.90	3.94E-5.46
chr11.125490667-125490901>STT3A and CHEK1	STT3A and CHEK1	6.31E-<-500	7.17E-95.82	6.83E-148.17	1.54E-14.95
chr11.47738539-47739064>FNBP4	FNBP4	3.24E-10.00	2.29E-3.47	2.00E-19.17	1.66E-29.34
chr11.61129205-61129720>CYBASC3	CYBASC3	2.94E-16.63	2.29E-28.81	7.91E-6.27	1.34E-2.28
chr11.62105383-62105784>saroro	saroro	2.68E-<-500	2.68E-<-500	2.68E->500	2.68E->500
chr11.6523983-6524156>FXC1 and DNHD1	FXC1 and DNHD1	2.16E-20.50	2.28E-3.58	7.96E-5.63	1.59E-2.15
chr11.7479027-7479174>veemee	veemee	5.89E-<-500	1.17E-3.62	3.17E-2.75	3.03E-6.49
chr11.836251-836525>CD151	CD151	4.18E-7.43	6.65E-5.80	1.16E-38.09	1.80E-15.64
chr11.89933252-89935719>CHORDC1	CHORDC1	8.39E-12.95	3.53E-4.87	4.83E-2.33	1.37E-8.21
chr12.10561988-10562183>KLRC4 and KLRK1	KLRC4 and KLRK1	2.87E-3.91	8.17E-2.76	1.16E-6.12	3.22E-33.90
chr12.40441853-40442012>SLC2A13	SLC2A13	6.39E-5.50	3.03E-8.23	7.21E->500	1.36E-18.27
chr12.48094974-48095387>RPAP3	RPAP3	6.56E-2.64	7.99E-1.59	2.33E-3.59	4.90E-7.84
chr12.54789679-54790160>ITGA5	ITGA5	9.53E-2.85	1.58E-6.27	5.00E-28.60	5.65E-20.66
chr12.58345541-58345678>XRCC6BP1	XRCC6BP1	4.42E-135.95	1.80E-7.31	1.49E-3.11	8.16E-15.47
chr12.6761437-6761584>ING4	ING4	1.90E-4.46	2.22E-2.56	1.61E-1.94	4.32E-3.55
chr12.96258857-96259166>SNRPF	SNRPF	6.80E-15.03	3.06E-<-500	1.16E-9.15	3.05E-Not Estimable
chr13.100543572-100543866>CLYBL	CLYBL	1.02E-2.73	8.81E-9.28	3.93E-47.46	7.38E-11.24
chr13.113864293-113864812>PCID2	PCID2	4.40E-10.60	6.02E-7.93	1.27E-4.99	1.01E-2.47
chr13.41593364-41593568>ELF1	ELF1	4.35E-<-500	9.67E-11.29	4.35E->500	2.23E-5.56
chr14.100743755-100744113>YY1	YY1	4.40E-3.15	1.05E-2.47	2.73E-26.26	3.87E-13.52
chr14.105236090-105236707>AKT1	AKT1	4.84E-8.22	2.03E-4.18	2.23E-18.04	8.26E-6.02
chr14.20872770-20872931>TEP1	TEP1	1.47E-2.28	8.24E-4.38	3.09E-3.06	1.40E-1.67
chr14.50246313-50246524>KLHDC2	KLHDC2	3.77E-1.71	4.58E-5.34	6.75E-2.34	1.83E-3.20
chr14.52957557-52957723>TXNDC16	TXNDC16	1.34E-4.79	3.06E-2.21	3.24E-3.59	7.61E-2.90
chr14.76107075-76107403>FLVCR2 and TTLL5 and C14orf179	FLVCR2 and TTLL5 and C14orf179	1.92E-2.58	6.71E-9.03	1.22E-1.36	6.13E-3.38
chr14.88431849-88431973>GALC	GALC	5.67E-3.67	2.77E-2.48	1.18E-3.01	1.19E-7.15
chr14.88452833-88452946>GALC	GALC	3.97E-3.47	2.38E-1.65	8.56E-6.09	1.30E-2.63
chr14.96997812-96999040>PAPOLA	PAPOLA	1.96E-2.78	6.03E-3.85	3.36E-4.77	8.69E-1.46
chr15.30711214-30711348>rukuru	rukuru	3.01E-11.05	9.53E-4.94	2.39E-3.45	5.73E-2.68
chr15.38619054-38620016>koyzawbu	koyzawbu	2.03E-2.87	5.39E-1.58	2.95E-5.53	9.82E-3.50

TABLE 7. Differential Exon Usage in the 5 Groups (p < 0.005, FC > |1.2|). FC-Fold Change

chr15.57545460-57545666>stoyguby	stoyguby	3.39E- 5.43	8.44E- -2.40	9.44E- 3.83	3.07E- 1.98
		05	04	05	03
chr15.59102429-59102587>FAM63B	FAM63B	3.05E- -3.01	8.90E- -4.60	2.53E- 10.19	5.47E- 5.82
		03	04	04	04
chr15.59943710-59944525>GTF2A2	GTF2A2	2.05E- -2.18	4.44E- -15.25	9.30E- 7.02	8.26E- 2.74
		02	04	04	03
chr15.64017491-64017712>HERC1	HERC1	3.68E- -3.52	1.84E- -4.37	1.36E- 2.59	6.20E- 1.99
		04	04	03	03
chr15.66811217-66811416>ZWILCH	ZWILCH	1.42E- -15.75	4.47E- -6.69	1.61E- 4.16	8.06E- 2.88
		06	06	05	05
chr15.66811217-66811467>ZWILCH	ZWILCH	1.42E- -15.75	4.47E- -6.69	1.61E- 4.16	8.06E- 2.88
		06	06	05	05
chr15.75165540-75165688>SCAMP2	SCAMP2	4.19E- -4.48	6.10E- -2.22	1.95E- 2.82	5.15E- 1.57
		04	03	03	02
chr15.80191177-80191467>ST20andMTHFS	ST20 and MTHFS	7.04E- -5.57	2.00E- -3.59	2.33E- 13.85	3.18E- 9.74
		04	03	04	04
chr15.94774950-94775234>MCTP2	MCTP2	4.31E- Not Estimable	9.26E- -11.80	1.11E- 9.54	4.31E- Not Estimable
		04	04	03	04
chr16.18799866-18800440>ARL6IP1andRPS15A	ARL6IP1 and RPS15A	2.45E- -6.56	2.34E- -2.85	1.10E- 2.06	8.95E- 3.74
		04	03	02	04
chr16.22277711-22277845>EEF2K	EEF2K	3.16E- -114.30	1.08E- -8.32	2.29E- 1.75	3.03E- 207.60
		05	04	02	05
chr16.30593851-30595166>syrrar	syrrar	4.87E- <-500	6.03E- -4.33	4.87E- >500	4.87E- >500
		05	04	05	05
chr16.3493611-3493837>ZNF174andNAT15andCLUAP1	ZNF174 and NAT15 and CLUAP1	3.54E- <-500	5.17E- -24.09	3.54E- >500	3.54E- >500
		04	04	04	04
chr17.18087711-18088067>jeeroy	jeeroy	1.76E- -13.21	6.59E- -4.99	1.02E- 43.74	1.19E- 26.41
		04	04	04	04
chr17.18486655-18486837>CCDC144B	CCDC144B	1.37E- -2.53	3.39E- <-500	3.82E- 76.21	1.16E- 7.53
		02	04	04	03
chr17.27581220-27581513>CRYBA1	CRYBA1	1.03E- -21.86	1.74E- -3.27	1.66E- 11.01	2.63E- 7.47
		04	03	04	04
chr17.36351796-36351996>TBC1D3	TBC1D3	3.07E- -28.30	5.13E- -3.10	4.66E- 12.72	6.73E- 8.57
		04	03	04	04
chr17.40280569-40280818>RAB5C	RAB5C	2.04E- -1.25	8.87E- -4.79	2.28E- 1.61	4.01E- 2.03
		01	05	02	03
chr17.57728564-57728677>CLTC	CLTC	3.52E- -2.77	3.21E- -7.06	8.42E- 4.33	1.79E- 3.34
		03	04	04	03
chr17.61473104-61473289>TANC2	TANC2	3.52E- -2.04	7.45E- -2.65	4.20E- 6.30	1.10E- 20.53
		03	04	05	05
chr17.62745780-62746126>LOC146880	LOC146880	3.51E- -2.39	1.24E- -3.00	4.23E- 4.10	2.41E- 5.09
		03	03	04	04
chr17.77079383-77079672>ENGASE	ENGASE	3.74E- Not Estimable	2.87E- -4.54	2.80E- 2.14	5.58E- 3.43
		04	03	02	03
chr18.48443613-48443878>ME2	ME2	1.24E- -1.52	1.43E- -5.39	4.98E- 3.20	4.15E- 17.42
		01	03	03	04
chr18.54318248-54318824>TXNL1	TXNL1	3.27E- -6.40	1.59E- -11.19	1.61E- 3.33	1.10E- 18.33
		04	04	03	04
chr18.67508480-67516323>DOK6	DOK6	2.50E- -3.44	3.70E- -5.86	1.18E- 2.00	1.02E- 4.24
		06	07	04	06
chr19.11411543-11411912>tojaw	tojaw	1.12E- -5.75	3.37E- -19.59	4.08E- 14.07	2.24E- 4.10
		03	04	04	03
chr19.13009896-13010199>SYCE2	SYCE2	5.66E- -1.66	1.16E- -220.29	3.22E- 9.45	1.70E- 23.14
		02	04	04	04
chr19.1877203-1877424>FAM108A1	FAM108A1	9.46E- -12.34	3.12E- -5.70	4.87E- 38.02	5.84E- 24.14
		06	05	06	06
chr19.1953385-1953505>C19orf34	C19orf34	4.17E- -3.77	1.47E- -6.50	3.53E- Not Estimable	9.95E- 8.89
		03	03	04	04
chr19.36515246-36515534>CLIP3	CLIP3	5.36E- -1.78	2.47E- <-500	2.47E- >500	2.48E- >500
		02	04	04	04
chr19.44128266-44128394>CADM4	CADM4	1.35E- -1.38	7.22E- -3.71	2.08E- 1.80	2.51E- 5.61
		01	04	02	04
chr19.44619641-44619995>ZNF225	ZNF225	1.90E- -12.35	3.11E- -7.83	1.23E- 2.14	4.26E- 6.35
		04	04	02	04
chr19.47646729-47646862>SAE1	SAE1	3.77E- -2.25	4.22E- -3.71	1.10E- 2.88	8.17E- 1.43

TABLE 7. Differential Exon Usage in the 5 Groups (p < 0.005, FC > |1.2|). FC-Fold Change

		03	04	03	02
chr19.47646751-47646862>SAE1	SAE1	3.77E- 2.25	4.22E- -3.71	1.10E- 2.88	8.17E- 1.43
chr19.49314066-49314178>BCAT2	BCAT2	03	04	03	02
		4.79E- -3.77	3.15E- -4.55	1.48E- 7.25	4.22E- Not
chr19.5208248-5208402>PTPRS	PTPRS	03	03	03	04 Estimable
		2.10E- -4.21	4.27E- -13.18	8.85E- 6.65	5.17E- 3.05
chr19.52207575-52207733>NCRNA00085	NCRNA00085	03	04	04	03
		6.15E- -5.27	1.16E- -18.46	8.15E- 41.81	1.56E- 12.72
chr19.54610118-54610266>NDUFA3	NDUFA3	05	05	06	05
		1.16E- -6.91	9.25E- -1.98	3.81E- 21.56	4.72E- 3.80
chr19.58423428-58423554>ZNF417 and ZNF814	ZNF417 and ZNF814	04	03	05	04
		2.95E- -3.70	3.90E- -15.56	2.11E- >500	1.83E- 2.20
chr19.58423428-58423557>ZNF417 and ZNF814	ZNF417 and ZNF814	03	04	04	02
		2.95E- -3.70	3.90E- -15.56	2.11E- Not	1.83E- 2.20
chr19.8441789-8441951>lyta	lyta	03	04	04 Estimable	02
		5.40E- -8.82	3.08E- -17.86	1.76E- 4.33	3.90E- 3.23
chr19.9720432-9722012>ZNF562 and ZNF561	ZNF562 and ZNF561	04	04	03	03
		6.18E- -29.45	4.65E- -469.78	4.39E- 4.01	5.13E- 75.31
chr2.110584278-110584424>RGPD5	RGPD5	04	04	03	04
		5.04E- -11.19	9.25E- -3.01	3.59E- 3.92	1.20E- 1.87
chr2.111302237-111302383>RGPD6	RGPD6	05	04	04	02
		5.04E- -11.19	9.25E- -3.01	3.59E- 3.92	1.20E- 1.87
chr2.113175261-113175491>RGPD8	RGPD8	05	04	04	02
		7.54E- -5.13	3.91E- -7.04	7.22E- >500	1.04E- 31.99
chr2.118864235-118864479>INSIG2	INSIG2	05	05	06	05
		5.60E- -1.54	1.23E- -7.34	2.27E- 2.62	9.07E- 3.27
chr2.172848099-172848599>HAT1	HAT1	02	04	03	04
		1.42E- -4.52	4.48E- -7.86	8.43E- 5.58	1.49E- 29.53
chr2.17953901-17954051>GEN1	GEN1	04	05	05	05
		9.89E- -25.31	6.70E- <-500	6.92E- 199.20	1.58E- 3.38
chr2.182339687-182340015>ITGA4	ITGA4	05	05	05	03
		1.90E- -7.51	4.08E- -1.92	1.03E- 3.82	1.08E- 11.34
chr2.198175302-198175503>ANKRD44	ANKRD44	05	03	04	05
		7.11E- -5.58	3.26E- -9.66	1.03E- 2.31	2.81E- 1.89
chr2.208446079-208446884>FAM119A	FAM119A	04	04	02	02
		3.71E- -9.30	3.05E- -3.59	4.39E- 2.08	5.29E- 7.28
chr2.231663444-231663879>CAB39	CAB39	05	04	03	05
		6.76E- -2.27	1.48E- -3.25	3.64E- 1.69	3.63E- 5.44
chr2.234112772-234113219>INPP5D	INPP5D	03	03	02	04
		1.03E- -3.44	4.25E- -4.68	1.22E- 9.78	2.17E- 2.82
chr2.242282407-242282508>SEPT2	SEPT2	03	04	04	03
		4.07E- -2.55	1.80E- -3.12	1.84E- 8.63	9.02E- 3.85
chr2.243168539-243168819>samemo	samemo	03	03	04	04
		4.94E- -2.98	1.72E- -2.18	2.23E- 37.87	5.29E- 8.73
chr2.73957016-73957156>TPRKB	TPRKB	03	02	04	04
		2.11E- -8.51	8.41E- -23.94	1.24E- 13.51	6.75E- 43.24
chr2.88336462-88336570>KRCC1	KRCC1	05	06	05	06
		1.75E- -3.55	5.15E- -2.62	2.74E- 1.86	1.75E- 15.65
chr20.18449588-18449705>POLR3F	POLR3F	03	03	02	04
		4.95E- -10.82	1.16E- -2.83	2.93E- 4.13	1.75E- Not
chr20.23401942-23402097>NAPB	NAPB	05	03	04	05 Estimable
		6.00E- <-500	4.50E- -5.29	5.97E- >500	1.09E- 17.28
chr20.30720816-30720929>TM9SF4	TM9SF4	05	04	05	04
		4.31E- -2.58	7.10E- -1.36	1.55E- 2.11	8.38E- 1.71
chr20.34487292-34487561>PHF20	PHF20	04	02	03	03
		1.17E- -5.87	7.20E- -8.27	4.74E- 12.86	2.59E- 3.97
chr20.416929-419485>TBC1D20	TBC1D20	03	04	04	03
		1.36E- -3.68	3.76E- -6.52	7.71E- 4.55	7.72E- 2.33
chr20.43808628-43808775>rotora	rotora	03	04	04	03
		2.81E- -11.96	1.75E- -3.84	4.47E- 7.75	3.40E- 3.09
chr21.40619627-40619758>BRWD1	BRWD1	04	03	04	03
		7.54E- -4.31	7.25E- -21.38	1.26E- 10.81	3.76E- 5.59
chr21.47608408-47608855>klorley	klorley	05	06	05	05
		1.80E- -2.14	1.56E- -4.41	4.26E- 10.24	6.69E- 2.71
chr22.20093700-20093800>DGCR8	DGCR8	02	03	04	03
		6.95E- -2.58	8.09E- -5.52	2.17E- 19.30	2.11E- 3.65

TABLE 7. Differential Exon Usage in the 5 Groups (p < 0.005, FC > |1.2|). FC-Fold Change

		03	04	04	03
chr22.31733654-31734031>sneypoy	sneypoy	5.37E- 1.82	3.99E- -39.22	1.49E- 6.03	1.08E- 2.67
		02	04	03	02
chr22.41175013-41175129>SLC25A17	SLC25A17	7.16E- -7.40	3.66E- -14.98	6.05E- 2.87	9.34E- 1.58
		04	04	03	02
chr22.45254869-45255776>PRR5-ARHGAP8	PRR5-ARHGAP8	1.71E- -2.04	9.61E- <-500	3.03E- 8.85	1.52E- 3.77
		02	05	04	03
chr22.50320903-50321181>CRELD2	CRELD2	1.98E- -4.87	3.50E- -1.97	5.27E- 14.94	4.59E- 19.20
		03	02	04	04
chr22.51221467-51221714>RABL2B	RABL2B	4.84E- <-500	9.09E- -18.75	5.55E- 85.86	2.67E- 7.08
		06	06	06	05
chr3.122283274-122283460>DTX3L	DTX3L	3.86E- -2.45	8.96E- -3.51	1.54E- 1.35	4.78E- 4.34
		03	04	01	04
chr3.137963865-137964523>vusmyby	vusmyby	4.47E- -6.75	1.85E- -2.01	7.96E- 4.93	2.47E- 10.96
		04	02	04	04
chr3.137963930-137964523>ARMC8	ARMC8	4.47E- -6.75	1.85E- -2.01	7.96E- 4.93	2.47E- 10.96
		04	02	04	04
chr3.137963930-137964524>ARMC8	ARMC8	4.47E- -6.75	1.85E- -2.01	7.96E- 4.93	2.47E- 10.96
		04	02	04	04
chr3.150280329-150280447>EIF2A	EIF2A	1.05E- -1.55	4.23E- -3.25	1.90E- 2.48	1.23E- 1.93
		02	05	04	03
chr3.15778540-15778740>ANKRD28	ANKRD28	1.71E- -3.90	1.21E- -23.79	1.60E- 2.36	2.11E- 11.26
		04	05	03	05
chr3.167452594-167452717>PDCD10	PDCD10	4.97E- -3.83	4.68E- Not	2.62E- 5.24	1.60E- 7.32
		03	04 Estimable	03	03
chr3.20019802-20020396>RAB5A	RAB5A	4.94E- -1.54	3.15E- -4.25	8.07E- 3.20	1.83E- 2.64
		02	04	04	03
chr3.23929058-23929280>UBE2E1	UBE2E1	1.32E- -3.40	3.40E- -5.78	6.07E- 1.57	2.24E- 7.41
		03	04	02	04
chr3.25637911-25639423>RARB	RARB	6.84E- -2.86	4.19E- -1.86	4.93E- 12.19	2.09E- 4.35
		03	02	04	03
chr3.39162488-39162680>TTC21A	TTC21A	2.31E- -1.64	3.37E- -3.48	5.93E- 6.73	3.03E- 10.81
		02	04	05	05
chr3.52385978-52386119>DNAH1	DNAH1	2.86E- -25.66	1.71E- -5.17	1.52E- 1.80	3.60E- 3.92
		05	04	02	04
chr3.52561845-52561947>NT5DC2	NT5DC2	5.07E- Not	5.07E- <-500	6.23E- 50.64	5.07E- Not
		05 Estimable	05	05	05 Estimable
chr3.69028819-69028938>C3orf64	C3orf64	4.34E- -276.88	1.44E- -7.40	6.00E- 25.32	9.40E- 11.26
		04	03	04	04
chr3.81552424-81552865>chordybo	chordybo	2.18E- -6.44	4.03E- Not	4.30E- 4.65	7.72E- 2.16
		04	05 Estimable	04	03
chr4.122723829-122723948>EXOSC9	EXOSC9	1.45E- -2.35	3.00E- -3.21	1.36E- 1.70	9.05E- 4.55
		03	04	02	05
chr4.122723829-122723983>EXOSC9	EXOSC9	1.45E- -2.35	3.00E- -3.21	1.36E- 1.70	9.05E- 4.55
		03	04	02	05
chr4.157731989-157732169>PDGFC	PDGFC	7.75E- -2.40	6.25E- -1.79	4.00E- 4.91	9.27E- 3.76
		04	03	05	05
chr4.175223190-175223337>KIAA1712	KIAA1712	3.59E- -10.22	9.07E- -1.55	6.69E- 2.62	1.66E- 4.04
		04	02	03	03
chr4.40800804-40800921>NSUN7	NSUN7	6.85E- -1.65	4.03E- -10.82	2.93E- 16.64	1.48E- 4.51
		02	04	04	03
chr4.76874494-76874938>sporsmorby	sporsmorby	8.09E- -2.96	4.72E- -28.20	2.56E- 2.16	2.57E- 1.34
		03	04	02	01
chr5.134343647-134343829>PCBD2andCATSPER3	PCBD2 and CATSPER3	1.80E- -2.37	6.68E- -3.17	3.53E- Not	5.92E- 17.76
		02	03	04 Estimable	04
chr5.139929370-139930496>APBB3andSRA1	APBB3 and SRA1	2.46E- -1.21	2.97E- -3.06	1.24E- 1.69	1.95E- 2.17
		01	04	02	03
chr5.140895496-140896575>DIAPH1	DIAPH1	2.42E- -3.84	3.56E- -14.80	2.77E- 23.85	9.58E- 5.96
		03	04	04	04
chr5.140895875-140896575>DIAPH1	DIAPH1	5.18E- -5.97	9.76E- -34.42	1.45E- 16.01	1.20E- 21.48
		05	06	05	05
chr5.14381239-14381361>TRIO	TRIO	7.18E- -3.91	1.44E- -1.95	2.22E- 6.59	1.32E- 3.25
		04	02	04	03
chr5.145493406-145493874>LARS	LARS	4.03E- -11.34	3.32E- -3.36	8.40E- 6.17	5.02E- 9.06
		04	03	04	04
chr5.35053745-35054334>fugey	fugey	4.00E- -9.01	8.14E- -5.54	3.29E- 10.88	1.32E- Not

TABLE 7. Differential Exon Usage in the 5 Groups (p < 0.005, FC > |1.2|). FC-Fold Change

		04	04	04	04	Estimable
chr5.39274505-39274630>FYB	FYB	1.63E- 2.33	3.89E- 24.35	1.29E- 6.00	4.56E- 1.85	
chr5.70531277-70532281>goychyby	goychyby	1.10E- 2.03	2.29E- 6.29	6.59E- 3.97	2.19E- 2.81	
chr5.77656415-77656552>SCAMP1	SCAMP1	1.07E- 4.46	2.97E- 9.88	4.46E- 7.11	3.67E- 1.79	
chr6.109248281-109249436>ARMC2	ARMC2	2.72E- 2.24	1.30E- 1.77	2.08E- 4.04	8.43E- 1.40	
chr6.122792844-122793050>SERINC1	SERINC1	1.45E- 2.14	5.74E- 2.63	2.50E- 3.31	3.03E- 9.93	
chr6.144289727-144290115>PLAGL1andHYMAI	PLAGL1 and HYMAI	1.74E- 1.44	4.00E- 32.52	4.43E- 23.92	4.81E- 3.42	
chr6.153291654-153292549>FBXO5	FBXO5	3.31E- 3.25	1.32E- 2.43	4.35E- 2.01	2.30E- 1.61	
chr6.153291660-153292549>FBXO5	FBXO5	3.31E- 3.25	1.32E- 2.43	4.35E- 2.01	2.30E- 1.61	
chr6.153291674-153292549>FBXO5	FBXO5	3.31E- 3.25	1.32E- 2.43	4.35E- 2.01	2.30E- 1.61	
chr6.158088239-158089557>fyjaw	fyjaw	8.63E- 4.25	2.52E- 1.85	1.77E- 3.33	2.99E- 7.26	
chr6.3021094-3022352>tevybo	tevybo	3.80E- 140.84	4.06E- 74.72	9.11E- 3.45	1.27E- 8.48	
chr6.34360041-34360260>RPS10andNUDT3	RPS10 and NUDT3	5.81E- 4.24	8.57E- 15.64	7.24E- 20.73	1.60E- 8.25	
chr6.41036580-41036692>C6orf130andUNC5CL	C6orf130 and UNC5CL	3.57E- 5.13	1.22E- 10.16	7.37E- 3.87	1.49E- 3.13	
chr6.41751200-41751976>PRICKLE4andTOMM6	PRICKLE4 and TOMM6	4.62E- 2.80	2.51E- 12.58	4.03E- 7.96	9.63E- 4.78	
chr6.79664949-79665569>PHIPandTRNAF13P	PHIP and TRNAF13P	1.35E- 2.92	2.55E- Not	1.30E- 6.84	5.14E- 15.62	
chr7.149598-152547>kehera	kehera	1.33E- 1.71	1.29E- 2.42	9.72E- 1.36	4.40E- 2.99	
chr7.22980878-22987334>FAM126A	FAM126A	5.13E- 2.56	4.24E- 4.72	8.77E- 1.71	1.84E- 2.09	
chr7.2635311-2636062>dochuby	dochuby	3.67E- 4.19	1.69E- 5.80	4.01E- 2.30	2.63E- 1.70	
chr7.29549802-29552165>klerky	klerky	1.88E- 6.48	3.73E- 2.44	2.29E- 1.77	8.77E- 1.46	
chr7.45083306-45083697>CCM2	CCM2	2.52E- 1.90	8.39E- 4.83	1.36E- 3.96	3.71E- 7.72	
chr7.5938415-5938550>CCZ1	CCZ1	5.04E- 252.68	2.41E- 8.08	7.48E- 4.89	1.37E- 12.27	
chr7.74166365-74166897>GTF2I	GTF2I	2.27E- 3.76	5.26E- 8.20	7.50E- 6.36	2.45E- 22.31	
chr7.76870183-76870364>CCDC146	CCDC146	1.69E- 12.37	4.46E- 6.24	4.43E- 2.97	6.52E- Not	
chr8.104455023-104455428>DCAF13	DCAF13	4.47E- 1.81	1.12E- 2.44	5.04E- 3.04	4.85E- 10.67	
chr8.133984843-133984986>TG	TG	3.27E- 1.99	2.69E- <-500	2.69E- Not	2.69E- >500	
chr8.24256387-24256553>ADAMDEC1	ADAMDEC1	1.89E- 2.37	1.55E- 6.56	3.81E- Not	5.79E- 1.82	
chr8.30948350-30948458>WRN	WRN	9.84E- 8.13	4.33E- 19.99	6.54E- 3.52	1.58E- 6.10	
chr8.62438536-62438671>ASPH	ASPH	1.08E- 5.20	5.24E- 2.88	2.06E- 2.07	3.63E- 11.88	
chr8.74858684-74859055>TCEB1	TCEB1	2.36E- 11.51	1.83E- 16.10	3.38E- 8.24	1.05E- 4.38	
chr9.17135038-17135423>CNTLN	CNTLN	3.03E- 1.91	1.90E- 3.97	8.64E- 5.73	4.80E- 8.60	
chr9.33264164-33264493>CHMP5	CHMP5	1.44E- 11.82	8.33E- 4.08	1.94E- 8.91	4.09E- 5.53	
chr9.35737655-35737936>GBA2	GBA2	6.33E- 3.43	4.89E- 96.76	1.37E- 8.06	5.25E- 55.35	
chrX.118985730-118985836>UPF3B	UPF3B	1.13E- <-500	1.55E- 3.93	3.89E- 2.93	8.72E- 4.99	

TABLE 7. Differential Exon Usage in the 5 Groups (p < 0.005, FC > 1.2). FC-Fold Change									
chrX.138864706-138864887>ATP11C	ATP11C	04	03	03	04	03	04	03	04
chrX.149924161-149924396>MTMR1	MTMR1	3.68E- -3.31	2.76E- -23.71	1.59E- 2.23	9.95E- 5.80	03	04	02	04
chrX.153744234-153744566>FAM3A	FAM3A	1.84E- -6.49	4.58E- <-500	2.92E- 4.89	6.99E- 3.33	03	04	03	03
chrX.15862547-15863639>AP1S2	AP1S2	1.07E- -54.24	3.85E- -7.03	2.63E- 9.43	8.88E- 4.53	04	04	04	04
chrX.16870674-16871149>RBBP7	RBBP7	9.09E- -5.62	1.65E- -4.42	4.01E- 2.12	6.08E- 1.46	05	04	03	02
chrX.16870674-16871149>RBBP7	RBBP7	6.02E- -2.99	2.65E- -3.99	8.60E- 7.37	3.25E- 29.04	03	03	04	04
chrX.2839944-2840065>ARSD	ARSD	1.44E- -3.53	4.55E- -1.67	3.00E- 2.86	3.95E- 6.06	03	02	03	04
chrX.74282163-74282417>ABCB7	ABCB7	1.09E- -5.81	8.03E- -7.10	1.32E- 2.36	3.38E- 19.17	03	04	02	04
chrX.76776266-76776394>ATRX	ATRX	3.40E- -5.28	1.40E- -2.35	1.89E- 1.75	6.84E- 4.23	06	04	03	06
chrX.77303661-77305892>ATP7A	ATP7A	1.55E- -10.33	2.03E- -3.04	3.29E- 1.22	1.05E- 3.70	04	03	01	03
Upregulated in Controls									
Marker ID	Gene Symbol	CE Stroke vs. Controls		Controls vs. ICH		Controls vs. LV		Controls vs. Lacunar	
		p-value	FC	p-value	FC	p-value	FC	p-value	FC
chr1.53416427-53416558>SCP2	SCP2	4.14E- -3.65	3.66E- 1.59	1.42E- 2.69	6.07E- 2.06	04	02	03	03
chr14.19683027-19683434>DUXAP10	DUXAP10	3.62E- -29.94	1.14E- 7.36	2.52E- >500	4.66E- 17.76	05	04	05	05
chr17.42982993-42984756>GFAP	GFAP	6.98E- -5.06	1.25E- 2.15	4.86E- 2.65	2.89E- 8.76	04	02	03	04
chr18.28642978-28643439>DSC2	DSC2	2.44E- -1.84	5.93E- 2.41	1.09E- 3.79	1.88E- 9.74	02	03	03	04
chr18.43417478-43417850>SIGLEC15	SIGLEC15	3.26E- <-500	2.04E- 5.10	1.43E- 2.49	4.84E- 1.87	04	03	02	02
chr19.39138368-39138547>ACTN4	ACTN4	1.33E- -8.92	1.30E- 3.51	5.83E- 22.30	3.57E- 5.30	05	04	06	05
chr19.45543176-45543569>SFRS16	SFRS16	1.43E- <-500	4.87E- 2.87	3.81E- 9.97	2.38E- 18.83	04	03	04	04
chr2.101606718-101606908>NPAS2	NPAS2	2.57E- -6.61	5.03E- 4.72	7.16E- 30.24	3.23E- 2.67	04	04	05	03
chr2.242611606-242612016>ATG4B	ATG4B	8.42E- -8.04	3.53E- 20.98	1.89E- 5.17	1.07E- 2.97	05	04	04	03
chr20.32880178-32880359>AHCY	AHCY	2.22E- -4.21	5.50E- 3.04	3.66E- 18.76	1.14E- 2.48	03	03	04	02
chr22.36892014-36892255>FOXRED2 and TXN2	FOXRED2 and TXN2	2.48E- -5.82	1.19E- 1.99	4.04E- 2.43	7.88E- 1.49	03	03	04	02
chr22.41252435-41253036>ST13	ST13	1.56E- -7.62	3.49E- 4.55	4.81E- >500	4.81E- >500	04	03	04	04
chr6.32806430-32806547>TAP2 and HLA-DOB	TAP2 and HLA-DOB	9.55E- <-500	2.92E- 3.07	2.70E- 9.81	7.48E- 5.03	05	03	04	04
chr7.101475858-101476865>snorkar	snorkar	2.78E- -23.06	2.33E- 2.05	2.70E- 3.68	6.83E- 2.75	04	02	03	03
chr9.140473077-140473340>WDR85	WDR85	3.68E- -31.77	4.74E- 3.93	1.31E- 6.90	6.73E- 11.64	05	04	04	05
chr9.95018962-95019082>IARS	IARS	1.52E- -7.76	2.30E- 3.02	7.17E- 4.05	2.90E- 5.60	05	04	05	05
chr9.96866557-96866667>PTPDC1	PTPDC1	3.10E- Not Estimable	7.27E- 1.95	8.40E- 13.03	3.13E- >500	07	04	07	07
chrX.48367956-48368344>PORCN	PORCN	4.63E- -86.44	4.10E- >500	4.91E- 58.47	7.98E- 16.02	05	05	05	05

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons											
Cardioembolic Stroke											
SIGNIFICANTLY ENRICHED CANONICAL PATHWAYS OF CARDIOEMBOLIC STROKE											
Ingenuity Canonical Pathways	-log(p-value)	B-H p-value	Ratio	Molecules							
Semaphorin Signaling in Neurons	1.41E00	6.9E-03-7.47E-02	1.89E-02	PLXNB1							
GENE ONTOLOGY OF CARDIOEMBOLIC STROKE											
Annotation Cluster 1 Enrichment Score: 1.5478345985149118											
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Benjamini	FDR
GOTERM_MF_FAT	GO:0046872~metal ion binding	9	47.37	0.03	STEAP3, ZNF33A, UPF1, LPP, ZNF417, ZNF814, TRPV5, TTN, SLC10A1	14	4140	12983	2.02	0.89	24.97
GOTERM_MF_FAT	GO:0043169~cation binding	9	47.37	0.03	STEAP3, ZNF33A, UPF1, LPP, ZNF417, ZNF814, TRPV5, TTN, SLC10A1	14	4179	12983	2.00	0.69	26.24
GOTERM_MF_FAT	GO:0043167~ion binding	9	47.37	0.03	STEAP3, ZNF33A, UPF1, LPP, ZNF417, ZNF814, TRPV5, TTN, SLC10A1	14	4241	12983	1.97	0.58	28.33

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons											
Annotation Cluster 2		Enrichment Score: 1.4272404656779223									
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichmen t	Benjamini	FDR
GOTERM_CC_FAT	GO:0005887~integral to plasma membrane	4	21.05	0.03	PLXNB1, PTPRN2, TRPV5, SLC10A1	9	1188	12782	4.78	0.75	25.81
GOTERM_CC_FAT	GO:0031226~intrinsic to plasma membrane	4	21.05	0.03	PLXNB1, PTPRN2, TRPV5, SLC10A1	9	1215	12782	4.68	0.53	27.17
GOTERM_CC_FAT	GO:0044459~plasma membrane part	5	26.32	0.03	PLXNB1, LPP, PTPRN2, TRPV5, SLC10A1	9	2203	12782	3.22	0.40	27.86
GOTERM_CC_FAT	GO:0005886~plasma membrane	6	31.58	0.05	STEAP3, PLXNB1, LPP, PTPRN2, TRPV5, SLC10A1	9	3777	12782	2.26	0.46	40.79
Annotation Cluster 3		Enrichment Score: 1.228190007997564									
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichmen t	Benjamini	FDR
GOTERM_BP_FAT	GO:0030001~metal ion transport	3	15.79	0.05	STEAP3, TRPV5, SLC10A1	12	465	13528	7.27	1.00	48.17
GOTERM_CC_FAT	GO:0005886~plasma membrane	6	31.58	0.05	STEAP3, PLXNB1, LPP, PTPRN2, TRPV5, SLC10A1	9	3777	12782	2.26	0.46	40.79
GOTERM_BP_FAT	GO:0006812~cation transport	3	15.79	0.07	STEAP3, TRPV5, SLC10A1	12	553	13528	6.12	1.00	59.48
Large Vessel IS											

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

SIGNIFICANTLY ENRICHED CANONICAL PATHWAYS OF LARGE VESSEL ISCHEMIC STROKE				
Ingenuity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules
Oxidized GTP and dGTP Detoxification	2.44E00	1E00	3.33E-01	NUDT1
UDP-N-acetyl-D-glucosamine Biosynthesis II	2.14E00	1E00	1.67E-01	GNPNAT1
Glycoaminoglycan-protein Linkage Region	2.08E00	1E00	1.43E-01	B3GAT3
Biosynthesis UDP-N-acetyl-D-galactosamine Biosynthesis II	1.97E00	1E00	1.11E-01	GNPNAT1
Thyroid Hormone Metabolism II (via Conjugation and/or Degradation)	1.44E00	7.92E-01	3.23E-02	B3GAT3
Nucleotide Excision Repair Pathway	1.38E00	7.92E-01	2.86E-02	ERCC5
GENE ONTOLOGY OF LARGE VESSEL ISCHEMIC STROKE				
Annotation Cluster 1	Enrichment Score: 1.9116473785151364			

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Benjamini	FDR
GOTERM_CC_FAT	GO:0070013~intracellular organelle lumen	8	26.67	0.01	PDK1, ERCC5, PNMA3, CENPF, PCSK6, DIMT1L, DNAJA3, CBX5	20	1779	12782	2.87	0.64	11.29
GOTERM_CC_FAT	GO:0043233~organelle lumen	8	26.67	0.01	PDK1, ERCC5, PNMA3, CENPF, PCSK6, DIMT1L, DNAJA3, CBX5	20	1820	12782	2.81	0.43	12.68
GOTERM_CC_FAT	GO:0031974~membrane-enclosed lumen	8	26.67	0.01	PDK1, ERCC5, PNMA3, CENPF, PCSK6, DIMT1L, DNAJA3, CBX5	20	1856	12782	2.75	0.34	13.98
Annotation Cluster 2 Enrichment Score: 1.6656724740255078											
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Benjamini	FDR
GOTERM_BP_FAT	GO:0043066~negative regulation of apoptosis	4	13.33	0.01	ERCC5, RIPK2, PCSK6, DNAJA3	20	354	13528	7.64	1.00	16.49
GOTERM_BP_FAT	GO:0043069~negative regulation of programmed cell death	4	13.33	0.01	ERCC5, RIPK2, PCSK6, DNAJA3	20	359	13528	7.54	0.95	17.07
GOTERM_BP_FAT	GO:0060548~negative regulation of cell death	4	13.33	0.01	ERCC5, RIPK2, PCSK6, DNAJA3	20	360	13528	7.52	0.87	17.19
GOTERM_BP_FAT	GO:0042981~regulation of apoptosis	4	13.33	0.10	ERCC5, RIPK2, PCSK6, DNAJA3	20	804	13528	3.37	0.96	77.51

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons											
Annotation Cluster 3		Enrichment Score: 1.3439751095199926									
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment _t	Benjamini	FDR
GOTERM_BP_FAT	GO:0016481~negative regulation of transcription	4	13.33	0.03	LMCD1, CENPF, NSD1, CBX5	20	459	13528	5.89	0.94	30.30
GOTERM_MF_FAT	GO:0003682~chromatin binding	3	10.00	0.03	CENPF, NSD1, CBX5	24	150	12983	10.82	0.98	28.76
GOTERM_BP_FAT	GO:0010629~negative regulation of gene expression	4	13.33	0.03	LMCD1, CENPF, NSD1, CBX5	20	504	13528	5.37	0.95	36.94
GOTERM_BP_FAT	GO:0045934~negative regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	4	13.33	0.03	LMCD1, CENPF, NSD1, CBX5	20	512	13528	5.28	0.89	38.15
GOTERM_BP_FAT	GO:0051172~negative regulation of nitrogen compound metabolic process	4	13.33	0.03	LMCD1, CENPF, NSD1, CBX5	20	519	13528	5.21	0.86	39.20
GOTERM_BP_FAT	GO:0010558~negative regulation of macromolecule biosynthetic process	4	13.33	0.04	LMCD1, CENPF, NSD1, CBX5	20	547	13528	4.95	0.87	43.44
GOTERM_BP_FAT	GO:0031327~negative regulation of cellular biosynthetic process	4	13.33	0.04	LMCD1, CENPF, NSD1, CBX5	20	561	13528	4.82	0.86	45.56
GOTERM_BP_FAT	GO:0009890~negative regulation of biosynthetic process	4	13.33	0.04	LMCD1, CENPF, NSD1, CBX5	20	573	13528	4.72	0.84	47.38
GOTERM_MF_FAT	GO:0008134~transcription factor binding	4	13.33	0.06	LMCD1, CENPF, NSD1, DNAJA3	24	513	12983	4.22	0.98	51.71

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons											
GOTERM_BP_FAT	GO:0010605~negative regulation of macromolecule metabolic process	4	13.33	0.08	LMCD1, CENPF, NSD1, CBX5	20	734	13528	3.69	0.96	69.72
GOTERM_BP_FAT	GO:0045892~negative regulation of transcription, DNA-dependent	3	10.00	0.09	LMCD1, NSD1, CBX5	20	356	13528	5.70	0.96	72.98
GOTERM_BP_FAT	GO:0051253~negative regulation of RNA metabolic process	3	10.00	0.09	LMCD1, NSD1, CBX5	20	362	13528	5.61	0.95	74.03
Lacunar IS											
SIGNIFICANTLY ENRICHED CANONICAL PATHWAYS OF LACUNAR ISCHEMIC STROKE											
Ingenuity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules							
Eumelanin Biosynthesis	2.34E00	7.03E-01	2.5E-01	DDT							
G Protein Signaling Mediated by Tubby	1.43E00	6.15E-01	3.03E-02	GNG3							
GENE ONTOLOGY OF LACUNAR ISCHEMIC STROKE											
Not Available with 0.1 Ease											

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

Intracerebral hemorrhage (ICH)				
SIGNIFICANTLY ENRICHED CANONICAL PATHWAYS OF HEM				
Inguinity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules
Regulation of eIF4 and p70S6K Signaling	3.54E00	1.14E00	4.79E-02	SHC1,AKT1,RPS10,ITGA5,RPS15A,EIF2A,ITGA4
PTEN Signaling	3.24E00	1.14E00	5.08E-02	MAST2,SHC1,AKT1,ITGA5,INPP5D,ITGA4
Actin Cytoskeleton Signaling	2.53E00	8.12E-01	3.23E-02	SHC1,DIAPH1,ITGA5,TRIO,SLC9A1,PDGFC,ITGA4
IL-3 Signaling	2.47E00	8.12E-01	5.63E-02	SHC1,AKT1,PPP3CB,INPP5D
Caveolar-mediated Endocytosis Signaling	2.45E00	8.12E-01	5.56E-02	RAB5A,RAB5C,ITGA5,ITGA4
Ephrin Receptor Signaling	2.38E00	8.12E-01	3.45E-02	SHC1,AKT1,ITGA5,GNCS,PDGFC,ITGA4
PI3K/AKT Signaling	2.36E00	8.12E-01	4.07E-02	SHC1,AKT1,ITGA5,INPP5D,ITGA4
FcγRIIB Signaling in B Lymphocytes	2.27E00	8.12E-01	7.32E-02	SHC1,AKT1,INPP5D
Clastrin-mediated Endocytosis Signaling	2.25E00	8.12E-01	3.24E-02	RAB5A,RAB5C,PPP3CB,CLTC,ITGA5,PDGFC
DNA Double-Strand Break Repair by Homologous Recombination	2.2E00	8.08E-01	1.43E-01	GEN1,ATRX

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

Neuregulin Signaling	2.14E00	8.08E-01	4.55E-02	SHC1,AKT1,ITGA5,ITGA4
PAK Signaling	2.12E00	8.08E-01	4.49E-02	SHC1,ITGA5,PDGFC,ITGA4
Telomerase Signaling	1.96E00	6.84E-01	4.04E-02	SHC1,AKT1,TEP1,ELF1
HGF Signaling	1.88E00	6.48E-01	3.81E-02	AKT1,ITGA5,ELF1,ITGA4
iCOS-iCOSL Signaling in T Helper Cells	1.83E00	6.48E-01	3.7E-02	SHC1,AKT1,PPP3CB,INPP5D
Natural Killer Cell Signaling	1.81E00	6.48E-01	3.64E-02	SHC1,AKT1,KLRK1,KLRK1,KLRK1,INPP5D
GM-CSF Signaling	1.78E00	6.48E-01	4.84E-02	SHC1,AKT1,PPP3CB
4-hydroxyproline Degradation I	1.76E00	6.48E-01	5E-01	HOGA1
Anandamide Degradation	1.76E00	6.48E-01	5E-01	FAAH
Macropinocytosis Signaling	1.67E00	5.8E-01	4.41E-02	RAB5A,ITGA5,PDGFC
EIF2 Signaling	1.64E00	5.8E-01	2.7E-02	SHC1,AKT1,RPS10,RPS15A,EIF2A
mTOR Signaling	1.61E00	5.8E-01	2.66E-02	AKT1,RPS10,RPS15A,PDGFC,ARHGAP8/PRR5-ARHGAP8
NF-κB Activation by Viruses	1.59E00	5.8E-01	4.11E-02	AKT1,ITGA5,ITGA4
Tyrosine Biosynthesis IV	1.59E00	5.8E-01	3.33E-01	PCBD2
FLT3 Signaling in Hematopoietic Progenitor Cells	1.57E00	5.8E-01	4.05E-02	SHC1,AKT1,INPP5D
IL-4 Signaling	1.55E00	5.69E-01	3.95E-02	SHC1,AKT1,INPP5D
PDGF Signaling	1.53E00	5.69E-01	3.9E-02	SHC1,PDGFC,INPP5D

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

Reelin Signaling in Neurons	1.5E00	5.57E-01	3.8E-02	AKT1,ITGA5,ITGA4
Phenylalanine Degradation I (Aerobic)	1.46E00	5.35E-01	2.5E-01	PCBD2
FAK Signaling	1.4E00	5E-01	3.45E-02	AKT1,ITGA5,ITGA4
CTLA4 Signaling in Cytotoxic T	1.38E00	5E-01	3.41E-02	AKT1,AP1S2,CLTC
Lymphocytes G Beta Gamma Signaling	1.38E00	5E-01	3.41E-02	SHC1,AKT1,GNNG5
Virus Entry via Endocytic Pathways	1.37E00	5E-01	3.37E-02	CLTC,ITGA5,ITGA4
VEGF Signaling	1.35E00	5E-01	3.3E-02	SHC1,AKT1,PDGFC
Fcy Receptor-mediated Phagocytosis in Macrophages and Monocytes	1.32E00	5E-01	3.23E-02	AKT1,FYB,INPP5D
PPAR Signaling	1.31E00	5E-01	3.19E-02	SHC1,SRA1,PDGFC
Tec Kinase Signaling	1.31E00	5E-01	2.53E-02	GTF2I,ITGA5,GNNG5,ITGA4
Glioma Signaling	1.3E00	5E-01	3.16E-02	SHC1,AKT1,PDGFC
Huntington's Disease Signaling	1.3E00	5E-01	2.17E-02	SHC1,AKT1,CLTC,GNNG5,NAPB
GENE ONTOLOGY OF HEM				
Annotation Cluster 1	Enrichment Score: 2.0008035747785273			

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Benjamini	FDR
GOTERM_BP_FAT	GO:0015031~protein transport	19	10.05291005	6.74E-04	RGPD6, SCAMP1, ARL6IP1, FYB, RGPD5, RGPD8, SCAMP2, RAB5C, CHMP5, NAPB, CLTC, AKT1, SFT2D2, AP1S2, TOMM6, ATG4C, LYST, FXC1, TOMM40L, RAB5A, PPP3CB	138	762	13528	2.44	0.57	1.09
GOTERM_BP_FAT	GO:0045184~establishment of protein localization	19	10.05291005	7.50E-04	RGPD6, SCAMP1, ARL6IP1, FYB, RGPD5, RGPD8, SCAMP2, RAB5C, CHMP5, NAPB, CLTC, AKT1, SFT2D2, AP1S2, TOMM6, ATG4C, LYST, FXC1, TOMM40L, RAB5A, PPP3CB	138	769	13528	2.42	0.37	1.21
GOTERM_BP_FAT	GO:0008104~protein localization	19	10.05291005	3.43E-03	RGPD6, SCAMP1, ARL6IP1, FYB, RGPD5, RGPD8, SCAMP2, RAB5C, CHMP5, NAPB, CLTC, AKT1, SFT2D2, AP1S2, TOMM6, ATG4C, LYST, FXC1, TOMM40L, RAB5A, PPP3CB	138	882	13528	2.11	0.76	5.43
GOTERM_BP_FAT	GO:0046907~intracellular transport	15	7.936507937	6.75E-03	RGPD6, ARL6IP1, FYB, SCAMP1, RGPD5, RGPD8, SCAMP2, KIF5B, CHMP5, NAPB, CLTC, AKT1, AP1S2, ATG4C, LYST, FXC1, PPP3CB	138	657	13528	2.24	0.88	10.42
GOTERM_BP_FAT	GO:0006886~intracellular protein transport	9	4.761904762	3.64E-02	FYB, ARL6IP1, AKT1, AP1S2, ATG4C, FXC1, PPP3CB, NAPB, CLTC	138	374	13528	2.36	1.00	45.30
GOTERM_BP_FAT	GO:0034613~cellular protein localization	9	4.761904762	5.75E-02	FYB, ARL6IP1, AKT1, AP1S2, ATG4C, FXC1, PPP3CB, NAPB, CLTC	138	411	13528	2.15	1.00	61.82
GOTERM_BP_FAT	GO:0070727~cellular macromolecule localization	9	4.761904762	5.95E-02	FYB, ARL6IP1, AKT1, AP1S2, ATG4C, FXC1, PPP3CB, NAPB, CLTC	138	414	13528	2.13	1.00	63.10
GOTERM_BP_FAT	GO:0006605~protein targeting	6	3.174603175	6.75E-02	FYB, ARL6IP1, AKT1, ATG4C, FXC1, PPP3CB	138	215	13528	2.74	0.99	67.90

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

Annotation Cluster 2		Enrichment Score: 1.946654262059368									
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Benjamini	FDR
GOTERM_CC_FAT	GO:0015630~microtubule cytoskeleton	16	8.465608466	3.54E-04	SDCCAG8, SEPT2, KIF5B, TLL5, DNHD1, CHEK1, DNAH1, WRN, AKT1, PBXIP1, CEP350, ATG4C, NAV1, LYST, FBXO5, CNTLN	128	549	12782	2.91	0.09	0.46
GOTERM_CC_FAT	GO:0005856~cytoskeleton	23	12.16931217	1.70E-02	FYB, CTTNBP2NL, SDCCAG8, SEPT2, KIF5B, DIAPH1, UBR4, DNHD1, TLL5, DNAH1, CHEK1, WRN, ZNF174, AKT1, MAST2, PBXIP1, NAV1, CEP350, ATG4C, LYST, FAAH, FBXO5, CNTLN	128	1381	12782	1.66	0.58	20.05
GOTERM_CC_FAT	GO:0043232~intracellular non-membrane-bounded organelle	37	19.57671958	1.85E-02	CTTNBP2NL, SDCCAG8, SEPT2, HMG2, DIAPH1, RPS15A, TLL5, DNAH1, CHEK1, ZNF174, AKT1, DCAF13, PBXIP1, DGCR8, FBXO5, CNTLN, ZWILCH, FYB, EXOSC9, KIF5B, UBR4, SYCE2, DNHD1, WRN, EXOSC1, ATRX, PAPOLA, MAST2, NAV1, APITD1, CEP350, ATG4C, LYST, FAAH, TEP1, RPS10, CORT, TBX19	128	2596	12782	1.42	0.54	21.53
GOTERM_CC_FAT	GO:0043228~non-membrane-bounded organelle	37	19.57671958	1.85E-02	CTTNBP2NL, SDCCAG8, SEPT2, HMG2, DIAPH1, RPS15A, TLL5, DNAH1, CHEK1, ZNF174, AKT1, DCAF13, PBXIP1, DGCR8, FBXO5, CNTLN, ZWILCH, FYB, EXOSC9, KIF5B, UBR4, SYCE2, DNHD1, WRN, EXOSC1, ATRX, PAPOLA, MAST2, NAV1, APITD1, CEP350, ATG4C, LYST, FAAH, TEP1, RPS10, CORT, TBX19	128	2596	12782	1.42	0.54	21.53
GOTERM_CC_FAT	GO:0044430~cytoskeleton part	15	7.936507937	9.00E-02	SDCCAG8, SEPT2, KIF5B, TLL5, DNHD1, CHEK1, DNAH1, WRN, AKT1, PBXIP1, CEP350, ATG4C, NAV1, FBXO5, CNTLN	128	952	12782	1.57	0.68	70.68

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons											
Annotation Cluster 3		Enrichment Score: 1.4567585294932377									
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Benjamini	FDR
GOTERM_CC_FAT	GO:0030136~clathrin-coated vesicle	6	3.174603175	0.01	SCAMP1, ATP7A, AP1S2, PI4K2A, RAB5A, CLTC	128	132	12782	4.54	0.58	12.44
GOTERM_CC_FAT	GO:0030665~clathrin-coated vesicle membrane	4	2.116402116	0.02	SCAMP1, AP1S2, PI4K2A, CLTC	128	53	12782	7.54	0.63	18.55
GOTERM_BP_FAT	GO:0006892~post-Golgi vesicle-mediated transport	4	2.116402116	0.02	SCAMP1, AP1S2, SCAMP2, CLTC	138	58	13528	6.76	0.99	29.07
GOTERM_CC_FAT	GO:0030135~coated vesicle	6	3.174603175	0.02	SCAMP1, ATP7A, AP1S2, PI4K2A, RAB5A, CLTC	128	159	12782	3.77	0.54	24.29
GOTERM_CC_FAT	GO:0030140~trans-Golgi network transport vesicle	3	1.587301587	0.02	ATP7A, AP1S2, CLTC	128	24	12782	12.48	0.49	26.56
GOTERM_CC_FAT	GO:0030133~transport vesicle	4	2.116402116	0.03	ATP7A, AP1S2, PI4K2A, CLTC	128	66	12782	6.05	0.51	30.76
GOTERM_CC_FAT	GO:0030662~coated vesicle membrane	4	2.116402116	0.04	SCAMP1, AP1S2, PI4K2A, CLTC	128	73	12782	5.47	0.54	37.96
GOTERM_CC_FAT	GO:0005768~endosome	8	4.232804233	0.04	SCAMP1, ATP7A, SCAMP2, RAB5C, CHMP5, PI4K2A, RAB5A, CYBASC3	128	315	12782	2.54	0.53	39.32
GOTERM_CC_FAT	GO:0030659~cytoplasmic vesicle membrane	5	2.645502646	0.05	SCAMP1, AP1S2, PI4K2A, RAB5A, CLTC	128	139	12782	3.59	0.60	48.53
GOTERM_CC_FAT	GO:0012506~vesicle membrane	5	2.645502646	0.06	SCAMP1, AP1S2, PI4K2A, RAB5A, CLTC	128	151	12782	3.31	0.65	57.50
GOTERM_CC_FAT	GO:0044431~Golgi apparatus part	7	3.703703704	0.07	SCAMP1, ATP7A, AP1S2, SCAMP2, PDGFC, CLIP3, CLTC	128	294	12782	2.38	0.68	62.65
GOTERM_CC_FAT	GO:0012505~endomembrane system	13	6.878306878	0.09	ARL6IP1, SCAMP1, RGPD6, RGPD5, RGPD8, SCAMP2, CLTC, AP1S2, STT3A, INSIG2, SERINC1, PI4K2A, RAB5A, PDGFC, ASPH	128	782	12782	1.66	0.69	69.95

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

GOTERM_CC_FAT	GO:005798-Golgi-associated vesicle	3	1.587301587	0.09	ATP7A, AP1S2, CLTC	128	51	12782	5.87	0.67	71.19
Annotation Cluster 4 Enrichment Score: 1.2483614903873126											
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Benjamini	FDR
GOTERM_BP_FAT	GO:006665-sphingolipid metabolic process	4	2.116402116	0.04	GBA2, SERINC1, LASS2, GALC	138	75	13528	5.23	1.00	48.90
GOTERM_BP_FAT	GO:006643-membrane lipid metabolic process	4	2.116402116	0.05	GBA2, SERINC1, LASS2, GALC	138	81	13528	4.84	1.00	55.78
GOTERM_BP_FAT	GO:006672-ceramide metabolic process	3	1.587301587	0.07	GBA2, LASS2, GALC	138	42	13528	7.00	1.00	67.83
GOTERM_BP_FAT	GO:0046519-sphingoid metabolic process	3	1.587301587	0.08	GBA2, LASS2, GALC	138	45	13528	6.54	1.00	72.33
Annotation Cluster 5 Enrichment Score: 1.1612816039563372											
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Benjamini	FDR
GOTERM_CC_FAT	GO:0042470-melanosome	4	2.116402116	0.06	RAB5C, RAB5A, CLTC, PRDX1	128	89	12782	4.49	0.64	54.53
GOTERM_CC_FAT	GO:0048770-pigment granule	4	2.116402116	0.06	RAB5C, RAB5A, CLTC, PRDX1	128	89	12782	4.49	0.64	54.53

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

GOTERM_CC_FAT	GO:0009898-internal side of plasma membrane	7	3.703703704	0.10	AP1S2, MTMR1, MAST2, RAB5C, RAB5A, CLTC, GNG5	128	316	12782	2.21	0.67	72.75
Controls											
SIGNIFICANTLY ENRICHED CANONICAL PATHWAYS OF CONTROLS											
Ingenuity Canonical Pathways	-log(p-value)	-log(B-H p-value)	Ratio	Molecules							
Antigen Presentation Pathway	3.35E00	1.71E00	5.41E-02	HLA-DOB, TAP2							
Bile Acid Biosynthesis, Neutral Pathway	1.96E00	8.31E-01	7.69E-02	SCP2							
Methionine Degradation I (to Homocysteine)	1.87E00	8.31E-01	6.25E-02	AHCY							
Cysteine Biosynthesis III (mammalia)	1.82E00	8.31E-01	5.56E-02	AHCY							
Superpathway of Methionine Degradation	1.58E00	8.31E-01	3.23E-02	AHCY							
B Cell Development	1.54E00	8.31E-01	2.94E-02	HLA-DOB							
tRNA Charging	1.48E00	8.31E-01	2.56E-02	IARS							

TABLE 8. Over-represented Pathways and Gene Ontology for the Upregulated Exons

SIGNIFICANTLY ENRICHED CANONICAL PATHWAYS OF CONTROLS										
Annotation Cluster 1 Enrichment Score: 1.556431804209894										
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Benjamini FDR
GOTERM_CC_FAT	GO:0044432~endoplasmic reticulum part	4	21.05263158	0.00	TAP2, FOXRED2, HLA-DOB, PORCN	14	347	12782	10.52	0.30
GOTERM_MF_FAT	GO:0001882~nucleoside binding	5	26.31578947	0.07	IARS, ACTN4, TAP2, FOXRED2, HLA-DOB	14	1612	12983	2.88	1.00
GOTERM_CC_FAT	GO:0005783~endoplasmic reticulum	4	21.05263158	0.07	TAP2, FOXRED2, HLA-DOB, PORCN	14	960	12782	3.80	0.94
										52.87
										52.80
Graft-versus-Host Disease Signaling	1.4E00	8.31E-01	2.08E-02		HLA-DOB					
Autoimmune Thyroid Disease Signaling	1.39E00	8.31E-01	2.04E-02		HLA-DOB					
Primary Immunodeficiency Signaling	1.36E00	8.31E-01	1.92E-02		TAP2					
Nur77 Signaling in T Lymphocytes	1.32E00	8.31E-01	1.75E-02		HLA-DOB					
Regulation of Cellular Mechanics by Calpain Protease	1.32E00	8.31E-01	1.75E-02		ACTN4					

DISCUSSION

[0147] Although DAS is implicated in many human diseases, this is the first study to report DAS for ICH, IS and controls, and is the first to show that DAS is different for different causes of IS. Identification of specific DAS for different stroke etiologies suggests the immune response varies for each condition. This will likely be important for understanding pathogenesis of each stroke cause and biomarker development.

[0148] This study identified several pathways, molecular functions and genes previously reported in human IS using 3'-biased microarrays [6, 11]. These include: actin cytoskeleton signaling, CCR5 signaling in macrophages, NF- κ B activation, α -adrenergic signaling, cellular growth and proliferation, cell death and survival, cell morphology, hematopoiesis, hematological system development and function and inflammatory response/disease [4, 5, 12, 13]. This study's small sample sizes preclude detailed interpretations of biological pathways. However, these pilot data suggest DAS involvement in IS and ICH pathophysiology which varies in ICH and in different IS etiologies.

[0149] Results suggest DAS differs in blood leukocytes following different cerebrovascular events. Due to the pilot nature of the study, and the lack of human transcriptome data following ICH, we will discuss only a few of the genes with differential exon usage in ICH. Among the genes that differentiated ICH were INPP5D (inositol poly-phosphate-5-phosphatase) and ITA4 (integrin alpha 4). INPP5D is a regulator of myeloid cell proliferation and programming and was previously identified as correlating with increased tendency to hemorrhagic transformation of ischemic stroke [14]. ITA4 is involved in leukocyte recruitment [15] and leukocytes are intimately associated with IS and ICH [11]. For example, leukocytes are involved in clotting, and interact with injured vessels and brain following ICH and IS [11]. In addition, vascular endothelial growth factor (VEGF) signaling, which predisposes to hemorrhage because of new vessel formation [16], was implicated in ICH by several DAS genes, including NAV1 (neuron navigator 1), PDGFC (platelet derived growth factor C) and CCM2 (cerebral cavernous malformation 2). CCM2 mutations cause cerebral cavernous malformations leading to a predisposition for abnormal vessels and cerebral hemorrhage [17]. Interestingly, exosomes may be involved in ICH as evidenced by the differential expression of EXOSC1 (exosome component 1) and EXOSC9 (exosome component 9), coding for core components of the exosome complex [18]. Although exosomes have been implicated in neuroinflammation, neurodegeneration and cancer, they have not previously been associated with ICH [19, 20]. Finally, DGCR8

(microprocessor complex subunit) is involved in the biogenesis of microRNAs [21], thus suggesting an interplay between alternative splicing and miRNA in ICH.

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[0150] It is understood that the examples and embodiments described herein are for
25 illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

30

CLAIMS

What is claimed is:

1. A method for diagnosing cardioembolic ischemic stroke (CE IS) or a predisposition for experiencing CE IS, the method comprising: determining a level of exon
5 or splice variant usage or expression of a plurality of biomarkers in a biological sample from a patient, wherein an increase of the level of exon usage or expression compared to a control indicates that the patient has suffered or is at risk of experiencing CE IS, wherein the plurality of exons or splice variants of the biomarkers is selected from the biomarkers set forth in Table 1A, thereby diagnosing CE IS or a predisposition for experiencing CE IS.
- 10 2. A method for diagnosing large vessel ischemic stroke (LV IS) or a predisposition for experiencing LV IS, the method comprising: determining a level of exon or splice variant usage or expression of a plurality of biomarkers in a biological sample from a patient, wherein an increase of the level of exon usage or expression compared to a control indicates that the patient has suffered or is at risk of experiencing LV IS, wherein
15 the plurality of exons or splice variants of the biomarkers is selected from the biomarkers set forth in Table 1B, thereby diagnosing LV IS or a predisposition for experiencing LV IS.
3. A method for diagnosing lacunar ischemic stroke (L IS) or a predisposition for experiencing L IS, the method comprising: determining a level of exon or splice variant usage or expression of a plurality of biomarkers in a biological sample from a
20 patient, wherein an increase of the level of exon usage or expression compared to a control indicates that the patient has suffered or is at risk of experiencing L IS, wherein the plurality of exons or splice variants of the biomarkers is selected from the biomarkers set forth in Table 1C, thereby diagnosing L IS or a predisposition for experiencing L IS.
4. A method for diagnosing intracerebral hemorrhage (ICH) or a
25 predisposition for experiencing ICH, the method comprising: determining a level of exon usage or expression of a plurality of biomarkers in a biological sample from a patient, wherein an increase of the level of exon or splice variant usage or expression compared to a control indicates that the patient has suffered or is at risk of experiencing ICH, wherein the plurality of exons or splice variants of the biomarkers is selected from the biomarkers set
30 forth in Table 1D, thereby diagnosing ICH or a predisposition for experiencing ICH.

5. A method of differentiating between ischemic stroke (IS) from intracerebral hemorrhage (ICH), the method comprising: determining a level of exon or splice variant usage or expression of a plurality of biomarkers set forth in Table 1A, a plurality of biomarkers set forth in Table 1B, a plurality of biomarkers set forth in Table 1C, and a plurality of biomarkers set forth in Table 1D, in a biological sample from a patient, wherein detecting:

a) an increase of the level of exon or splice variant usage or expression of a plurality of exons of the biomarkers set forth in Table 1A compared to a control indicates that the patient has suffered or is at risk of experiencing cardioembolic ischemic stroke (CE IS);

b) an increase of the level of exon or splice variant usage or expression of a plurality of exons of the biomarkers set forth in Table 1B compared to a control indicates that the patient has suffered or is at risk of experiencing large vessel ischemic stroke (LV IS);

c) an increase of the level of exon or splice variant usage or expression of a plurality of exons of the biomarkers set forth in Table 1C compared to a control indicates that the patient has suffered or is at risk of experiencing lacunar ischemic stroke (L IS); and

d) an increase of the level of exon or splice variant usage or expression of a plurality of exons of the biomarkers set forth in Table 1D compared to a control indicates that the patient has suffered or is at risk of experiencing ICH; thereby differentiating between ischemic stroke (IS) from ICH.

6. The method of any one of claims 1 to 5, wherein the determining step is performed at 3 or more hours after a suspected ischemic stroke or ICH.

7. The method of any one of claims 1 to 5, wherein the determining step is performed at 3 or fewer hours after a suspected ischemic stroke or ICH.

8. The method of any one of claims 1 to 6, wherein the determining step is performed at 24 or fewer hours after a suspected ischemic stroke or ICH.

9. The method of any one of claims 1 to 6, wherein the determining step is performed at least 24 hours after a suspected ischemic stroke or ICH.

10. The method of any one of claims 1 to 9, wherein the level of expression of the biomarker is determined at the transcriptional level.

11. The method of any one of claims 1 to 10, wherein the level of expression is determined by detecting hybridization of a nucleic acid probe to gene transcripts of the biomarkers in the biological sample.

12. The method of claim 11, wherein the hybridization step is performed
5 on a nucleic acid microarray chip.

13. The method of claim 11, wherein the hybridization step is performed in a microfluidics assay plate.

14. The method of any one of claims 1 to 10, wherein the level of expression is determined by direct RNA sequencing of gene transcripts of the biomarkers.

10 15. The method of any one of claims 1 to 10, wherein the level of expression is determined by amplification of gene transcripts of the biomarkers.

16. The method of claim 15, wherein the amplification reaction is a polymerase chain reaction (PCR).

17. The method of claim 15, wherein the amplification reaction
15 comprises quantitative reverse transcription polymerase chain reaction (qRT-PCR).

18. The method of claim 15, wherein the amplification reaction comprises reverse transcription (RT) followed by a ligase detection reaction (LDR) with single-pair fluorescence resonance energy transfer (spFRET) (RT-LDR/spFRET).

19. The method of any one of claims 1 to 9, wherein the level of
20 expression of the biomarker isoform is determined at the protein level.

20. The method of any one of claims 1 to 19, wherein the level of expression of at least 15 biomarkers is determined.

21. The method of any one of claims 1 to 20, further comprising the step of obtaining a biological sample.

25 22. The method of any one of claims 1 to 21, wherein the biological sample is blood, serum or plasma.

23. The method of any one of claims 1 to 22, wherein the increased level of exon usage of a biomarker is at least about 1.2-fold in comparison to a control.

24. The method of any one of claims 1 to 23, wherein the control is the expression level of the same biomarker in an individual with no history of stroke, heart
5 attack, or peripheral vascular disease.

25. The method of any one of claims 1 to 24, wherein the control is a threshold level of expression representative of a population of individuals with no history of stroke, heart attack, peripheral vascular disease.

26. The method of any one of claims 24 to 25, wherein the individual or
10 the population of individuals has at least one vascular risk factor.

27. The method of any one of claims 1 to 26, wherein the control is an individual or population of individuals who have increased expression of one or more biomarkers set forth in Table 1E.

28. The method of any one of claims 1 to 27, further comprising the step
15 of providing a diagnosis for ischemic stroke/ICH to the patient based on the determination and identification of the level of expression of the set of ischemic stroke/ICH biomarkers.

29. The method of any one of claims 1 to 28, further comprising the step of providing an appropriate treatment or prevention regime for ischemic stroke/ICH to the patient.

20 30. The method of any one of claims 1 to 29, wherein the subject has experienced or is suspected of having experienced ischemic stroke or ICH.

31. The method of any one of claims 1 to 30, wherein if the patient has experienced or has a predisposition to experience ischemic stroke or ICH, further comprising the step of determining the cause or risk of the ischemic stroke or ICH

25 32. A solid support comprising a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers set forth in Table 1A.

33. A solid support comprising a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers set forth in Table 1B.

34. A solid support comprising a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers set forth in Table 1C.

35. A solid support comprising a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers set forth in Table 1D.

5 36. A solid support comprising a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers set forth in Table 1A, Table 1B, Table 1C and Table 1D.

37. The solid support of any one of claims 32 to 35, wherein the solid support is a microarray.

10 38. The solid support of claim 37, wherein the microarray is suitable or configured for use in a microfluidic device.

39. The solid support of any one of claims 32 to 38, further comprising a plurality of oligonucleotide probes that hybridize to a plurality of the biomarkers set forth in Table 1E.

15 40. A reaction mixture comprising one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1A.

41. A reaction mixture comprising one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1B.
20

42. A reaction mixture comprising one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1C.

43. A reaction mixture comprising one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1D.
25

44. A reaction mixture comprising one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1A, Table 1B, Table 1C and Table 1D.

5 45. The reaction mixture of any one of claims 40 to 44, further comprising one or more primer pairs or a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1E.

46. A kit comprising the solid support of any one of claims 32 to 39.

47. A kit comprising the reaction mixture of any one of claims 40 to 45.

10 48. A kit comprising a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1A.

49. A kit comprising a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1B.

50. A kit comprising a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1C.

15 51. A kit comprising a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1D.

52. A kit comprising a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1A, Table 1B, Table 1C and Table 1D.

20 53. The kit of any one of claims 46 to 52, further comprising a set of primers for amplifying one or more exons of a plurality of the biomarkers set forth in Table 1E.

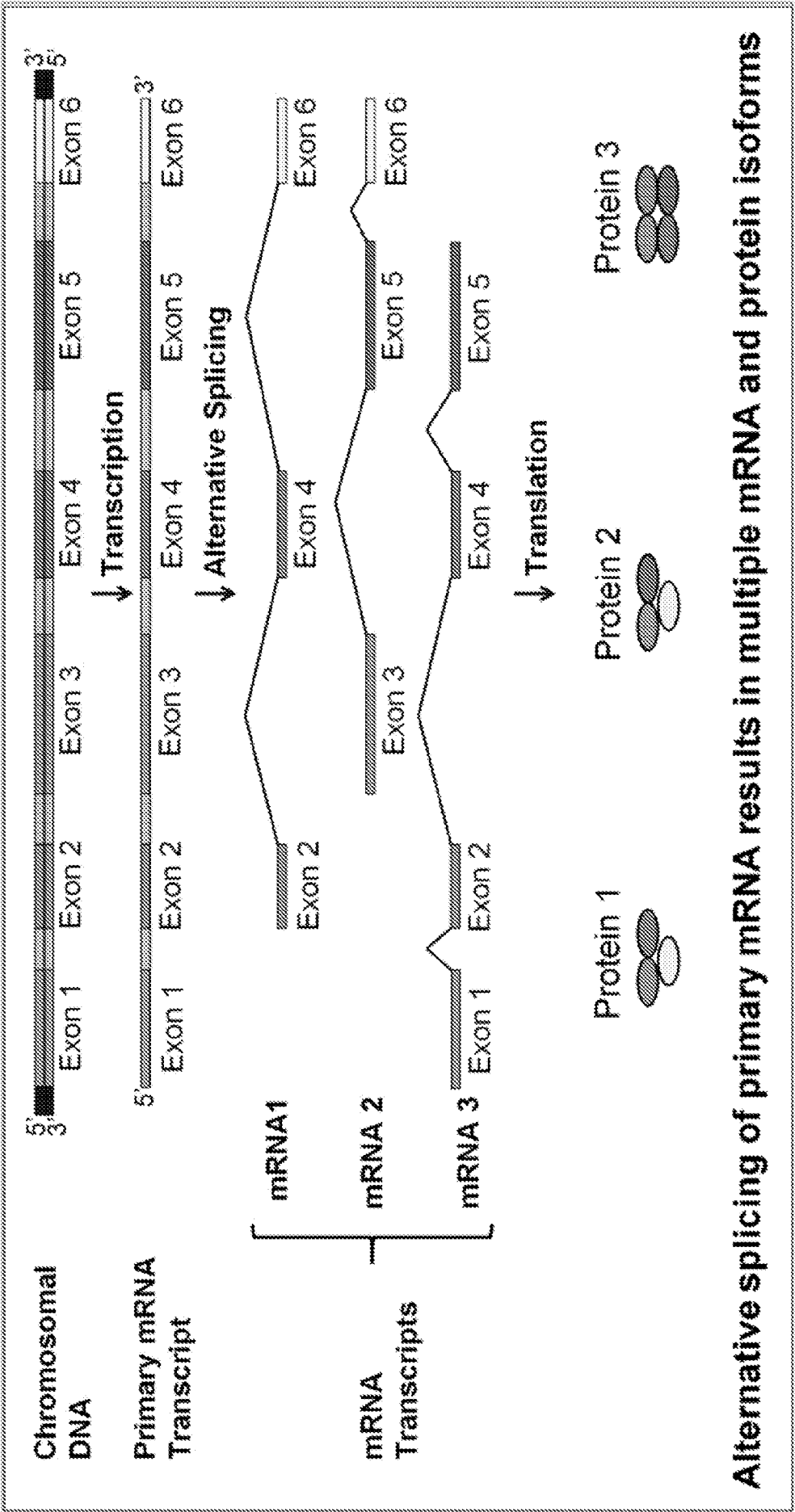
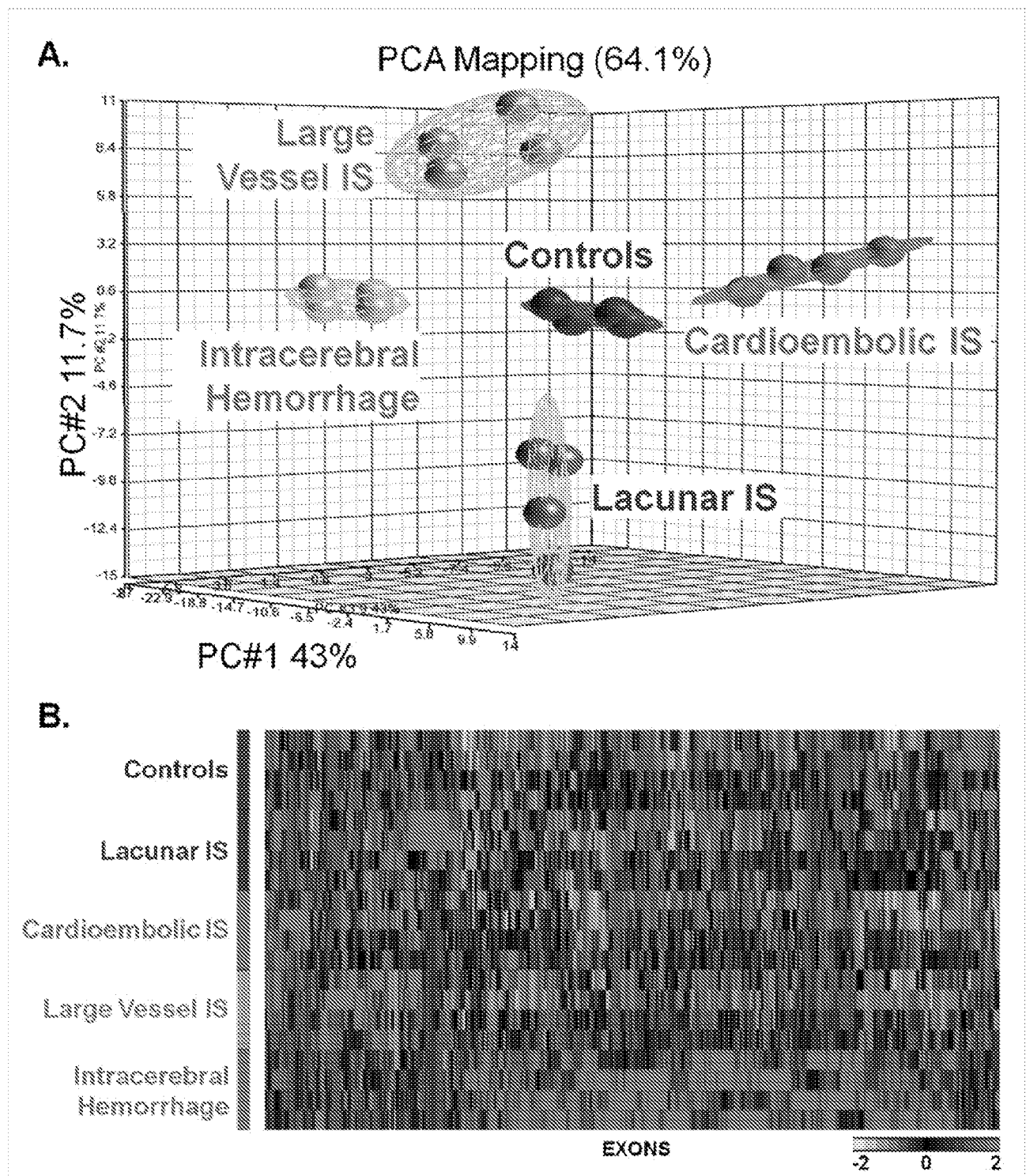


Fig. 1

2/3

**Fig. 2**

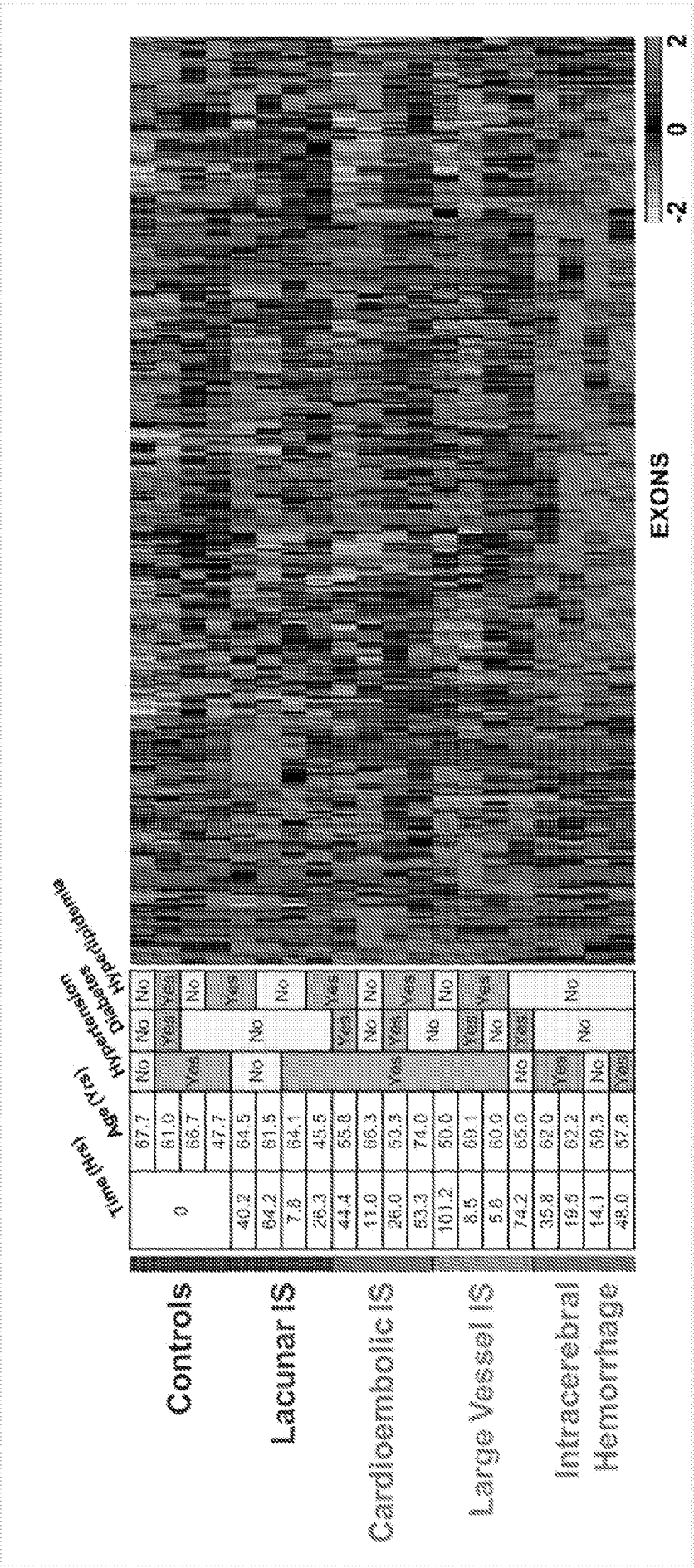


Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/31028

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - C12Q 1/68; G01N 33/68; C40B 40/06, 40/10 (2016.01) CPC - C12Q 1/6883, 1/6876; G01N 33/6893; C40B 40/06, 40/10 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8) Classifications: C12Q 1/68; G01N 33/68, 33/53; C40B 30/04, 40/06, 40/10; A61P 9/10 (2016.01) CPC Classifications: C12Q 1/68, 1/6876, 1/6883; G01N 33/68, 33/6893, 33/53; C40B 30/04, 40/06, 40/10 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google; Google Scholar; PubMed; EBSCO; strok*, lacunar*, cardioembolic*, ischemic*, diagnos*, distinguish*, intracerebral*, hemorrhag*, larg*, vessel*, prim*, pair*, set*, kit*, amplif*, react*, mixtur*, solid*, support*, prob*, hybridiz*, sampl*, blood*, exon*, splic*, biomarker*, 'small vessel'		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015/0018234 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 15 January 2015; paragraphs [0009], [0031], [0037], [0038], [0040], [0102], [0103], [0106], [0107], [0129], [0136], [0140], [0145], [0149], [0164], [0166].	34, 37/34, 38/37/34, 42 50
A	US 2012/0015904 A1 (SHARP, et al.) 19 January 2012; table 8; paragraphs [0009], [0012], [0013], [0015], [0029], [0032], [0146], [0148], [0155], [0159], [0169], [0170], [0172].	1-5, 6/1-5, 7/1-5, 32-33, 35-36, 37/32-33, 37/35, 38/37/32-33, 38/37/35, 40-41, 43-44, 45/40-41, 45/43-44, 48-49, 51-52
A	US 2012/0065087 A1 (SHARP, et al.) 15 March 2012; Table 13B; paragraphs [0016], [0017], [0019], [0020], [0038], [0246], [0247], [0261].	1-2, 6/1-2, 7/1-2
A	WO 2012/115885 A1 (CARIS LIFE SCIENCES LUXEMBOURG HOLDINGS, S.A.R.L.) 30 August 2012; tables 1, 5, 14; figure 59f; paragraphs [0009], [0010], [0022], [0032], [00266], [00490], [00502], [00506], [00774], [00789], [00810], [00857], [00961], [00972], [00995], [001098], [001104], [001109], [001131], [001200], [001201].	1, 4, 5, 6/1, 6/4, 6/5, 7/1, 7/4, 7/5, 32-33, 35-36, 37/32-33, 37/35, 38/37/32-33, 38/37/35, 40
A	PERISIC, et al. Profiling Of Atherosclerotic Lesions By Gene And Tissue Microarrays Reveals PCSK6 As A Novel Protease In Unstable Carotid Atherosclerosis. Arterioscler Thromb Vasc Biol. 2013, Vol. 33, pages 2432-2443, DOI: 10.1161/ATVBAHA.113.301743; page 2432, objective; first paragraph; page 2442, second paragraph.	2, 6/2, 7/2
☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 18 July 2016 (18.07.2016)		Date of mailing of the international search report 26 AUG 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300		Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/31028

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COELHO, T. Stroke Genetics And Genomics. Faculdade de Medicina da Universidade de Lisboa, PhD Thesis. 2010, pages 1-225; entire document.	2, 3, 6/2-3, 7/2-3
A	WO 2012/121978 A2 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 13 September 2012; paragraphs [0010], [0011].	3, 6/3, 7/3
A	US 2014/0220580 A1 (BROWN, et al.) 7 August 2014; tables 1, 5, 20, 22; paragraphs [0011], [0012], [0176], [0347].	4, 6/4, 7/4
A	US 2010/0086481 A1 (BAIRD, et al.) 8 April 2010; paragraphs [0005], [0013]-[0014], [0017], [0022], [0082], [0301]-[0303].	4, 5, 6/4-5, 7/4-5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/31028

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 8-31, 39, 46, 47, 53
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.