Network-Based Approach to Identify Potential Targets and Drugs that Promote Neuroprotection and Neurorepair in Acute Ischemic Stroke

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1. Basic datasets compilation and preprocessing

The datasets used in our work include AIS MeSH headings, AIS disease-gene relationships, human protein-protein interactions and drug-target relationships. We will introduce the main compilation and preprocessing tasks in the following sections.

1.1Disease-gene relationships

To identify the AIS related disease terms, we searched the Medical Subject Headings (MeSH, 2014 version) terminology database using the key words "stroke" and "infarction" on the MeSH Browser website (https://www.nlm.nih.gov/mesh/MBrowser.html) and ultimately confirmed (by the neurobiologists in our author list) 12 AIS related MeSH headings (**Table S1**)

With these 12 MeSH headings as disease keywords, we downloaded 1425 significant disease-gene associations ($p<0.05$)in batch mode from Coremine database[1].

1.2 Curation of AIS disease-gene associations

Since we have downloaded all the related PubMed identifiers relevant to each disease-gene association, we manually checked the reliability of each disease-gene association by the several following key steps. 1) We ranked the related PubMed literatures of disease-gene associations in descending order by their publication date; 2) For each disease-gene associations, we manually checked each of the related PubMed literatures from the latest one. 3)If we find there are clear declarations in the literatures to indicate the disease-gene association is exactly positive, then the corresponding disease-gene association would be considered as reliable. 4) Otherwise, if we find clear indications to show that the disease-gene association is negative, then we would annotate the corresponding disease-gene association as false one. 5) If we cannot confirm from the current literature, we would go next literature, which is published earlier than the current one. When we go through all the PubMed literatures of a disease-gene association, but could not confirm whether it is true or not, we would exclude it from our final results as well. There are more than 4500 PubMed literatures been readed.

From PubMed literatures, we found out the sentences supporting or objecting to the disease-gene associations. If there is evidence supporting a disease-gene association, it will be a real relationship and gene in it is a credible gene. Finally, 1042 (1042/1425 = 73.12%) real relationships were confirmed

containing 606 distinct genes. To evaluate quality of our data, we checked two other well-known disease-gene association databases: OMIM[2](http://www.omim.org/) and DiseaseConnect[3] (http://disease-connect.org/). We find that there are9 AIS genotype-phenotype relationships containing 6 genes in the OMIM database and 3 disease–gene relationships with 2 genes in the DiseaseConnect database. It is interesting that all of these genes are included in our AIS disease-gene associations curated from CoreMine database. (**Data S1**)

1.3 Human protein-protein interactions

Although with numerous curation efforts, human protein-protein interactome(PPI) data is incomplete. However, there are several integrated high quality PPI databases like STRING 9.1 database[4](http://www.string-db.org/)that we could utilize. STRING 9 database is a comprehensive PPI data source developed by integrating various data sources of experimental, predicted and transferred interactions, together with interactions obtained through text mining.It conteins about 5 million proteins and >200 million interactions. There is a confidence level of each interaction. The interactions whose score≥700 have high confidence or better. We filtered to obtain the high quality human PPI records by the weighted score≥700 and finally obtained 218,409 PPI records with 15,551 proteins.

1.4 AIS existing drugs-targets associations

In recent years, the American College of Cardiology (ACC) and the American Heart Association (AHA) have classified ischemic stroke into the study of atherosclerotic cardiovascular disease events[5]. We obtained 87 known AIS drugs from the guideline designed by AHA and American Stroke Association (ASA) professionals[6, 7]. Comprehensive information about these drugs was obtained from the DrugBank database[8](http://www.drugbank.ca/). And there are totally 161 targets of these drugs. (Table S2)

2 Detection of PPI topological modules

Community structures are widely existed in complex network, for each community it comprises of nodes that are densely connected among its members and sparsely connected with nodes in other modules[9]. There are various community detection algorithms that can be used for identifying the topological modules from large-scale network. We used the widely used algorithm (called BGLL) [10], which is based on modularity evaluation, to obtain the

topological modules of the whole PPI network. Because BGLL would get some modules with very large (e.g. several thousand) member nodes, we iteratively divided the modules by BGLL and finally obtained the topological modules with the number of member nodes between 5 and 400. However, different community detection algorithms would exactly obtain different results. Therefore, to validate the possible influence to our results, we performed another network partition method based on NMF algorithm to get the similar number of communities for comparison.

We identified 301 modules from String 9.1 PPI network. We assumed that if the module results are similar, we could find similar communities from another module set for a given module in one module set. Therefore, we calculated the Jaccard similarity between each pairs of modules derived from two module sets. Then we calculated the module similarity distribution. The similarities of 78.095% modules are more than 0.6(Figure S1). So there is no siginificant differences between these two therapies.

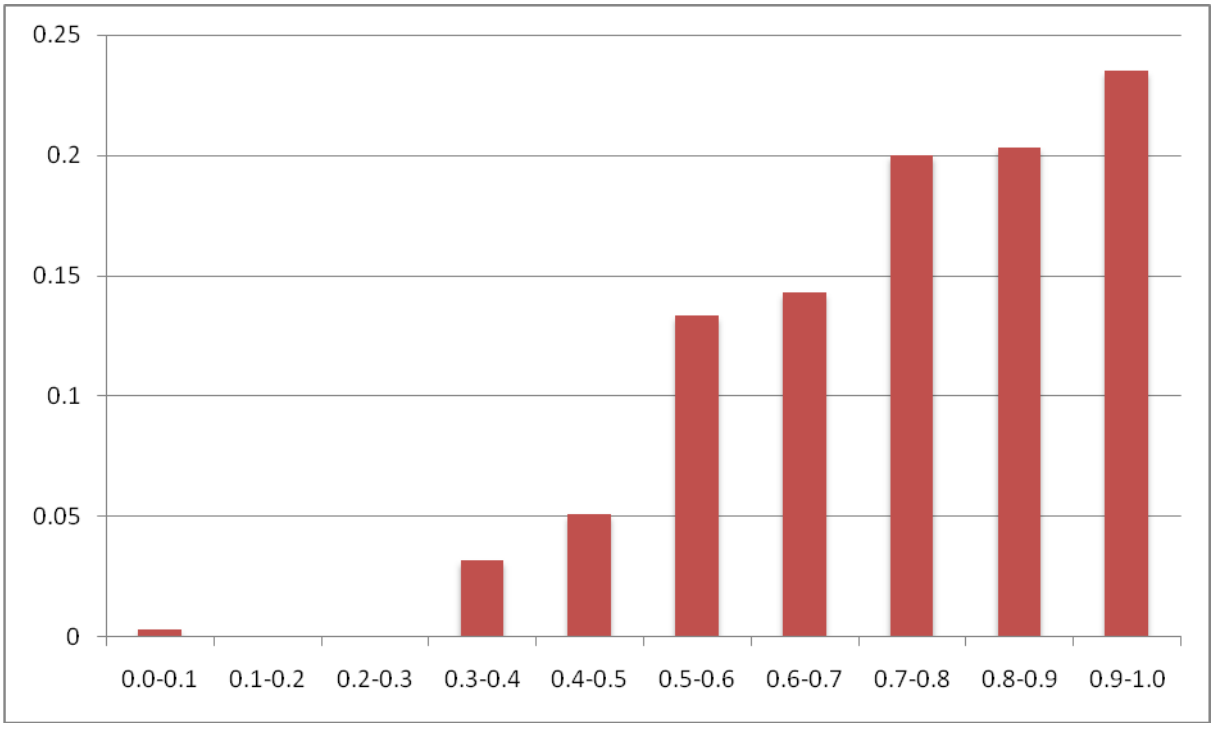

Figure S1.Jaccard similarity between different modules results.

We counted the number of disease genes in each module and calculate OR (Odds Ratio). Assume that there are *A* disease genes in the whole PPI metwork and distribute in many modules in which there totally are *M* nodes. If there are *a* disease genes in a module which has *m* nodes, then the OR of this module is:

$$\mathrm{OR} = \frac{a/(m-a)}{A/(M-A)}, \quad (1)$$

There are 71 modules whose OR>1.0 and 29 modules whose OR>2.0. In the **Data S2**, there are the nodes information of the 29 modules.

3 GO enrichment analysis

The GeneOntology database[11] provides three different types of annotations for proteins: biological process, molecular function, and cellular component. GO enrichment analysis can define gene groups based on the categories in the GeneOntology database[12].With the plugin BiNGO 2.44 of Cytoscape 2.8.2[13, 14], an open-source software platform for visualizing molecular interaction networks, we analyzed the disease genes, existing drug targets, and proteins in the modules. And the statistical test is Hypergeometric test and Benjamini & Hochberg False Discovery Rate (FDR) correction to gain a corrected P-value. The significance level is 0.05.

In the result of AIS credible genes, there are 1392 Biological process terms, 216 Molecular function terms and 108 Cellular component terms. Here we list part of them. **(Table S3-S5, Data S3)**

In the GO enrichment analysis result of AIS existing durg targets, there are 860 Biological process terms, 213 Molecular function terms and 88 Cellular component terms. **(Data S4)**

The GO analysis result of 29 modules (OR>2) are showed in **Data S5.**

4 Pathway enrichment analysis

Pathway analysis has become a vitally important method for gaining insight into the underlying biological functions of genes and proteins. The Reactome database is a manually curated open-source and open-data resource of human pathways. We obtained the enriched Reactome pathways using the KOBAS2.0 online software[15](http://kobas.cbi.pku.edu.cn/home.do). In the pathway analysis result of AIS credible genes, there are 84 enriched pathways. All of them are listed in **Table S6.** And enriched pathways of AIS existing drug targets（Data S6）and 29 modules(OR >2) are showed in **Data S7**.

5 Shortest paths between drug targets and seed genes

The shortest paths are a significant topological statistical quantity used for the analysis of social and biological networks. The most outstanding example of its use is likely to be the well-known small world property of many complex networks16. We used the Dijkstra's algorithm to find the shortest path lengths between AIS drug targets and credible genes17. To obtain random controls for the target-gene, we generated 100 independent randomized samples in the PPI network. Significant difference was calculated statistically using t-test analysis. In PPI network, the hubs is not suitable for AIS treatment18. However the shortest paths analysis result showed that the distances between AIS drug targets and credible genes are enriched at the low range distances (i.e. <=1). This means that existing AIS drugs regulate disease by targeting disease genes directly or neighbors of AIS genes. Otherwise we caculated the degrees of AIS related drug targets in which degrees of more than 45% targets are bigger than 50. It is statistically higher than those of the whole PPI network (Table S7).

6 Analysis of potential targets

6.1 Potential targets in M64

In M64, there are 184 nodes containing 21 AIS genes and 57 drug targets in DrugBank database. Proteins in it are enriched in 81 Reactome pathways. Here we list the top 20 pathways containing 7 pathways shared with the result of AIS credible genes (**Table S8** and **Table S9**). Between these 7 pathways, there is an including and included relationship **(Figure S2)**.With the pathway "Unblocking of NMDA receptor, glutamate binding and activation", we identified 9 potential targets whose lenth from AIS genes is ≤1.

6.2 Analysis of M145

In M64, there are 145 nodes containing 9 AIS genes and 47 drug targets in Drugbank. Proteins in it are enriched in 28 Reactome pathways. And 20 pathways are shared with the result of AIS credible genes (**Table S10**). The most enriched pathway "G Alpha (i) Signaling Events" is at the bottom of the pathway tree. There are 14 potential targets on this pathway. The distances between them and AIS genes are 0 or 1.

7 Potential Drugs

With the potential targets in M64 and M145, we screened out some drugs from DrugBank database. With the analysis of M64, we found out 21 potential drugs. Otherwise, 25 potential drugs were based on the analysis of M145. All of them are showed in **Table S11**.

Table S1. Acute ischemic stroke–related MeSH headings.

Unique ID	**Unidentified MeSH headings**	**Identified MeSH headings**	**Scope Note**
D002544	Cerebral Infarction	Cerebral Infarction	The formation of an area of necrosis in the cerebrum caused by an insufficiency of arterial or venous blood flow. Infarcts of the cerebrum are generally classified by hemisphere (i.e., left vs. right), lobe (e.g., frontal lobe infarction), arterial distribution (e.g., infarction, anterior cerebral artery), and etiology (e.g., embolic infarction).
D020767	Intracranial Thrombosis	Intracranial Thrombosis	Formation or presence of a blood clot (thrombus) in a blood vessel within the SKULL. Intracranial thrombosis can lead to thrombotic occlusions and brain infarction. The majority of the thrombotic occlusions are associated with arterosclerosis.
D020766	Intracranial Embolism	Intracranial Embolism	Blocking of a blood vessel in the skull by an embolus which can be a blood clot (thrombus) or other undissolved material in the blood stream. Most emboli are of cardiac origin and are associated with heart diseases. Other non-cardiac sources of emboli are usually associated with vascular diseases.

D002542	Intracranial Embolism and Thrombosis	Intracranial Embolism and Thrombosis	Embolism or thrombosis involving blood vessels which supply intracranial structures. Emboli may originate from extracranial or intracranial sources. Thrombosis may occur in arterial or venous structures.
D020243	Infarction, Anterior Cerebral Artery	Infarction, Anterior Cerebral Artery	necrosis occurring in the anterior cerebral artery system, including branches such as Heubner's artery. These arteries supply blood to the medial and superior parts of the cerebral hemisphere, Infarction in the anterior cerebral artery usually results in sensory and motor impairment in the lower body.
D020244	Infarction, Middle Cerebral Artery	Infarction, Middle Cerebral Artery	necrosis occurring in the middle cerebral artery distribution system which brings blood to the entire lateral aspects of each cerebral hemisphere. Clinical signs include impaired cognition; aphasia; agraphia; weak and numbness in the face and arms, contralaterally or bilaterally depending on the infarction.
D020762	Infarction, Posterior Cerebral Artery	Infarction, Posterior Cerebral Artery	Necrosis induced by ischemia in the posterior cerebral artery distribution system which supplies portions of the brain stem; the thalamus; temporal lobe, and occipital lobe. Depending on the size and location of infarction, clinical features include olfaction disorders and visual problems.
D002546	Ischemic Attack, Transient	Ischemic Attack, Transient	Brief reversible episodes of focal, nonconvulsive ischemic dysfunction of the brain having a duration of less than 24 hours, and usually less

			than one hour, caused by transient thrombotic or embolic blood vessel occlusion or stenosis. Events may be classified by arterial distribution, temporal pattern, or etiology
D046589	CADASIL	CADASIL	A familial, cerebral arteriopathy mapped to chromosome 19q12, and characterized by the presence of granular deposits in small cerebral arteries producing ischemic stroke; pseudobulbar palsy; and multiple subcortical infarcts. CADASIL is an acronym for Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy. CADASIL differs from binswanger disease by the presence of migraine with aura and usually by the lack of history of arterial hypertension.
D020925	Hypoxia-Ischemia, Brain	Hypoxia-Ischemia, Brain	A disorder characterized by a reduction of oxygen in the blood combined with reduced blood flow (ischemia) to the brain from a localized obstruction of a cerebral artery or from systemic hypoperfusion. Prolonged hypoxia-ischemia is associated with ischemic attack, transient; brain infarction; brain edema; coma; and other conditions.
D059409	Stroke, Lacunar	Stroke, Lacunar	Stroke caused by lacunar infarction or other small vessel diseases of the brain. It features hemiparesis, hemisensory, or hemisensory motor loss.

D002545	Brain Ischemia	Brain Ischemia	Localized reduction of blood flow to brain tissue due to arterial obstruction or systemic hypoperfusion. This frequently occurs in conjunction with brain hypoxia. Prolonged ischemia is associated with brain infarction.
D020521	Stroke		

Table S2. AIS existing Drug-target associations. There are 292 associations between 87drugs and161 targets.

DrugID	Drug name	Groups	Target
DB00009	Alteplase	Approved	SERPINE1
DB00009	Alteplase	Approved	PLG
DB00009	Alteplase	Approved	FGA
DB00009	Alteplase	Approved	PLAUR
DB00013	Urokinase	Approved, Investigational, Withdrawn	SERPINE1
DB00013	Urokinase	Approved, Investigational, Withdrawn	PLG
DB00013	Urokinase	Approved, Investigational, Withdrawn	PLAUR
DB00013	Urokinase	Approved, Investigational, Withdrawn	PLAU
DB00013	Urokinase	Approved, Investigational, Withdrawn	LRP2
DB00013	Urokinase	Approved, Investigational, Withdrawn	SERPINB2
DB00013	Urokinase	Approved, Investigational, Withdrawn	PLAT
DB00013	Urokinase	Approved, Investigational, Withdrawn	ST14
DB00013	Urokinase	Approved, Investigational, Withdrawn	SERPINA5
DB00013	Urokinase	Approved, Investigational, Withdrawn	NID1
DB00015	Reteplase	Approved	SERPINE1
DB00015	Reteplase	Approved	PLG
DB00015	Reteplase	Approved	FGA

DB00015	Reteplase	Approved	PLAUR
DB00029	Anistreplase	Approved	SERPINE1
DB00029	Anistreplase	Approved	PLG
DB00029	Anistreplase	Approved	FGA
DB00029	Anistreplase	Approved	PLAUR
DB00031	Tenecteplase	Approved	SERPINE1
DB00031	Tenecteplase	Approved	PLG
DB00031	Tenecteplase	Approved	CANX
DB00031	Tenecteplase	Approved	FGA
DB00031	Tenecteplase	Approved	PLAUR
DB00031	Tenecteplase	Approved	SERPINB2
DB00031	Tenecteplase	Approved	ANXA2
DB00031	Tenecteplase	Approved	CLEC3B
DB00031	Tenecteplase	Approved	KRT8
DB00031	Tenecteplase	Approved	CALR
DB00031	Tenecteplase	Approved	LRP1
DB00062	Human Serum Albumin	Approved	AMBP
DB00062	Human Serum Albumin	Approved	APOE
DB00062	Human Serum Albumin	Approved	SAA1
DB00063	Eptifibatide	Approved, Investigational	ITGB3
DB00115	Cyanocobalamin	Approved, Nutraceutical	MMAA
DB00115	Cyanocobalamin	Approved, Nutraceutical	MTR
DB00115	Cyanocobalamin	Approved, Nutraceutical	MTRR
DB00115	Cyanocobalamin	Approved, Nutraceutical	MUT
DB00115	Cyanocobalamin	Approved, Nutraceutical	MMACHC
DB00115	Cyanocobalamin	Approved, Nutraceutical	MTHFR

DB00158	Folic Acid	Approved, Nutraceutical	FOLR2
DB00158	Folic Acid	Approved, Nutraceutical	FOLR3
DB00165	Pyridoxine	Approved, Nutraceutical	PDXK
DB00175	Pravastatin	Approved	HMGCR
DB00178	Ramipril	Approved	ACE
DB00208	Ticlopidine	Approved	P2RY12
DB00214	Torasemide	Approved	SLC12A1
DB00227	Lovastatin	Approved, Investigational	ITGAL
DB00227	Lovastatin	Approved, Investigational	HMGCR
DB00227	Lovastatin	Approved, Investigational	HDAC2
DB00270	Isradipine	Approved	CACNA2D1
DB00270	Isradipine	Approved	CACNA1H
DB00270	Isradipine	Approved	CACNA1C
DB00270	Isradipine	Approved	CACNB2
DB00270	Isradipine	Approved	CACNA1S
DB00270	Isradipine	Approved	CACNA1D
DB00270	Isradipine	Approved	CACNA2D2
DB00278	Argatroban	Approved, Investigational	F2
DB00310	Chlorthalidone	Approved	SLC12A1
DB00316	Acetaminophen	Approved	PTGS2
DB00316	Acetaminophen	Approved	PTGS1
DB00368	Norepinephrine	Approved	ADRB1
DB00368	Norepinephrine	Approved	ADRA2A
DB00368	Norepinephrine	Approved	ADRA2C
DB00368	Norepinephrine	Approved	ADRB3
DB00368	Norepinephrine	Approved	ADRB2
DB00368	Norepinephrine	Approved	ADRA1D
DB00368	Norepinephrine	Approved	ADRA2B
DB00368	Norepinephrine	Approved	ADRA1B

DB00368	Norepinephrine	Approved	PAH
DB00368	Norepinephrine	Approved	ADRA1A
DB00384	Triamterene	Approved	SCNN1B
DB00384	Triamterene	Approved	SCNN1A
DB00384	Triamterene	Approved	SCNN1D
DB00384	Triamterene	Approved	SCNN1G
DB00388	Phenylephrine	Approved	ADRA1D
DB00388	Phenylephrine	Approved	ADRA1B
DB00388	Phenylephrine	Approved	ADRA1A
DB00393	Nimodipine	Approved	CACNB1
DB00393	Nimodipine	Approved	CACNA1C
DB00393	Nimodipine	Approved	NR3C2
DB00393	Nimodipine	Approved	CACNB2
DB00393	Nimodipine	Approved	CACNA1S
DB00393	Nimodipine	Approved	CACNB4
DB00393	Nimodipine	Approved	CACNA1F
DB00393	Nimodipine	Approved	CACNB3
DB00393	Nimodipine	Approved	CACNA1D
DB00393	Nimodipine	Approved	AHR
DB00421	Spironolactone	Approved	AR
DB00421	Spironolactone	Approved	NR3C2
DB00436	Bendroflumethiazide	Approved	CA1
DB00436	Bendroflumethiazide	Approved	CA2
DB00436	Bendroflumethiazide	Approved	CA4
DB00436	Bendroflumethiazide	Approved	KCNMA1
DB00436	Bendroflumethiazide	Approved	SLC12A3
DB00519	Trandolapril	Approved	ACE
DB00524	Metolazone	Approved	SLC12A3
DB00542	Benazepril	Approved, Investigational	ACE

DB00584	Enalapril	Approved	ACE
DB00594	Amiloride	Approved	SCNN1B
DB00594	Amiloride	Approved	SCNN1A
DB00594	Amiloride	Approved	ABP1
DB00594	Amiloride	Approved	ACCN2
DB00594	Amiloride	Approved	ACCN1
DB00594	Amiloride	Approved	PLAU
DB00594	Amiloride	Approved	SLC9A1
DB00594	Amiloride	Approved	SCNN1D
DB00594	Amiloride	Approved	SCNN1G
DB00606	Cyclothiazide	Approved	FXYD2
DB00606	Cyclothiazide	Approved	CA1
DB00606	Cyclothiazide	Approved	CA2
DB00606	Cyclothiazide	Approved	CA4
DB00622	Nicardipine	Approved	CHRM1
DB00622	Nicardipine	Approved	CHRM3
DB00622	Nicardipine	Approved	CHRM5
DB00622	Nicardipine	Approved	CHRM4
DB00622	Nicardipine	Approved	CACNA2D1
DB00622	Nicardipine	Approved	ADRA1D
DB00622	Nicardipine	Approved	CALM1
DB00622	Nicardipine	Approved	CHRM2
DB00622	Nicardipine	Approved	CACNA1C
DB00622	Nicardipine	Approved	ADRA1B
DB00622	Nicardipine	Approved	ADRA1A
DB00622	Nicardipine	Approved	CACNB2
DB00622	Nicardipine	Approved	CACNA1D
DB00622	Nicardipine	Approved	PDE1A
DB00622	Nicardipine	Approved	PDE1B

DB00641	Simvastatin	Approved	ITGB2
DB00641	Simvastatin	Approved	HMGCR
DB00653	Magnesium Sulfate	Approved	CACNB1
DB00653	Magnesium Sulfate	Approved	CACNG1
DB00653	Magnesium Sulfate	Approved	CACNA2D1
DB00653	Magnesium Sulfate	Approved	CACNA1C
DB00653	Magnesium Sulfate	Approved	CACNB2
DB00653	Magnesium Sulfate	Approved	CACNA1S
DB00682	Warfarin	Approved	VKORC1
DB00691	Moexipril	Approved	ACE
DB00691	Moexipril	Approved	ACE2
DB00695	Furosemide	Approved	CA2
DB00695	Furosemide	Approved	SLC12A1
DB00758	Clopidogrel	Approved, Nutraceutical	P2RY12
DB00774	Hydroflumethiazide	Approved	CA1
DB00774	Hydroflumethiazide	Approved	CA2
DB00774	Hydroflumethiazide	Approved	CA4
DB00774	Hydroflumethiazide	Approved	KCNMA1
DB00774	Hydroflumethiazide	Approved	ATP1A1
DB00774	Hydroflumethiazide	Approved	SLC12A1
DB00774	Hydroflumethiazide	Approved	CA12
DB00774	Hydroflumethiazide	Approved	CA9
DB00775	Tirofiban	Approved	ITGA2B
DB00775	Tirofiban	Approved	ITGB3
DB00790	Perindopril	Approved	ACE
DB00796	Candesartan	Approved	AGTR1
DB00806	Pentoxifylline	Approved, Investigational	ADORA1
DB00806	Pentoxifylline	Approved, Investigational	PDE5A
DB00806	Pentoxifylline	Approved, Investigational	ADORA2A

DB00806	Pentoxifylline	Approved, Investigational	PDE4B
DB00806	Pentoxifylline	Approved, Investigational	NT5E
DB00806	Pentoxifylline	Approved, Investigational	PDE4A
DB00808	Indapamide	Approved	KCNQ1
DB00808	Indapamide	Approved	KCNE1
DB00819	Acetazolamide	Approved	CA1
DB00819	Acetazolamide	Approved	CA2
DB00819	Acetazolamide	Approved	CA4
DB00819	Acetazolamide	Approved	AQP1
DB00819	Acetazolamide	Approved	CA3
DB00819	Acetazolamide	Approved	CA7
DB00819	Acetazolamide	Approved	CA14
DB00829	Diazepam	Approved, Illicit	GABRR1
DB00829	Diazepam	Approved, Illicit	GABRA2
DB00829	Diazepam	Approved, Illicit	GABRA3
DB00829	Diazepam	Approved, Illicit	TSPO
DB00829	Diazepam	Approved, Illicit	GABRA5
DB00829	Diazepam	Approved, Illicit	GABRA1
DB00829	Diazepam	Approved, Illicit	GABRB1
DB00829	Diazepam	Approved, Illicit	GABRB3
DB00829	Diazepam	Approved, Illicit	GABRB2
DB00829	Diazepam	Approved, Illicit	GABRG2
DB00829	Diazepam	Approved, Illicit	GABRG1
DB00829	Diazepam	Approved, Illicit	GABRG3
DB00829	Diazepam	Approved, Illicit	GABRE
DB00829	Diazepam	Approved, Illicit	GABRP
DB00829	Diazepam	Approved, Illicit	GABRQ
DB00829	Diazepam	Approved, Illicit	GABRR2
DB00829	Diazepam	Approved, Illicit	GABRD

DB00829	Diazepam	Approved, Illicit	GABRR3
DB00876	Eprosartan	Approved	AGTR1
DB00880	Chlorothiazide	Approved	CA1
DB00880	Chlorothiazide	Approved	CA2
DB00880	Chlorothiazide	Approved	CA4
DB00880	Chlorothiazide	Approved	SLC12A3
DB00881	Quinapril	Approved, Investigational	ACE
DB00887	Bumetanide	Approved	SLC12A5
DB00887	Bumetanide	Approved	SLC12A2
DB00887	Bumetanide	Approved	SLC12A4
DB00887	Bumetanide	Approved	SLC12A1
DB00887	Bumetanide	Approved	CFTR
DB00903	Ethacrynic acid	Approved	ATP1A1
DB00903	Ethacrynic acid	Approved	SLC12A1
DB00945	Acetylsalicylic acid	Approved	AKR1C1
DB00945	Acetylsalicylic acid	Approved	PTGS2
DB00945	Acetylsalicylic acid	Approved	PTGS1
DB00975	Dipyridamole	Approved	PDE5A
DB00975	Dipyridamole	Approved	PDE10A
DB00975	Dipyridamole	Approved	PDE4A
DB00975	Dipyridamole	Approved	ADA
DB00999	Hydrochlorothiazide	Approved	CA1
DB00999	Hydrochlorothiazide	Approved	CA2
DB00999	Hydrochlorothiazide	Approved	CA4
DB00999	Hydrochlorothiazide	Approved	KCNMA1
DB00999	Hydrochlorothiazide	Approved	SLC12A3
DB00999	Hydrochlorothiazide	Approved	CA12
DB00999	Hydrochlorothiazide	Approved	CA9
DB01021	Trichlormethiazide	Approved	CA1

DB01021	Trichlormethiazide	Approved	CA2
DB01021	Trichlormethiazide	Approved	CA4
DB01021	Trichlormethiazide	Approved	ATP1A1
DB01021	Trichlormethiazide	Approved	SLC12A1
DB01029	Irbesartan	Approved, Investigational	AGTR1
DB01029	Irbesartan	Approved, Investigational	JUN
DB01050	Ibuprofen	Approved	PTGS1
DB01050	Ibuprofen	Approved	PPARG
DB01050	Ibuprofen	Approved	BCL2
DB01050	Ibuprofen	Approved	PTGS2
DB01050	Ibuprofen	Approved	CFTR
DB01050	Ibuprofen	Approved	PLAT
DB01050	Ibuprofen	Approved	THBD
DB01050	Ibuprofen	Approved	FABP2
DB01054	Nitrendipine	Approved	CACNG1
DB01054	Nitrendipine	Approved	CACNA2D1
DB01054	Nitrendipine	Approved	CACNA1H
DB01054	Nitrendipine	Approved	CACNA1C
DB01054	Nitrendipine	Approved	CACNB2
DB01054	Nitrendipine	Approved	CACNA1S
DB01054	Nitrendipine	Approved	CACNA1D
DB01054	Nitrendipine	Approved	CACNA2D2
DB01076	Atorvastatin	Approved	DPP4
DB01076	Atorvastatin	Approved	HMGCR
DB01076	Atorvastatin	Approved	AHR
DB01095	Fluvastatin	Approved	HMGCR
DB01098	Rosuvastatin	Approved	HMGCR
DB01109	Heparin	Approved, Investigational	F10
DB01109	Heparin	Approved, Investigational	SERPINC1

DB01109	Heparin	Approved, Investigational	SELP
DB01166	Cilostazol	Approved	PDE3A
DB01183	Naloxone	Approved	ESR1
DB01183	Naloxone	Approved	OPRD1
DB01183	Naloxone	Approved	OPRM1
DB01183	Naloxone	Approved	CREB1
DB01183	Naloxone	Approved	OPRK1
DB01183	Naloxone	Approved	TLR4
DB01197	Captopril	Approved	MMP9
DB01197	Captopril	Approved	ACE
DB01197	Captopril	Approved	MMP2
DB01225	Enoxaparin	Approved	F10
DB01225	Enoxaparin	Approved	SERPINC1
DB01340	Cilazapril	Approved	ACE
DB01599	Probucol	Approved	ABCA1
DB01599	Probucol	Approved	CES1
DB04841	Flunarizine	Approved	CACNA1I
DB04841	Flunarizine	Approved	CACNA1H
DB04841	Flunarizine	Approved	CALM1
DB04841	Flunarizine	Approved	HRH1
DB04841	Flunarizine	Approved	CACNA1G
DB06209	Prasugrel	Approved	P2RY12
DB06228	Rivaroxaban	Approved	F10
DB06605	Apixaban	Approved	F10
DB06693	Mevastatin	Approved	HMGCR
DB06695	Dabigatran etexilate	Approved	F2
DB06779	Dalteparin	Approved	VEGFA
DB06779	Dalteparin	Approved	SERPINC1
DB06779	Dalteparin	Approved	TFPI

DB06779	Dalteparin	Approved	SELP
DB06822	Tinzaparin	Approved	SERPINC1
DB06822	Tinzaparin	Approved	ITGA4
DB06822	Tinzaparin	Approved	CXCL12
DB08813	Nadroparin	Approved	SERPINC1
DB08813	Nadroparin	Approved	FOS
DB08813	Nadroparin	Approved	SELP
DB08814	Triflusal	Approved	NOS2
DB08814	Triflusal	Approved	PTGS1
DB08814	Triflusal	Approved	PDE10A
DB08814	Triflusal	Approved	NFKB1
DB08816	Ticagrelor	Approved	P2RY12
DB08836	Temocapril	Investigational	ACE

Table S3. GO enrichment analysis-Biological process terms of AIS genes. Here we showed the toppest 200 Biological process terms of AIS credible genes. The PV and CPV respectively mean P-value and Corrected p-value.

GO-ID	**Description**	**PV**	**CPV**
GO:0006950	response to stress	2.81E-60	1.13E-56
GO:0042221	response to chemical stimulus	6.37E-53	1.28E-49
GO:0043067	regulation of programmed cell death	1.03E-47	1.37E-44
GO:0042981	regulation of apoptosis	1.93E-47	1.94E-44
GO:0010941	regulation of cell death	2.72E-47	2.19E-44
GO:0051239	regulation of multicellular organismal process	1.04E-45	6.94E-43
GO:0065008	regulation of biological quality	1.74E-45	9.99E-43
GO:0050896	response to stimulus	8.44E-45	4.23E-42
GO:0009611	response to wounding	1.92E-41	8.55E-39
GO:0048518	positive regulation of biological process	1.6E-39	6.44E-37

GO:0010033	response to organic substance	4.22E-37	1.54E-34
GO:0048522	positive regulation of cellular process	7.05E-35	2.36E-32
GO:0060548	negative regulation of cell death	3.97E-34	1.17E-31
GO:0065007	biological regulation	4.07E-34	1.17E-31
GO:0048519	negative regulation of biological process	6.32E-34	1.69E-31
GO:0043066	negative regulation of apoptosis	1.18E-32	2.96E-30
GO:0043069	negative regulation of programmed cell death	2.99E-32	7.06E-30
GO:0042592	homeostatic process	8.27E-30	1.84E-27
GO:0023052	signaling	1.61E-29	3.41E-27
GO:0048731	system development	1.89E-29	3.8E-27
GO:0048856	anatomical structure development	2.25E-29	4.3E-27
GO:0032501	multicellular organismal process	7.41E-29	1.35E-26
GO:0048523	negative regulation of cellular process	1.04E-28	1.81E-26
GO:0032502	developmental process	9.9E-28	1.66E-25
GO:0051240	positive regulation of multicellular organismal process	2.83E-27	4.55E-25
GO:0044057	regulation of system process	4.71E-26	7.28E-24
GO:0050789	regulation of biological process	6.59E-26	9.79E-24
GO:0048583	regulation of response to stimulus	8.61E-26	1.23E-23
GO:0048878	chemical homeostasis	1.43E-25	1.99E-23
GO:0032879	regulation of localization	1.61E-25	2.15E-23
GO:0007275	multicellular organismal development	1.67E-25	2.16E-23
GO:0010646	regulation of cell communication	3.69E-25	4.63E-23
GO:0009605	response to external stimulus	5.2E-25	6.32E-23
GO:0006916	anti-apoptosis	6.21E-25	7.34E-23
GO:0051241	negative regulation of multicellular organismal process	6.49E-25	7.44E-23
GO:0032101	regulation of response to external stimulus	7.72E-25	8.61E-23
GO:0042060	wound healing	5.22E-24	5.66E-22
GO:0019725	cellular homeostasis	1.54E-23	1.62E-21
GO:0065009	regulation of molecular function	2.01E-23	2.07E-21

GO:0050794	regulation of cellular process	4.47E-23	4.49E-21
GO:0050793	regulation of developmental process	8.38E-23	8.2E-21
GO:0009628	response to abiotic stimulus	3.79E-22	3.62E-20
GO:0007399	nervous system development	5.53E-22	5.16E-20
GO:0023060	signal transmission	8.03E-22	7.16E-20
GO:0023046	signaling process	8.03E-22	7.16E-20
GO:0051049	regulation of transport	1.17E-21	1.03E-19
GO:0043068	positive regulation of programmed cell death	3.27E-21	2.79E-19
GO:0010942	positive regulation of cell death	5.36E-21	4.48E-19
GO:0044093	positive regulation of molecular function	7.23E-21	5.92E-19
GO:0043065	positive regulation of apoptosis	1.07E-20	8.55E-19
GO:0023033	signaling pathway	1.62E-20	1.27E-18
GO:0007166	cell surface receptor linked signaling pathway	3.2E-20	2.47E-18
GO:0007610	behavior	3.67E-20	2.78E-18
GO:0051716	cellular response to stimulus	1.34E-19	9.99E-18
GO:0050817	coagulation	1.48E-19	1.06E-17
GO:0007596	blood coagulation	1.48E-19	1.06E-17
GO:0080134	regulation of response to stress	1.99E-19	1.4E-17
GO:0050801	ion homeostasis	2.54E-19	1.76E-17
GO:0050878	regulation of body fluid levels	2.6E-19	1.77E-17
GO:0050804	regulation of synaptic transmission	2.7E-19	1.81E-17
GO:0006873	cellular ion homeostasis	2.85E-19	1.88E-17
GO:0051094	positive regulation of developmental process	3.76E-19	2.42E-17
GO:0050790	regulation of catalytic activity	3.8E-19	2.42E-17
GO:0048513	organ development	5.26E-19	3.27E-17
GO:0001666	response to hypoxia	5.38E-19	3.27E-17
GO:0031644	regulation of neurological system process	5.38E-19	3.27E-17
GO:0051050	positive regulation of transport	6.2E-19	3.68E-17
GO:0055082	cellular chemical homeostasis	6.23E-19	3.68E-17

GO:0007599	hemostasis	9.39E-19	5.46E-17
GO:0043085	positive regulation of catalytic activity	1.54E-18	8.83E-17
GO:0009607	response to biotic stimulus	1.6E-18	9.07E-17
GO:0006979	response to oxidative stress	2.48E-18	1.38E-16
GO:0051969	regulation of transmission of nerve impulse	3.46E-18	1.89E-16
GO:0030334	regulation of cell migration	3.48E-18	1.89E-16
GO:0070482	response to oxygen levels	4.26E-18	2.28E-16
GO:0000302	response to reactive oxygen species	1.01E-17	5.33E-16
GO:0007154	cell communication	3.15E-17	1.64E-15
GO:0040012	regulation of locomotion	3.92E-17	2.02E-15
GO:0009991	response to extracellular stimulus	4.37E-17	2.22E-15
GO:0043523	regulation of neuron apoptosis	5.12E-17	2.54E-15
GO:0042127	regulation of cell proliferation	5.17E-17	2.54E-15
GO:0006952	defense response	5.19E-17	2.54E-15
GO:0070887	cellular response to chemical stimulus	5.33E-17	2.58E-15
GO:0042493	response to drug	7.18E-17	3.43E-15
GO:0051789	response to protein stimulus	8.31E-17	3.92E-15
GO:0048869	cellular developmental process	1.23E-16	5.75E-15
GO:0051270	regulation of cellular component movement	1.63E-16	7.54E-15
GO:0051246	regulation of protein metabolic process	1.9E-16	8.66E-15
GO:0030154	cell differentiation	2.01E-16	9.08E-15
GO:0007268	synaptic transmission	2.27E-16	1.01E-14
GO:0045595	regulation of cell differentiation	3.29E-16	1.45E-14
GO:0042391	regulation of membrane potential	3.76E-16	1.64E-14
GO:0006954	inflammatory response	3.88E-16	1.67E-14
GO:0050818	regulation of coagulation	4.52E-16	1.93E-14
GO:0019226	transmission of nerve impulse	4.57E-16	1.93E-14
GO:0009653	anatomical structure morphogenesis	5.62E-16	2.35E-14
GO:0010035	response to inorganic substance	7.83E-16	3.24E-14

GO:0009719	response to endogenous stimulus	8.9E-16	3.65E-14
GO:0030193	regulation of blood coagulation	1.04E-15	4.2E-14
GO:0010647	positive regulation of cell communication	1.07E-15	4.29E-14
GO:0031667	response to nutrient levels	1.66E-15	6.58E-14
GO:0048514	blood vessel morphogenesis	1.77E-15	6.95E-14
GO:0042542	response to hydrogen peroxide	1.84E-15	7.18E-14
GO:0032268	regulation of cellular protein metabolic process	1.87E-15	7.2E-14
GO:0003013	circulatory system process	2.84E-15	1.08E-13
GO:0008015	blood circulation	2.84E-15	1.08E-13
GO:0048699	generation of neurons	3.32E-15	1.24E-13
GO:0050727	regulation of inflammatory response	4.18E-15	1.55E-13
GO:0001568	blood vessel development	8.26E-15	3.04E-13
GO:0061041	regulation of wound healing	8.74E-15	3.19E-13
GO:0022008	neurogenesis	9.55E-15	3.45E-13
GO:0031099	regeneration	1.73E-14	6.18E-13
GO:0007267	cell-cell signaling	1.84E-14	6.54E-13
GO:0001944	vasculature development	2.38E-14	8.38E-13
GO:0008219	cell death	2.72E-14	9.5E-13
GO:0042325	regulation of phosphorylation	3.21E-14	1.11E-12
GO:0009266	response to temperature stimulus	3.65E-14	1.25E-12
GO:0007165	signal transduction	3.78E-14	1.29E-12
GO:0016265	death	3.92E-14	1.32E-12
GO:0032496	response to lipopolysaccharide	3.95E-14	1.32E-12
GO:0002682	regulation of immune system process	4.7E-14	1.56E-12
GO:0002237	response to molecule of bacterial origin	5.73E-14	1.89E-12
GO:0051338	regulation of transferase activity	5.95E-14	1.94E-12
GO:0009725	response to hormone stimulus	6.96E-14	2.25E-12
GO:0051174	regulation of phosphorus metabolic process	7.11E-14	2.26E-12
GO:0019220	regulation of phosphate metabolic process	7.11E-14	2.26E-12

GO:0014070	response to organic cyclic substance	7.72E-14	2.44E-12
GO:0051347	positive regulation of transferase activity	1.96E-13	6.16E-12
GO:0043549	regulation of kinase activity	2.03E-13	6.31E-12
GO:0008217	regulation of blood pressure	2.48E-13	7.65E-12
GO:0033674	positive regulation of kinase activity	2.92E-13	8.95E-12
GO:0044092	negative regulation of molecular function	3.21E-13	9.77E-12
GO:0051098	regulation of binding	3.65E-13	1.1E-11
GO:0031325	positive regulation of cellular metabolic process	3.69E-13	1.11E-11
GO:0009893	positive regulation of metabolic process	3.75E-13	1.12E-11
GO:0045860	positive regulation of protein kinase activity	4.32E-13	1.27E-11
GO:0006915	apoptosis	4.9E-13	1.44E-11
GO:0045859	regulation of protein kinase activity	7.6E-13	2.21E-11
GO:0007611	learning or memory	9.69E-13	2.8E-11
GO:0030182	neuron differentiation	1.02E-12	2.91E-11
GO:0012501	programmed cell death	1.06E-12	3E-11
GO:0035466	regulation of signaling pathway	1.06E-12	3E-11
GO:0045429	positive regulation of nitric oxide biosynthetic process	1.5E-12	4.2E-11
GO:0002376	immune system process	2.1E-12	5.85E-11
GO:0001817	regulation of cytokine production	2.23E-12	6.17E-11
GO:0048666	neuron development	2.3E-12	6.33E-11
GO:0048545	response to steroid hormone stimulus	2.38E-12	6.51E-11
GO:0045428	regulation of nitric oxide biosynthetic process	2.43E-12	6.6E-11
GO:0009892	negative regulation of metabolic process	2.55E-12	6.87E-11
GO:0048167	regulation of synaptic plasticity	2.67E-12	7.15E-11
GO:0009891	positive regulation of biosynthetic process	2.71E-12	7.22E-11
GO:0050819	negative regulation of coagulation	2.89E-12	7.62E-11
GO:0030335	positive regulation of cell migration	3.45E-12	9.04E-11
GO:0090066	regulation of anatomical structure size	3.61E-12	9.42E-11
GO:0031328	positive regulation of cellular biosynthetic process	3.82E-12	9.9E-11

GO:0051046	regulation of secretion	3.92E-12	1.01E-10
GO:0045597	positive regulation of cell differentiation	4.77E-12	1.22E-10
GO:0030194	positive regulation of blood coagulation	6.8E-12	1.73E-10
GO:0051704	multi-organism process	8.86E-12	2.24E-10
GO:0051047	positive regulation of secretion	1.04E-11	2.6E-10
GO:0002685	regulation of leukocyte migration	1.05E-11	2.62E-10
GO:0022603	regulation of anatomical structure morphogenesis	1.09E-11	2.71E-10
GO:0051899	membrane depolarization	1.15E-11	2.82E-10
GO:0032103	positive regulation of response to external stimulus	1.31E-11	3.21E-10
GO:0051272	positive regulation of cellular component movement	1.76E-11	4.25E-10
GO:0040017	positive regulation of locomotion	1.76E-11	4.25E-10
GO:0048468	cell development	1.87E-11	4.49E-10
GO:0030195	negative regulation of blood coagulation	2.03E-11	4.86E-10
GO:0009617	response to bacterium	2.12E-11	5.03E-10
GO:0031175	neuron projection development	2.55E-11	6.02E-10
GO:0010627	regulation of intracellular protein kinase cascade	2.63E-11	6.17E-10
GO:0006800	oxygen and reactive oxygen species metabolic process	3.2E-11	7.47E-10
GO:0006986	response to unfolded protein	4.24E-11	9.85E-10
GO:0002687	positive regulation of leukocyte migration	4.78E-11	1.1E-09
GO:0051093	negative regulation of developmental process	5.02E-11	1.15E-09
GO:0012502	induction of programmed cell death	5.05E-11	1.15E-09
GO:0009967	positive regulation of signal transduction	5.14E-11	1.17E-09
GO:0055066	di-, tri-valent inorganic cation homeostasis	6.99E-11	1.58E-09
GO:0055074	calcium ion homeostasis	7.11E-11	1.59E-09
GO:0023056	positive regulation of signaling process	8.72E-11	1.95E-09
GO:0009966	regulation of signal transduction	9.06E-11	2.01E-09
GO:0055065	metal ion homeostasis	9.21E-11	2.03E-09
GO:0035468	positive regulation of signaling pathway	1.04E-10	2.29E-09
GO:0045765	regulation of angiogenesis	1.05E-10	2.29E-09

GO:0031399	regulation of protein modification process	1.08E-10	2.34E-09
GO:0050820	positive regulation of coagulation	1.19E-10	2.56E-09
GO:0023051	regulation of signaling process	1.2E-10	2.59E-09
GO:0051173	positive regulation of nitrogen compound metabolic process	1.25E-10	2.68E-09
GO:0055080	cation homeostasis	1.32E-10	2.8E-09
GO:0006874	cellular calcium ion homeostasis	1.36E-10	2.88E-09
GO:0042312	regulation of vasodilation	1.43E-10	3.01E-09
GO:0051707	response to other organism	1.57E-10	3.28E-09
GO:0006917	induction of apoptosis	1.73E-10	3.61E-09
GO:0003008	system process	1.87E-10	3.87E-09
GO:0033554	cellular response to stress	2.02E-10	4.15E-09
GO:0040008	regulation of growth	2.04E-10	4.19E-09
GO:0060284	regulation of cell development	2.15E-10	4.38E-09
GO:0032583	regulation of gene-specific transcription	2.19E-10	4.44E-09
GO:0050729	positive regulation of inflammatory response	2.25E-10	4.54E-09
GO:0060341	regulation of cellular localization	2.49E-10	5E-09

Table S4. GO enrichment analysis-Molecular Function terms of AIS genes.

GO-ID	**Description**	**PV**	**CPV**
GO:0005102	receptor binding	7.81E-24	7.64E-21
GO:0005515	protein binding	2.43E-22	1.19E-19
GO:0046983	protein dimerization activity	1.64E-20	5.35E-18
GO:0008066	glutamate receptor activity	7.21E-14	1.76E-11
GO:0042802	identical protein binding	2.40E-12	4.71E-10
GO:0019899	enzyme binding	6.38E-12	1.04E-09
GO:0046982	protein heterodimerization activity	5.04E-11	7.04E-09
GO:0005234	extracellular-glutamate-gated ion channel activity	1.19E-10	1.45E-08

GO:0042803	protein homodimerization activity	3.01E-10	3.28E-08
GO:0005231	excitatory extracellular ligand-gated ion channel activity	4.57E-10	4.48E-08
GO:0015267	channel activity	5.83E-10	5.14E-08
GO:0022803	passive transmembrane transporter activity	6.30E-10	5.14E-08
GO:0004970	ionotropic glutamate receptor activity	9.02E-10	6.79E-08
GO:0008201	heparin binding	2.58E-09	1.81E-07
GO:0005539	glycosaminoglycan binding	3.37E-09	2.20E-07
GO:0022838	substrate-specific channel activity	6.79E-09	4.10E-07
GO:0016209	antioxidant activity	7.13E-09	4.10E-07
GO:0020037	heme binding	1.41E-08	7.64E-07
GO:0022891	substrate-specific transmembrane transporter activity	2.08E-08	1.00E-06
GO:0030247	polysaccharide binding	2.23E-08	1.00E-06
GO:0001871	pattern binding	2.23E-08	1.00E-06
GO:0022892	substrate-specific transporter activity	2.25E-08	1.00E-06
GO:0015075	ion transmembrane transporter activity	2.97E-08	1.26E-06
GO:0005216	ion channel activity	3.60E-08	1.47E-06
GO:0046906	tetrapyrrole binding	4.25E-08	1.67E-06
GO:0022857	transmembrane transporter activity	4.74E-08	1.78E-06
GO:0008083	growth factor activity	6.46E-08	2.34E-06
GO:0043498	cell surface binding	1.47E-07	5.15E-06
GO:0005230	extracellular ligand-gated ion channel activity	1.99E-07	6.57E-06
GO:0022836	gated channel activity	2.01E-07	6.57E-06
GO:0005215	transporter activity	2.27E-07	7.16E-06
GO:0008324	cation transmembrane transporter activity	4.17E-07	1.27E-05
GO:0015276	ligand-gated ion channel activity	4.93E-07	1.42E-05
GO:0022834	ligand-gated channel activity	4.93E-07	1.42E-05
GO:0032403	protein complex binding	5.67E-07	1.59E-05
GO:0070325	lipoprotein receptor binding	6.69E-07	1.81E-05

GO:0005488	binding	6.86E-07	1.81E-05
GO:0016667	oxidoreductase activity, acting on sulfur group of donors	1.12E-06	2.88E-05
GO:0005179	hormone activity	1.61E-06	3.97E-05
GO:0005506	iron ion binding	1.62E-06	3.97E-05
GO:0005261	cation channel activity	3.72E-06	8.87E-05
GO:0002020	protease binding	4.54E-06	1.06E-04
GO:0001664	G-protein-coupled receptor binding	7.45E-06	1.70E-04
GO:0004972	N-methyl-D-aspartate selective glutamate receptor activity	8.21E-06	1.83E-04
GO:0043028	caspase regulator activity	1.05E-05	2.28E-04
GO:0004871	signal transducer activity	1.11E-05	2.32E-04
GO:0060089	molecular transducer activity	1.11E-05	2.32E-04
GO:0005310	dicarboxylic acid transmembrane transporter activity	1.28E-05	2.60E-04
GO:0017153	sodium:dicarboxylate symporter activity	1.31E-05	2.63E-04
GO:0004175	endopeptidase activity	1.50E-05	2.93E-04
GO:0008289	lipid binding	1.62E-05	3.12E-04
GO:0030246	carbohydrate binding	2.28E-05	4.30E-04
GO:0015277	kainate selective glutamate receptor activity	2.39E-05	4.34E-04
GO:0015368	calcium:cation antiporter activity	2.39E-05	4.34E-04
GO:0009055	electron carrier activity	2.53E-05	4.50E-04
GO:0030234	enzyme regulator activity	2.68E-05	4.69E-04
GO:0004857	enzyme inhibitor activity	2.90E-05	4.98E-04
GO:0043027	caspase inhibitor activity	3.89E-05	6.45E-04
GO:0050750	low-density lipoprotein receptor binding	3.89E-05	6.45E-04
GO:0016491	oxidoreductase activity	4.06E-05	6.62E-04
GO:0005126	cytokine receptor binding	4.53E-05	7.08E-04
GO:0004517	nitric-oxide synthase activity	4.70E-05	7.08E-04
GO:0015038	glutathione disulfide oxidoreductase activity	4.70E-05	7.08E-04

GO:0016527	brain-specific angiogenesis inhibitor activity	4.70E-05	7.08E-04
GO:0034617	tetrahydrobiopterin binding	4.70E-05	7.08E-04
GO:0070011	peptidase activity, acting on L-amino acid peptides	5.20E-05	7.48E-04
GO:0035326	enhancer binding	5.20E-05	7.48E-04
GO:0003705	RNA polymerase II transcription factor activity, enhancer binding	5.20E-05	7.48E-04
GO:0016595	glutamate binding	5.42E-05	7.64E-04
GO:0015036	disulfide oxidoreductase activity	5.46E-05	7.64E-04
GO:0050660	FAD binding	5.81E-05	8.02E-04
GO:0001530	lipopolysaccharide binding	6.13E-05	8.34E-04
GO:0019900	kinase binding	6.35E-05	8.52E-04
GO:0061134	peptidase regulator activity	8.13E-05	1.08E-03
GO:0047485	protein N-terminus binding	8.49E-05	1.11E-03
GO:0005509	calcium ion binding	9.01E-05	1.16E-03
GO:0004601	peroxidase activity	9.59E-05	1.20E-03
GO:0016684	oxidoreductase activity, acting on peroxide as acceptor	9.59E-05	1.20E-03
GO:0047498	calcium-dependent phospholipase A2 activity	1.05E-04	1.31E-03
GO:0008233	peptidase activity	1.07E-04	1.31E-03
GO:0015296	anion:cation symporter activity	1.19E-04	1.44E-03
GO:0015035	protein disulfide oxidoreductase activity	1.35E-04	1.59E-03
GO:0043499	eukaryotic cell surface binding	1.35E-04	1.59E-03
GO:0008238	exopeptidase activity	1.71E-04	1.99E-03
GO:0015037	peptide disulfide oxidoreductase activity	1.83E-04	2.04E-03
GO:0043125	ErbB-3 class receptor binding	1.83E-04	2.04E-03
GO:0005432	calcium:sodium antiporter activity	1.83E-04	2.04E-03
GO:0034618	arginine binding	1.83E-04	2.04E-03
GO:0016597	amino acid binding	2.17E-04	2.38E-03
GO:0015491	cation:cation antiporter activity	2.61E-04	2.83E-03

GO:0004866	endopeptidase inhibitor activity	2.63E-04	2.83E-03
GO:0004197	cysteine-type endopeptidase activity	2.81E-04	2.99E-03
GO:0061135	endopeptidase regulator activity	2.84E-04	2.99E-03
GO:0005125	cytokine activity	2.93E-04	3.05E-03
GO:0030971	receptor tyrosine kinase binding	2.98E-04	3.07E-03
GO:0016502	nucleotide receptor activity	3.11E-04	3.14E-03
GO:0001614	purinergic nucleotide receptor activity	3.11E-04	3.14E-03
GO:0004869	cysteine-type endopeptidase inhibitor activity	3.70E-04	3.69E-03
GO:0005178	integrin binding	4.10E-04	4.06E-03
GO:0051400	BH domain binding	4.45E-04	4.23E-03
GO:0001609	adenosine receptor activity, G-protein coupled	4.45E-04	4.23E-03
GO:0001875	lipopolysaccharide receptor activity	4.45E-04	4.23E-03
GO:0051787	misfolded protein binding	4.45E-04	4.23E-03
GO:0005543	phospholipid binding	4.53E-04	4.24E-03
GO:0005313	L-glutamate transmembrane transporter activity	4.55E-04	4.24E-03
GO:0030414	peptidase inhibitor activity	5.02E-04	4.63E-03
GO:0015298	solute:cation antiporter activity	5.07E-04	4.64E-03
GO:0005057	receptor signaling protein activity	5.74E-04	5.21E-03
GO:0005516	calmodulin binding	5.91E-04	5.31E-03
GO:0001948	glycoprotein binding	6.00E-04	5.34E-03
GO:0019901	protein kinase binding	6.20E-04	5.47E-03
GO:0015172	acidic amino acid transmembrane transporter activity	6.63E-04	5.77E-03
GO:0005507	copper ion binding	6.66E-04	5.77E-03
GO:0070851	growth factor receptor binding	7.25E-04	6.20E-03
GO:0043176	amine binding	7.28E-04	6.20E-03
GO:0019207	kinase regulator activity	8.13E-04	6.86E-03
GO:0070513	death domain binding	8.66E-04	7.19E-03
GO:0030151	molybdenum ion binding	8.66E-04	7.19E-03
GO:0050662	coenzyme binding	8.94E-04	7.35E-03

GO:0031406	carboxylic acid binding	9.56E-04	7.80E-03
GO:0008237	metallopeptidase activity	1.01E-03	8.13E-03
GO:0004620	phospholipase activity	1.15E-03	9.26E-03
GO:0005159	insulin-like growth factor receptor binding	1.27E-03	9.68E-03
GO:0004392	heme oxygenase (decyclizing) activity	1.30E-03	9.68E-03
GO:0070492	oligosaccharide binding	1.30E-03	9.68E-03
GO:0043546	molybdopterin cofactor binding	1.30E-03	9.68E-03
GO:0004909	interleukin-1, Type I, activating receptor activity	1.30E-03	9.68E-03
GO:0031711	bradykinin receptor binding	1.30E-03	9.68E-03
GO:0005314	high-affinity glutamate transmembrane transporter activity	1.30E-03	9.68E-03
GO:0051434	BH3 domain binding	1.30E-03	9.68E-03
GO:0001641	group II metabotropic glutamate receptor activity	1.30E-03	9.68E-03
GO:0004051	arachidonate 5-lipoxygenase activity	1.30E-03	9.68E-03
GO:0042277	peptide binding	1.34E-03	9.89E-03
GO:0022832	voltage-gated channel activity	1.41E-03	1.02E-02
GO:0005244	voltage-gated ion channel activity	1.41E-03	1.02E-02
GO:0015179	L-amino acid transmembrane transporter activity	1.44E-03	1.03E-02
GO:0004931	extracellular ATP-gated cation channel activity	1.47E-03	1.03E-02
GO:0050786	RAGE receptor binding	1.47E-03	1.03E-02
GO:0035381	ATP-gated ion channel activity	1.47E-03	1.03E-02
GO:0051920	peroxiredoxin activity	1.47E-03	1.03E-02
GO:0019838	growth factor binding	1.56E-03	1.08E-02
GO:0050661	NADP or NADPH binding	1.94E-03	1.34E-02
GO:0005343	organic acid:sodium symporter activity	2.12E-03	1.45E-02
GO:0005246	calcium channel regulator activity	2.17E-03	1.48E-02
GO:0043121	neurotrophin binding	2.30E-03	1.55E-02
GO:0004623	phospholipase A2 activity	2.53E-03	1.70E-02
GO:0016860	intramolecular oxidoreductase activity	2.57E-03	1.71E-02

GO:0010843	promoter binding	2.60E-03	1.72E-02
GO:0022829	wide pore channel activity	2.76E-03	1.81E-02
GO:0008144	drug binding	3.04E-03	1.98E-02
GO:0004091	carboxylesterase activity	3.06E-03	1.98E-02
GO:0004955	prostaglandin receptor activity	3.35E-03	2.13E-02
GO:0016668	oxidoreductase activity, acting on sulfur group of donors, NAD or NADP as acceptor	3.35E-03	2.13E-02
GO:0017127	cholesterol transporter activity	3.35E-03	2.13E-02
GO:0044212	DNA regulatory region binding	3.41E-03	2.15E-02
GO:0015485	cholesterol binding	3.45E-03	2.17E-02
GO:0008047	enzyme activator activity	3.78E-03	2.18E-02
GO:0016298	lipase activity	3.80E-03	2.18E-02
GO:0015272	ATP-activated inward rectifier potassium channel activity	3.82E-03	2.18E-02
GO:0070653	high-density lipoprotein receptor binding	3.82E-03	2.18E-02
GO:0004351	glutamate decarboxylase activity	3.82E-03	2.18E-02
GO:0008242	omega peptidase activity	3.82E-03	2.18E-02
GO:0004971	alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate selective glutamate receptor activity	3.82E-03	2.18E-02
GO:0033691	sialic acid binding	3.82E-03	2.18E-02
GO:0004784	superoxide dismutase activity	3.82E-03	2.18E-02
GO:0060230	lipoprotein lipase activator activity	3.82E-03	2.18E-02
GO:0031708	endothelin B receptor binding	3.82E-03	2.18E-02
GO:0031705	bombesin receptor binding	3.82E-03	2.18E-02
GO:0005148	prolactin receptor binding	3.82E-03	2.18E-02
GO:0016721	oxidoreductase activity, acting on superoxide radicals as acceptor	3.82E-03	2.18E-02
GO:0004063	aryldialkylphosphatase activity	3.82E-03	2.18E-02

GO:0016705	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen	3.84E-03	2.18E-02
GO:0019904	protein domain specific binding	3.90E-03	2.21E-02
GO:0019887	protein kinase regulator activity	4.14E-03	2.33E-02
GO:0004709	MAP kinase kinase kinase activity	4.25E-03	2.36E-02
GO:0001540	beta-amyloid binding	4.25E-03	2.36E-02
GO:0004872	receptor activity	4.37E-03	2.42E-02
GO:0004954	prostanoid receptor activity	4.66E-03	2.54E-02
GO:0004953	icosanoid receptor activity	4.66E-03	2.54E-02
GO:0016594	glycine binding	4.66E-03	2.54E-02
GO:0005262	calcium channel activity	4.73E-03	2.56E-02
GO:0048037	cofactor binding	4.95E-03	2.66E-02
GO:0004702	receptor signaling protein serine/threonine kinase activity	5.20E-03	2.78E-02
GO:0004888	transmembrane receptor activity	5.28E-03	2.81E-02
GO:0004177	aminopeptidase activity	5.44E-03	2.86E-02
GO:0048306	calcium-dependent protein binding	5.44E-03	2.86E-02
GO:0015248	sterol transporter activity	6.24E-03	3.23E-02
GO:0035035	histone acetyltransferase binding	6.24E-03	3.23E-02
GO:0005243	gap junction channel activity	6.24E-03	3.23E-02
GO:0033130	acetylcholine receptor binding	7.46E-03	3.67E-02
GO:0050544	arachidonic acid binding	7.46E-03	3.67E-02
GO:0004157	dihydropyrimidinase activity	7.46E-03	3.67E-02
GO:0050321	tau-protein kinase activity	7.46E-03	3.67E-02
GO:0004945	angiotensin type II receptor activity	7.46E-03	3.67E-02
GO:0004974	leukotriene receptor activity	7.46E-03	3.67E-02
GO:0051637	Gram-positive bacterial cell surface binding	7.46E-03	3.67E-02
GO:0001595	angiotensin receptor activity	7.46E-03	3.67E-02
GO:0004064	arylesterase activity	7.46E-03	3.67E-02

GO:0004067	asparaginase activity	7.46E-03	3.67E-02
GO:0010181	FMN binding	8.10E-03	3.94E-02
GO:0015297	antiporter activity	8.12E-03	3.94E-02
GO:0003824	catalytic activity	8.12E-03	3.94E-02
GO:0008134	transcription factor binding	8.50E-03	4.10E-02
GO:0030545	receptor regulator activity	8.66E-03	4.15E-02
GO:0005496	steroid binding	9.58E-03	4.57E-02
GO:0015300	solute:solute antiporter activity	9.85E-03	4.66E-02
GO:0015370	solute:sodium symporter activity	9.85E-03	4.66E-02
GO:0005520	insulin-like growth factor binding	1.01E-02	4.71E-02
GO:0016504	peptidase activator activity	1.01E-02	4.71E-02
GO:0016564	transcription repressor activity	1.01E-02	4.71E-02
GO:0070491	transcription repressor binding	1.02E-02	4.71E-02
GO:0004622	lysophospholipase activity	1.02E-02	4.71E-02
GO:0005344	oxygen transporter activity	1.02E-02	4.71E-02
GO:0004879	ligand-dependent nuclear receptor activity	1.08E-02	4.94E-02
GO:0015291	secondary active transmembrane transporter activity	1.10E-02	5.00E-02

Table S5. GO enrichment analysis-Cellular component terms of AIS genes.

GO-ID	**Description**	**PV**	**CPV**
GO:0005615	extracellular space	2.94E-26	1.34E-23
GO:0044421	extracellular region part	4.47E-25	1.02E-22
GO:0000267	cell fraction	5.36E-22	8.15E-20
GO:0044459	plasma membrane part	2.44E-20	2.79E-18
GO:0043005	neuron projection	7.28E-19	6.64E-17
GO:0005576	extracellular region	1.07E-17	8.15E-16
GO:0005626	insoluble fraction	2.08E-17	1.36E-15
GO:0005887	integral to plasma membrane	9.04E-17	5.11E-15
GO:0031226	intrinsic to plasma membrane	1.01E-16	5.11E-15

GO:0005886	plasma membrane	2.27E-16	1.03E-14
GO:0009986	cell surface	2.88E-16	1.19E-14
GO:0005624	membrane fraction	9.97E-16	3.79E-14
GO:0042995	cell projection	9.85E-14	3.45E-12
GO:0030425	dendrite	2.66E-13	8.65E-12
GO:0005737	cytoplasm	4.76E-13	1.45E-11
GO:0045202	synapse	1.40E-12	4.00E-11
GO:0014069	postsynaptic density	2.37E-12	6.36E-11
GO:0044444	cytoplasmic part	3.32E-12	8.41E-11
GO:0031982	vesicle	3.91E-11	9.39E-10
GO:0044297	cell body	4.75E-11	1.01E-09
GO:0043025	neuronal cell body	4.75E-11	1.01E-09
GO:0044456	synapse part	4.89E-11	1.01E-09
GO:0031410	cytoplasmic vesicle	6.09E-11	1.21E-09
GO:0044463	cell projection part	1.04E-10	1.98E-09
GO:0031988	membrane-bounded vesicle	1.27E-09	2.31E-08
GO:0008328	ionotropic glutamate receptor complex	2.00E-09	3.48E-08
GO:0030424	axon	2.06E-09	3.48E-08
GO:0016023	cytoplasmic membrane-bounded vesicle	3.61E-09	5.87E-08
GO:0045121	membrane raft	6.60E-09	1.04E-07
GO:0042734	presynaptic membrane	9.67E-09	1.47E-07
GO:0044309	neuron spine	2.38E-08	3.39E-07
GO:0043197	dendritic spine	2.38E-08	3.39E-07
GO:0031975	envelope	3.58E-08	4.95E-07
GO:0009897	external side of plasma membrane	4.39E-08	5.88E-07
GO:0005625	soluble fraction	6.03E-08	7.85E-07
GO:0005829	cytosol	7.51E-08	9.51E-07
GO:0030141	stored secretory granule	4.24E-07	5.23E-06
GO:0045211	postsynaptic membrane	7.39E-07	8.87E-06

GO:0032994	protein-lipid complex	1.49E-06	1.67E-05
GO:0034358	plasma lipoprotein particle	1.49E-06	1.67E-05
GO:0030426	growth cone	1.50E-06	1.67E-05
GO:0031967	organelle envelope	1.72E-06	1.87E-05
GO:0030427	site of polarized growth	1.78E-06	1.89E-05
GO:0017146	N-methyl-D-aspartate selective glutamate receptor complex	2.38E-06	2.47E-05
GO:0034385	triglyceride-rich lipoprotein particle	2.80E-06	2.78E-05
GO:0034361	very-low-density lipoprotein particle	2.80E-06	2.78E-05
GO:0031983	vesicle lumen	4.08E-06	3.95E-05
GO:0005901	caveola	4.15E-06	3.95E-05
GO:0043235	receptor complex	4.53E-06	4.22E-05
GO:0033267	axon part	6.34E-06	5.78E-05
GO:0016020	membrane	7.18E-06	6.42E-05
GO:0031091	platelet alpha granule	7.40E-06	6.49E-05
GO:0042597	periplasmic space	1.01E-05	8.55E-05
GO:0030288	outer membrane-bounded periplasmic space	1.01E-05	8.55E-05
GO:0034364	high-density lipoprotein particle	1.11E-05	9.21E-05
GO:0019717	synaptosome	1.46E-05	1.19E-04
GO:0005739	mitochondrion	1.55E-05	1.24E-04
GO:0031012	extracellular matrix	1.86E-05	1.45E-04
GO:0031093	platelet alpha granule lumen	1.87E-05	1.45E-04
GO:0005740	mitochondrial envelope	1.94E-05	1.48E-04
GO:0043195	terminal button	1.99E-05	1.49E-04
GO:0060205	cytoplasmic membrane-bounded vesicle lumen	2.34E-05	1.72E-04
GO:0030054	cell junction	2.38E-05	1.72E-04
GO:0042627	chylomicron	3.01E-05	2.14E-04
GO:0030313	cell envelope	4.75E-05	3.28E-04
GO:0044462	external encapsulating structure part	4.75E-05	3.28E-04

GO:0030312	external encapsulating structure	7.18E-05	4.88E-04
GO:0034366	spherical high-density lipoprotein particle	8.55E-05	5.73E-04
GO:0034363	intermediate-density lipoprotein particle	1.56E-04	1.03E-03
GO:0043679	axon terminus	2.67E-04	1.72E-03
GO:0044306	neuron projection terminus	2.67E-04	1.72E-03
GO:0043198	dendritic shaft	2.74E-04	1.74E-03
GO:0042383	sarcolemma	3.18E-04	1.99E-03
GO:0031970	organelle envelope lumen	3.72E-04	2.29E-03
GO:0042598	vesicular fraction	3.99E-04	2.43E-03
GO:0044433	cytoplasmic vesicle part	4.21E-04	2.52E-03
GO:0031966	mitochondrial membrane	4.88E-04	2.89E-03
GO:0005578	proteinaceous extracellular matrix	5.10E-04	2.98E-03
GO:0048786	presynaptic active zone	7.40E-04	4.27E-03
GO:0048471	perinuclear region of cytoplasm	7.86E-04	4.48E-03
GO:0005635	nuclear envelope	9.39E-04	5.29E-03
GO:0044304	main axon	1.15E-03	6.36E-03
GO:0044429	mitochondrial part	1.16E-03	6.36E-03
GO:0032281	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid selective glutamate receptor complex	1.17E-03	6.36E-03
GO:0005788	endoplasmic reticulum lumen	1.36E-03	7.28E-03
GO:0005792	microsome	1.83E-03	9.72E-03
GO:0019867	outer membrane	1.97E-03	1.03E-02
GO:0005921	gap junction	3.25E-03	1.68E-02
GO:0032059	bleb	3.43E-03	1.74E-02
GO:0008282	ATP-sensitive potassium channel complex	3.43E-03	1.74E-02
GO:0005741	mitochondrial outer membrane	3.66E-03	1.84E-02
GO:0032279	asymmetric synapse	4.01E-03	1.99E-02
GO:0031968	organelle outer membrane	4.49E-03	2.20E-02

GO:0045177	apical part of cell	5.20E-03	2.52E-02
GO:0043204	perikaryon	5.67E-03	2.69E-02
GO:0005758	mitochondrial intermembrane space	5.67E-03	2.69E-02
GO:0030666	endocytic vesicle membrane	6.43E-03	3.02E-02
GO:0005850	eukaryotic translation initiation factor 2 complex	6.71E-03	3.12E-02
GO:0034362	low-density lipoprotein particle	6.98E-03	3.22E-02
GO:0031974	membrane-enclosed lumen	7.93E-03	3.62E-02
GO:0008021	synaptic vesicle	8.03E-03	3.63E-02
GO:0031594	neuromuscular junction	8.39E-03	3.75E-02
GO:0019866	organelle inner membrane	9.45E-03	4.19E-02
GO:0005783	endoplasmic reticulum	1.02E-02	4.48E-02
GO:0033268	node of Ranvier	1.09E-02	4.66E-02
GO:0031088	platelet dense granule membrane	1.09E-02	4.66E-02
GO:0030877	beta-catenin destruction complex	1.09E-02	4.66E-02

Table S6. Reactome Pathway enrichment analysis of AIS genes.

Pathway	**Number of genes**	**PV**	**CPV**
Formation of Fibrin Clot (Clotting Cascade)	16	2.98E-08	3.25E-06
Common Pathway of Fibrin Clot Formation	11	9.48E-07	5.89E-05
Intrinsic Pathway for Apoptosis	13	3.05E-06	0.00016
Neuronal System	39	3.27E-06	0.000168
Unblocking of NMDA receptor, glutamate binding and activation	9	6.56E-06	0.000294
Hemostasis	59	6.99E-06	0.00031
Platelet activation, signaling and aggregation	31	3.15E-05	0.001092
Apoptotic factor-mediated response	6	3.58E-05	0.001221
Response to elevated platelet cytosolic Ca2+	17	4.04E-05	0.001322

MyD88:Mal cascade initiated on plasma membrane	18	4.06E-05	0.001322
Toll Like Receptor TLR6:TLR2 Cascade	18	4.06E-05	0.001322
Toll Like Receptor 2 (TLR2) Cascade	18	5.84E-05	0.001759
Toll Like Receptor TLR1:TLR2 Cascade	18	5.84E-05	0.001759
Cellular responses to stress	34	5.91E-05	0.001767
Platelet degranulation	16	6.68E-05	0.001955
Detoxification of Reactive Oxygen Species	9	7.35E-05	0.002092
MyD88-independent cascade	18	8.26E-05	0.002294
Toll Like Receptor 3 (TLR3) Cascade	18	8.26E-05	0.002294
TRIF-mediated TLR3/TLR4 signaling	18	8.26E-05	0.002294
Regulation of HSF1-mediated heat shock response	8	0.000103	0.002634
NGF-independant TRKA activation	5	0.000105	0.002669
Activated TLR4 signalling	19	0.00012	0.003003
MyD88 cascade initiated on plasma membrane	16	0.000125	0.003087
Toll Like Receptor 10 (TLR10) Cascade	16	0.000125	0.003087
Toll Like Receptor 5 (TLR5) Cascade	16	0.000125	0.003087
TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation	16	0.000141	0.003407
Toll Like Receptor 4 (TLR4) Cascade	20	0.000147	0.003527
Transmission across Chemical Synapses	27	0.00016	0.003743
MyD88 dependent cascade initiated on endosome	16	0.000179	0.004105
Toll Like Receptor 7/8 (TLR7/8) Cascade	16	0.000179	0.004105
Activation of TRKA receptors	5	0.000184	0.004163
Pre-NOTCH Processing in the Endoplasmic Reticulum	5	0.000184	0.004163
Signaling by NOTCH	18	0.000216	0.004696
CREB phosphorylation through the activation of CaMKII	7	0.000243	0.005158
Toll Like Receptor 9 (TLR9) Cascade	16	0.000251	0.005258
Toll-Like Receptors Cascades	21	0.000295	0.006067
Interleukin-1 processing	5	0.0003	0.006168

Tandem pore domain potassium channels	6	0.000304	0.006225
Gastrin-CREB signalling pathway via PKC and MAPK	27	0.000371	0.007226
DEx/H-box helicases activate type I IFN and inflammatory cytokines production	6	0.000423	0.008153
Activation of NMDA receptor upon glutamate binding and postsynaptic events	10	0.000434	0.008321
Arachidonic acid metabolism	11	0.000486	0.009126
Extrinsic Pathway of Fibrin Clot Formation	8	0.000548	0.010008
Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)	7	0.000683	0.011933
Sodium/Calcium exchangers	5	0.000691	0.012048
Eicosanoid ligand-binding receptors	6	0.000769	0.012773
Signalling by NGF	31	0.000902	0.014501
Activation of caspases through apoptosome-mediated cleavage	4	0.000955	0.015104
Cytochrome c-mediated apoptotic response	4	0.000955	0.015104
SMAC binds to IAPs	4	0.000955	0.015104
SMAC-mediated apoptotic response	4	0.000955	0.015104
SMAC-mediated dissociation of IAP:caspase complexes	4	0.000955	0.015104
Cellular response to heat stress	9	0.000994	0.015501
CRMPs in Sema3A signaling	6	0.001008	0.015651
Inflammasomes	6	0.0013	0.018792
G alpha (q) signalling events	23	0.001363	0.019502
Signaling by PDGF	22	0.001411	0.020048
NOTCH2 intracellular domain regulates transcription	5	0.001858	0.024376
Programmed Cell Death	20	0.001955	0.025355
NGF signalling via TRKA from the plasma membrane	23	0.001979	0.025476
Ras activation uopn Ca2+ infux through NMDA receptor	6	0.002073	0.026325

Scavenging by Class A Receptors	6	0.002073	0.026325
Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways	10	0.002095	0.026533
Transport of inorganic cations/anions and amino acids/oligopeptides	14	0.002438	0.029629
Advanced glycosylation endproduct receptor signaling	5	0.002456	0.029672
Chylomicron-mediated lipid transport	5	0.002456	0.029672
Dissolution of Fibrin Clot	5	0.002456	0.029672
Notch-HLH transcription pathway	5	0.002456	0.029672
PERK regulates gene expression	7	0.002757	0.032561
RIP-mediated NFkB activation via ZBP1	6	0.003151	0.035608
Attenuation phase	5	0.003182	0.035823
Synthesis of Prostaglandins (PG) and Thromboxanes (TX)	5	0.003182	0.035823
CREB phosphorylation through the activation of Ras	7	0.003261	0.036556
Pre-NOTCH Transcription and Translation	7	0.003261	0.036556
Transport of gamma-carboxylated protein precursors from the endoplasmic reticulum to the Golgi apparatus	4	0.00328	0.036732
Apoptosis	18	0.003323	0.036973
HSF1-dependent transactivation	6	0.003824	0.040854
Intrinsic Pathway of Fibrin Clot Formation	6	0.003824	0.040854
Cell surface interactions at the vascular wall	14	0.004373	0.044892
ATF6-alpha activates chaperone genes	4	0.004531	0.046103
Gamma-carboxylation of protein precursors	4	0.004531	0.046103
Regulation of gene expression by Hypoxia-inducible Factor	4	0.004531	0.046103
Removal of aminoterminal propeptides from gamma-carboxylated proteins	4	0.004531	0.046103
MAP kinase activation in TLR cascade	10	0.004664	0.047314

Table S7. The degrees of AIS existing drug targets. There are totally 161 targets in which 152 are included in the String9.1 PPI network. And more than 45% have degrees larger than 50.

AIS drug targes	Degree	AIS drug targes	Degree
VEGFA	345	CACNB3	45
ESR1	328	CACNA2D1	44
JUN	305	PLAT	44
FOS	296	CACNB2	44
CALM1	271	CACNA1H	43
PTGS2	209	HMGCR	43
PPARG	170	PDE5A	41
NFKB1	170	CACNA1I	40
CHRM2	169	ACE	40
HDAC2	165	LRP2	40
CHRM4	164	DPP4	38
OPRM1	163	F10	30
ITGB3	161	MTR	29
AR	158	MUT	27
AGTR1	150	CA2	26
CHRM3	149	SLC9A1	25
ADORA1	148	THBD	23
OPRD1	147	ADA	21
ADRA2A	146	KRT8	21
OPRK1	146	ACE2	17
ADRA2C	145	SERPINA5	17
ADRA2B	145	KCNMA1	16
P2RY12	144	PAH	16
CHRM1	140	MTHFR	16
CREB1	138	NID1	16
ITGB2	135	GABRG2	15
ADRA1B	132	SLC12A2	14
ADRA1D	130	TFPI	14
CHRM5	128	CES1	14
TLR4	127	GABRB2	12
MMP9	125	CACNA2D2	12
MMP2	123	SERPINB2	11
SERPINE1	112	KCNE1	11
ITGA4	112	GABRB1	11
BCL2	109	CA9	11
ITGA2B	105	FXYD2	10

CXCL12	102	GABRA2	10
F2	96	GABRA3	10
ADRB2	94	GABRA5	10
NT5E	92	GABRA1	10
PLG	91	GABRB3	10
PLAU	89	GABRG3	10
CANX	88	AKR1C1	9
TSPO	83	SCNN1B	9
ADRB1	82	ATP1A1	8
ADRB3	79	ST14	8
CFTR	76	SAA1	8
PDE4A	74	PDXK	7
PLAUR	73	SCNN1A	7
FGA	72	MMAA	7
ADORA2A	71	AQP1	7
NOS2	68	ADRA1A	7
APOE	66	SLC12A3	6
SERPINC1	65	SCNN1G	6
KCNQ1	61	SLC12A1	6
CALR	61	NR3C2	6
PDE1A	61	CA4	5
PDE4B	60	HRH1	5
PDE1B	60	MTRR	5
SELP	59	MMACHC	5
ABCA1	58	ACCN1	4
PDE3A	58	VKORC1	4
CACNA1S	56	FABP2	4
AMBP	55	GABRR2	4
CACNA1C	54	CA3	4
ITGAL	53	GABRR1	3
PDE10A	53	SCNN1D	3
AHR	51	CA7	3
CACNA1G	50	CA1	2
CACNA1D	48	ACCN2	2
CACNA1F	47	CLEC3B	2
PTGS1	45	GABRR3	2
CACNB1	45	SLC12A5	1
CACNG1	45	CA12	1
ANXA2	45	GABRE	1
CACNB4	45	GABRD	1

Table S8. Enriched Reactome pathway of the 10 significant modules. Here we list the highly enriched pathways of 10 classic module. PV and CPV respectively are P-value and Corrected P-value. And the in the time line we annotated the time of the events occur in ischemic cascade. “s”, “m”, “h”, “d”, “w”, “M” and “y” respectively mean second, minutes, hours, days, weeks, months and years.

Module	Pathway	PV	CPV	Time frame
58	Glycerophospholipid biosynthesis	1.82E-39	7.07E-42	mhdwM
58	Acyl chain remodelling of PC	4.74E-28	6.92E-30	
58	Acyl chain remodelling of PE	1.86E-23	3.71E-25	
58	Synthesis of Leukotrienes (LT) and Eoxins (EX)	3.47E-14	1.18E-15	mh
58	Hydrolysis of LPC	2.70E-08	1.42E-09	mh
64	Activation of NMDA receptor upon glutamate binding and postsynaptic events	1.73E-20	1.36E-18	mh
64	Glutamate Binding, Activation of AMPA Receptors and Synaptic Plasticity	3.54E-20	2.63E-18	smh
64	Trafficking of AMPA receptors	3.54E-20	2.63E-18	hd
64	Unblocking of NMDA receptor, glutamate binding and activation	4.17E-19	2.99E-17	mh
64	Depolarization of the Presynaptic Terminal Triggers the Opening of Calcium Channels	1.22E-15	6.96E-14	mh
94	Toll-Like Receptors Cascades	2.00E-19	6.94E-23	hdw
94	MyD88:Mal cascade initiated on plasma membrane	2.10E-14	5.85E-17	mh

94	Toll Like Receptor TLR6:TLR2 Cascade	2.10E-14	5.85E-17	hdw
94	Toll Like Receptor TLR1:TLR2 Cascade	3.09E-14	1.02E-16	hdw
94	Toll Like Receptor 2 (TLR2) Cascade	3.09E-14	1.02E-16	hdw
94	Interleukin-1 signaling	2.09E-12	9.94E-15	hd
97	Cytokine Signaling in Immune system	7.86E-07	2.80E-08	hd
97	Interleukin receptor SHC signaling	0.000191	1.20E-05	hd
97	Activation of the AP-1 family of transcription factors	0.000381	2.58E-05	sh
97	G beta:gamma signalling through PI3Kgamma	0.001171	8.91E-05	
97	Platelet activation, signaling and aggregation	0.001221	9.36E-05	
103	Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways	2.88E-12	3.41E-14	mh
103	Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways	2.88E-12	3.41E-14	mhw
103	BH3-only proteins associate with and inactivate anti-apoptotic BCL-2 members	6.07E-12	7.48E-14	mhw
103	Activation of BH3-only proteins	1.14E-10	1.92E-12	mhw
103	Apoptotic factor-mediated response	9.13E-09	2.04E-10	mhw
121	Signaling by NOTCH1	1.38E-25	4.95E-28	dwMy

121	Signaling by NOTCH1	1.38E-25	4.95E-28	dwMy
121	Signaling by NOTCH1 HD+PEST Domain Mutants in Cancer	1.38E-25	4.95E-28	
121	Activated NOTCH1 Transmits Signal to the Nucleus	7.51E-25	2.96E-27	dwMy
121	Signaling by NOTCH2	7.51E-23	4.04E-25	dwMy
193	Formation of Fibrin Clot (Clotting Cascade)	1.24E-31	1.80E-34	
193	Gamma-carboxylation, transport, and amino-terminal cleavage of proteins	7.50E-15	1.06E-16	
193	Removal of aminoterminal propeptides from gamma-carboxylated proteins	2.07E-13	3.52E-15	
193	Gamma-carboxylation of protein precursors	2.07E-13	3.52E-15	
193	Dissolution of Fibrin Clot	1.61E-12	2.90E-14	
194	Metabolism of Angiotensinogen to Angiotensins	6.69E-11	3.79E-14	
194	Peptide hormone metabolism	6.64E-08	3.01E-10	mhd
194	Degradation of the extracellular matrix	0.005496	0.000193	hwM
194	Activation of Matrix Metalloproteinases	0.010589	0.000438	hd
194	Extracellular matrix organization	0.032326	0.002071	hdwMy
202	HDL-mediated lipid transport	1.37E-06	4.42E-08	hdwMy
202	Retinoid metabolism and transport	1.79E-06	6.21E-08	hd
202	Binding and Uptake of Ligands by Scavenger Receptors	4.91E-05	2.86E-06	hdwM

202	Formation of Fibrin Clot (Clotting Cascade)	4.91E-05	2.86E-06	
202	Scavenging of heme from plasma	8.10E-05	5.00E-06	
202	GRB2:SOS provides linkage to MAPK signaling for Integrins	0.004614	0.000519	hd
244	Tie2 Signaling	3.08E-11	2.92E-14	hdwMy
244	Cell surface interactions at the vascular wall	2.63E-07	1.66E-09	hd
244	NGF signalling via TRKA from the plasma membrane	3.69E-05	5.13E-07	hdwMy
244	NCAM signaling for neurite out-growth	3.69E-05	5.24E-07	hdwMy
244	IGF1R signaling cascade	7.78E-05	1.50E-06	hdwMy

Table S9. M64 Reactome Pathway analysis. There are 81 enriched pathways. 53 pathways involved in the process of ischemic stroke. These events can appear in the stages in minutes(m), hours(h), days(d), weeks(w), month(M) or years(y). The stage a pathways involved is displayed in the "Timing". And "Unblocking of NMDA receptor, glutamate binding and activation" is the sinificant pathway of M64.[19, 20]

Pathway	**PV**	**CPV**	**Time frame**
Activation of NMDA receptor upon glutamate binding and postsynaptic events	1.73E-20	1.36E-18	mh
Glutamate Binding, Activation of AMPA Receptors and Synaptic Plasticity	3.54E-20	2.63E-18	smh
Trafficking of AMPA receptors	3.54E-20	2.63E-18	hd

Unblocking of NMDA receptor, glutamate binding and activation	4.17E-19	2.99E-17	mh
Depolarization of the Presynaptic Terminal Triggers the Opening of Calcium Channels	1.22E-15	6.96E-14	mh
Post NMDA receptor activation events	1.62E-15	8.97E-14	mh
Ras activation uopn Ca2+ infux through NMDA receptor	4.55E-14	2.27E-12	mh
CREB phosphorylation through the activation of CaMKII	5.85E-13	2.78E-11	mh
CREB phosphorylation through the activation of Ras	1.72E-12	7.69E-11	mh
Integration of energy metabolism	2.59E-11	1.01E-09	m
NCAM1 interactions	8.29E-10	2.84E-08	h
Rap1 signalling	6.49E-09	1.97E-07	hd
NCAM signaling for neurite out-growth	7.11E-08	1.84E-06	dwMy
PKA activation	2.28E-07	5.62E-06	mh
PKA activation in glucagon signalling	3.06E-07	7.43E-06	mh
PKA-mediated phosphorylation of CREB	3.06E-07	7.43E-06	mh
Ca2+ activated K+ channels	5.35E-07	1.20E-05	m
Calmodulin induced events	3.62E-06	6.79E-05	h
CaM pathway	3.62E-06	6.79E-05	h
Ca-dependent events	5.14E-06	9.32E-05	h
cGMP effects	6.48E-06	0.000114	h
Transmembrane transport of small molecules	7.07E-06	0.000124	h
Aquaporin-mediated transport	7.76E-06	0.000132	h

DAG and IP3 signaling	8.34E-06	0.00014	h
Potassium Channels	8.89E-06	0.000148	mh
EGFR interacts with phospholipase C-gamma	1.12E-05	0.000183	h
PLC-gamma1 signalling	1.12E-05	0.000183	h
Axon guidance	1.30E-05	0.000207	dwMy
HSF1-dependent transactivation	1.89E-05	0.000294	h
Nitric oxide stimulates guanylate cyclase	2.27E-05	0.000348	h
Activation of Ca-permeable Kainate Receptor	3.83E-05	0.000554	h
Ionotropic activity of Kainate Receptors	3.83E-05	0.000554	mh
Hormone-sensitive lipase (HSL)-mediated triacylglycerol hydrolysis	3.83E-05	0.000554	d
Trafficking of GluR2-containing AMPA receptors	3.83E-05	0.000554	hd
PLC beta mediated events	4.05E-05	0.000583	mh
G-protein mediated events	4.54E-05	0.000645	hd
Phospholipase C-mediated cascade	6.26E-05	0.000867	mh
PKA-mediated phosphorylation of key metabolic factors	0.000102	0.001355	h
Cellular response to heat stress	0.000191	0.002408	h
CREB phosphorylation through the activation of Adenylate Cyclase	0.000215	0.002687	h
Opioid Signalling	0.000828	0.008484	hd
Inwardly rectifying K+ channels	0.000913	0.00917	mh
Activation of Kainate Receptors upon glutamate binding	0.001017	0.010062	mh

Developmental Biology	0.001263	0.011948	dwMy
Downstream signaling of activated FGFR	0.002011	0.017725	hd
Stimuli-sensing channels	0.002059	0.01809	hd
Lipid digestion, mobilization, and transport	0.002167	0.018795	h
Signaling by FGFR	0.003062	0.025326	hd
NGF signalling via TRKA from the plasma membrane	0.003669	0.029059	hdwMy
Hedgehog 'off' state	0.003683	0.029059	h
NrCAM interactions	0.00524	0.038775	h
Signaling by FGFR in disease	0.005454	0.040059	h
Ion channel transport	0.006766	0.046636	hd

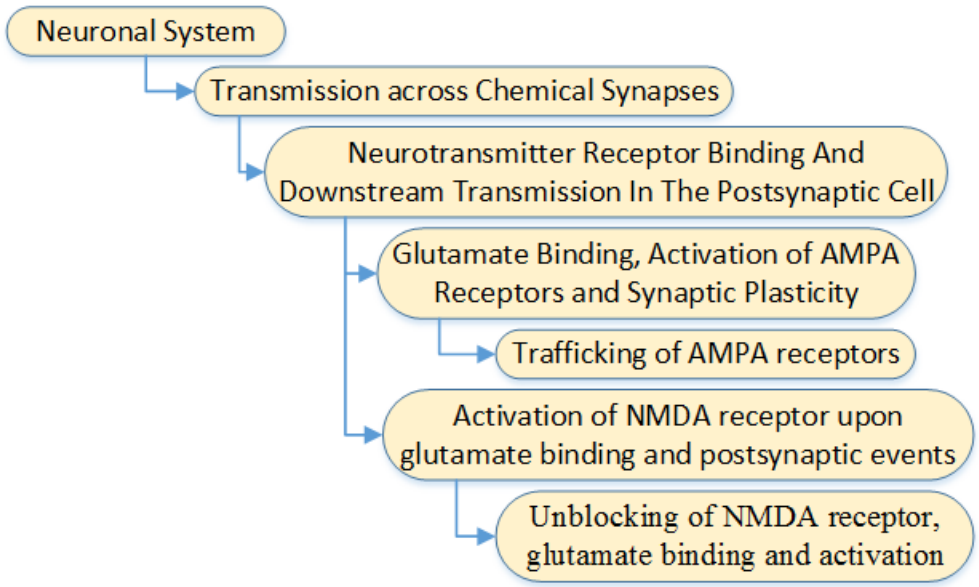

Figure S2. The tree of Reactome pathways of M64. There shows the including and included relationships of enriched Reactome pathways of M64.

Table S10. M145 Reactome Pathway analysis. There are 28 enriched pathways. The 20 pathways in red are shared with the analysis result of credible genes. The most highly enriched pathway "G alpha (i) signalling events" is sinificant pathway of M145.

Pathway	**PV**	**CPV**	**Time frame**
G alpha (i) signalling events	2.49E-119	8.99E-116	mh
Class A/1 (Rhodopsin-like receptors)	1.78E-97	3.21E-94	
Defective ACTH causes Obesity and Pro-opiomelanocortinin deficiency (POMCD)	1.94E-84	1.75E-81	
GPCR ligand binding	1.94E-84	1.75E-81	mh
Metabolic disorders of biological oxidation enzymes	2.08E-71	1.50E-68	m
Peptide ligand-binding receptors	1.51E-67	9.10E-65	m
GPCR downstream signaling	1.40E-63	7.23E-61	mh
Signaling by GPCR	1.82E-59	7.32E-57	mh
Signal Transduction	7.81E-33	1.66E-30	
Chemokine receptors bind chemokines	2.81E-32	5.63E-30	h
Amine ligand-binding receptors	3.07E-16	1.73E-14	
Serotonin receptors	2.13E-07	3.82E-06	mh
Nucleotide-like (purinergic) receptors	8.11E-07	1.24E-05	
Lysosphingolipid and LPA receptors	1.56E-06	2.33E-05	
G alpha (z) signalling events	1.71E-05	0.00020565	mh
Activation of C3 and C5	2.54E-05	0.00029046	hd
P2Y receptors	8.89E-05	0.00087765	dwMy
Dopamine receptors	0.00019433	0.00169135	h
Alternative complement activation	0.00019433	0.00169135	dwMy
Formyl peptide receptors bind formyl peptides and many other ligands	0.00040689	0.00312696	
Adrenoceptors	0.00072891	0.00514766	

Regulation of Complement cascade	0.00098933	0.00658094	dwMy
Eicosanoid ligand-binding receptors	0.00252302	0.01446533	
Complement cascade	0.00397903	0.02080628	dwMy
Muscarinic acetylcholine receptors	0.00475556	0.02426144	
Initial triggering of complement	0.00517063	0.02599931	dwMy

Table S11. Novel drugs about neuroprotection of AIS. "Action" means the interaction between drugs and targets. Based on the analysis of M64, There are 21 potential drugs. And 25 potential drugs are screened out based on M145 analysis.

Module	Potential Targets	Action	Novel Drugs
M64	CAMK2G	inhibitor	Bosutinib
	GRIA1	antagonist	Perampanel, Enflurane, Isoflurane, Desflurane, Sevoflurane, Methoxyflurane
	GRIA2	antagonist	Hexobarbital, Heptabarbital, Methylphenobarbital, Quinidine barbiturate, Primidone, Pentobarbital, Phenobarbital, Thiopental, Secobarbital
	GRIN1	antagonist	Orphenadrine, Pethidine
	GRIN2A	antagonist	Halothane, Memantine, Felbamate, Pethidine
M145	ADORA3	agonist	Adenosine
	DRD2	agonist	Amantadine, Apomorphine, Bromocriptine, Cabergoline, Dopamine, Ergotamine, Ketamine, Levodopa, Lisuride, Minaprine, Pramipexole, Ropinirole, Rotigotine
	HTR1A	agonist	Apomorphine, Bromocriptine, Cabergoline, Cinitapride, Eletriptan, Lisuride, Methysergide, Naratriptan, Ropinirole, Rotigotine, Sumatriptan, Vilazodone, Zolmitriptan
	HTR1D	agonist	Almotriptan, Apomorphine, Bromocriptine, Cabergoline, Dihydroergotamine, Eletriptan, Ergotamine, Frovatriptan,

			Lisuride, Naratriptan, Rizatriptan, Ropinirole, Sumatriptan, Zolmitriptan
	HTR1E	agonist	Eletriptan
	HTR1F	agonist	Eletriptan, Naratriptan, Rizatriptan, Sumatriptan, Zolmitriptan

In addition, there are additional supplementary data files as following, all of which will be supplied if necessary.

Data S1. Identified disease-gene relationships of AIS from Coremine

Data S2. The nodes in 29 modules (OR>2).

Data S3. GO analysis of AIS confirmed genes

Data S4.GO analysis of AIS existing drug targets.

Data S5. GO analysis of 29(OR>2) AIS related modules.

Data S6. Pathway analysis of AIS drug targets.

Data S7. Pathway analysis of 29 AIS related modules.

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