ISSN 1819-7124, Neurochemical Journal, 2018, Vol. 12, No. 3, pp. 210–221. © Pleiades Publishing, Ltd., 2018.

THEORETICAL ARTICLES

A Predicted Molecular Model for Development of Human Intelligence[1, 2]

Hadi Najafi[a], Seyed Mostafa Hosseini[b], Mahmood Tavallaie[b, 3], and Bahram M. Soltani[a]

[a] *Tarbiat Modares University, faculty of biological sciences, Tehran, Iran*

[b] *Department of genetics, Baqiyatallah University of Medical Sciences, Tehran, Iran*

Received June 26, 2017; in final form, October 26, 2017

Abstract—Intelligence is the core construct of behavioral genetics studies and is one of the most heritable behavioral traits. Molecular genetics studies attempt to identify the genes which are responsible for the levels of intelligence and its heritability. In order to understand the main signaling and biochemical pathways that are involved in intelligence, functional genomics could be applied. Herein, we selected a total of 181 intelligence-related genes (IRGs), selected from genome-wide association studies and literatures, to incorporate these genes in related signaling pathways, aiming to understand the underlying biological mechanisms. Disregarding the tissue types, computational pathway analyses demonstrated that IRGs were mostly enriched in the Wnt signaling pathway. Nevertheless, pathway enrichment of brain-specific IRGs, highlighted the role of G-protein- and dopamine-mediated signaling pathways. These findings represent a comprehensive and assembled intracellular molecular network for intelligence. It is of great importance to identify RNA or protein molecules, responsible for regulation of these signaling pathways.

Keywords: bioinformatics, intelligence, Wnt pathway, molecular model, systems biology

DOI: 10.1134/S1819712418030091

INTRODUCTION

For a long period of time, intelligence was one of the first human traits to be the target of genetic research. Studies in the 1950s-1960s showed the important contribution of genetics to individual differences for diverse cognitive and learning abilities [1, 2]. In 1963, a review in Science of genetic research on intelligence presented the convergence of evidence from family, twin, and adoption studies pointing to genetic influence [3]. Influence of genetics in complex traits and bolding the role of environmental factors made an intense criticism on the field of behavioral genetic research [4], especially researches in the area of intelligence [5]. However, another influential Science article [6], followed by other studies [7, 8] accepted genetic influence on intelligence. Nowadays, it is concluded that the human intelligence is affected by interaction of genetic and environmental factors, with contribution of about 56 and 12% for genetics and environment, respectively [9]. There is currently a large body of candidate-gene studies that have shown associations between genes and intelligence [3, 9, 10]. Intelligence is also one of the most heritable behavioral traits (about 20% in infancy to 80% in later adulthood) [10]. Genetic studies attempting to link genes to intelligence have uncovered many "candidates" but without conclusive evidence. In other words, no gene or set of genes has been conclusively linked to the development of intelligence.

In this study, we exploit the data of published articles to prepare a list of intelligence-related genes and draw corresponding signaling pathways which would be useful to understand the mechanism of action of genetics in the brain's performance.

METHODS

Dataset preparation. We exploited the data of original research articles and reviews in the published literature to find the genes which previously were considered as intelligence-related genes (IRGs). The resultant genes belong to many independent studies that were done on different world population groups. The raw list of these genes was compared among different populations to remove redundancy. The acquired non-redundant list, which includes a total of 181 genes, was afterward used as "input" for following investigations (S1 file).

[1] The article is published in the original.

[2] Supplementary materials are available for this article at 10.1134/S1819712418030091 and are accessible for authorized users.

[3] Corresponding author; address: Baqiyatallah University of Medical Sciences, Tehran Province, Tehran, Vanak Square, Molla-Sadra Avenue, P.O. box: 19945, Iran; phone: +98(21) 86034956; e-mail: mahmood_259@yahoo.com.

Unifying the gene names. Since the genes in the literature were represented as official or unofficial symbols, after preparing the gene list, we must unify this heterogeneity to be recognized and processed by the functional enrichment tools. To this end, the DAVID conversion tool (https://david.ncifcrf.gov/conversion.jsp) was used and unofficial gene symbols and aliases were converted to official NCBI gene symbols. In addition, the full name of the listed genes was retrieved from the DAVID conversion tool and then included in the gene list (S1 file).

Gene classification based on subcellular localization. Subcellular localization of genes may reflect their functional roles. Therefore, all collected IRGs were analyzed in databases of human genome to determine their subcellular localization. For this purpose, the genes were searched in the NCBI-Entrez gene (http://www.ncbi.nlm.nih.gov/gene), Gene Ontology consortium (http://geneontology.org/) and UniProt (http://www.uniprot.org/) which display the information of subcellular localization of genes. The data of subcellular localization of all studied proteins are represented in the supplementary data (S1 file). This data was also used to classify the studied proteins based on their subcellular localizations and represented in the supplementary data (S2 file).

Gene classification based on protein classes and biological processes. Functional enrichment analyses of the intelligence-related and brain-enriched genes were performed by categorizing the studied genes in different protein classes and biological processes. For this purpose, a gene set was submitted to PANTHER functional classifier website (http://pantherdb.org/), then the protein classification was performed. Gene Ontology enrichment of biological processes was also performed for the studied genes by the same way (using the PANTHER website).

Gene classification and overrepresentation analyses. After collecting the IRGs from the literature, we decided to investigate in which signaling pathway(s) these genes are primarily enriched. For this purpose, pathway analysis of the 181 IRGs was performed by PANTHER pathway analyzer.

Another pathway analysis by PANTHER, was performed to explore the putative signaling pathway(s) associated with those of IRGs, whose expression is enriched in the human brain (brain-enriched IRGs). To this end, the brain-enriched genes were initially identified and selected from the 181-gene list by DAVID tissue enrichment tool (https://david.ncifcrf.gov/tools.jsp), and were then analyzed by PANTHER pathways prediction. The PANTHER Overrepresentation Test (Version 12.0; Released 2017-08-14) was used to search the data against the PANTHER database and the GO database to identify either protein classes or GO annotations overrepresented in our data when compared to a reference human genome. P-values were adjusted using a Bonferroni correction [11].

To check the validity of the predicted signaling pathways for brain-enriched IRGs, previously-known Wnt pathway-related genes (S3 file) were used as query, and were separately investigated in parallel with the analysis of the genes-of interest.

Accuracy test of the predicted signaling pathways. The process of representing a gene set in signaling pathways, associated with the neural system was carried out by the PANTHER pathway analyzer (http://pantherdb.org/). To test the accuracy of that prediction, several pathway analyzer tools including Reactome (http://www.reactome.org/), KEGG (http://www.genome.jp/kegg/) and GeneMANIA (http://www.genemania.org/) were used. Based on the quality, quantity, and completeness of the computational analyses and experimental evidences elsewhere, a proposed model for development of human intelligence was built.

RESULTS

Identification of intelligence-related genes. More is known about the genetics of intelligence than about any other behavioral trait. In order to address specific genes responsible for intelligence, we assume basic understanding of the brain physiology and included the genes which are potentially linked to functionality of the human brain. The genes mostly were described in previous articles where are functionally linked to brain functioning. Some other genes are derived from the articles that performed GWAS [12, 13] and microarray [14], in addition to OMIM database (https://www.omim.org/) to identify the intelligence related genes. After search in the literature, a total of 181 genes were selected and included in the downstream pathway analyses. The heterogeneously reported gene names in various references used in this study were converted by DAVID tool into official gene symbols and represented in the supplementary data (S1 file).

Intelligence-related genes are localized to different compartments of the cell. Knowing the localization of proteins may provide key insights to their function. Therefore, we firstly decided to classify the intelligence-related genes based on their localization patterns.

Furthermore, it is unlikely that proteins with different subcellular could interact with each other. For this reason the data of subcellular classification of proteins is helpful to make a more accurate molecular model and avoiding false-positive results. Accordingly, secretory proteins were excluded in downstream analyses and the co-located proteins were used as input for deducing an intracellular signaling network. These include plasma membrane integral proteins, nuclear outer membrane proteins, cytoplasmic proteins and cytoskeleton-bound proteins (Fig. 1). The categorized list of proteins are also represented in supplementary

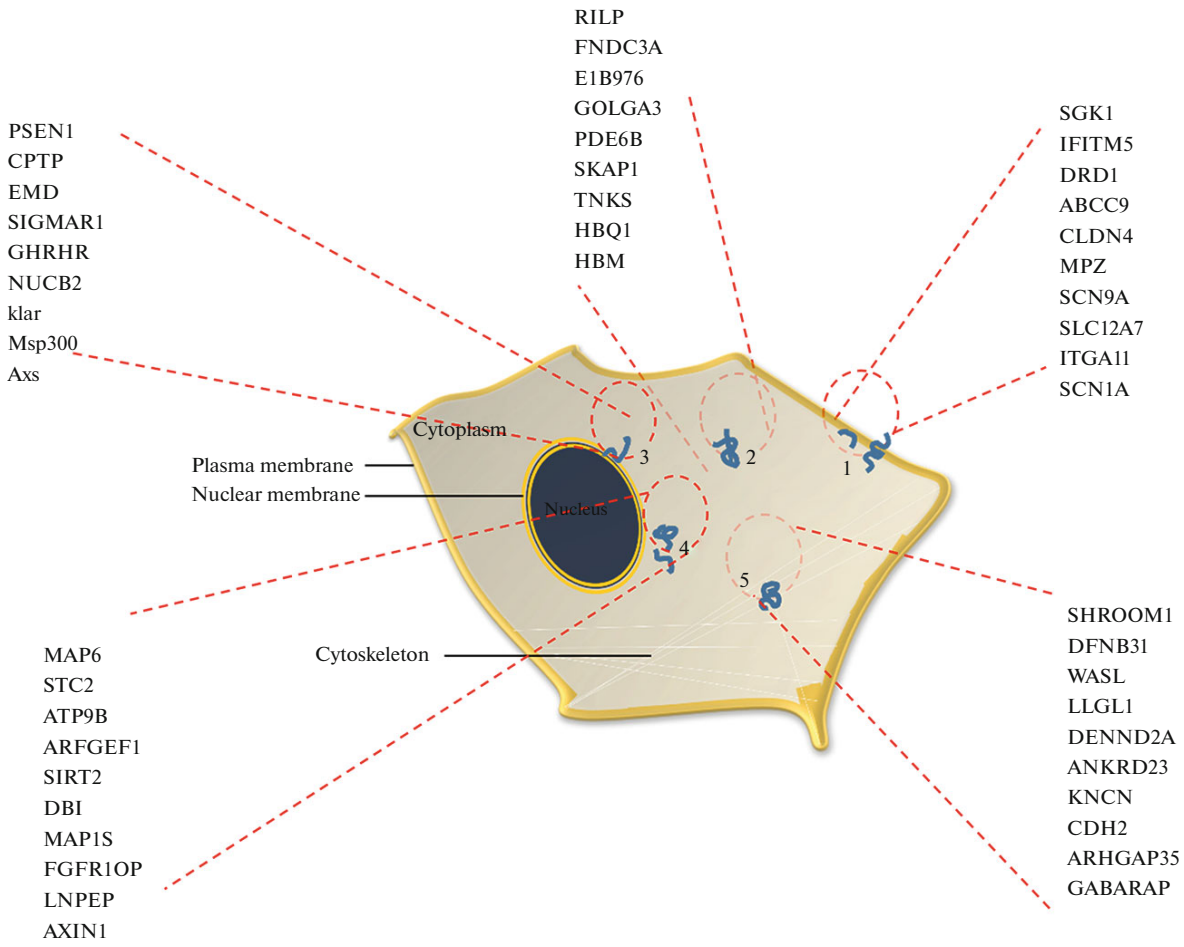

Fig. 1. IRGs, classified based on subcellular locations. While the intelligence-related genes may be localized inside or outside of the cells, only the intracellular ones were followed to draw a signaling network. The number of each class refers to as: Integral components of plasma membrane (1); nuclear outer membrane proteins (2); cytoplasmic proteins (3); perinuclear region of cytoplasm (4); actin cytoskeleton (5).

data with their full name descriptions (S2 file). Categorizing the proteins based on their subcellular localizations showed that significant number of IRGs encodes for the proteins that are distributed in various compartments of the cell (Fig. 1). Such diverse subcellular localizations enable the proteins of different compartments to form a signaling cascade within the cell [15].

IRGs are enriched for neurodevelopmental processes. Analysis of the 181 IRGs by PANTHER "protein class" identifier, demonstrated that the most relevant classes are nucleic acid binding, signaling molecule, receptors, transferase and enzyme modulator (Table 1), suggesting that they have a potential to be involved in biological processes. To investigate which biological processes could be mediated by these genes, they were analyzed by PANTHER annotation of "Gene Ontology (GO)-biological process". Interestingly, data showed significant enrichment for the biological processes linked to the neural system development (Table 2).

IRGs with cytoplasmic localization are enriched in the wnt signaling pathway. A biological pathway is an ordered series of molecular events that results in a new molecular product, or a change in a cellular state or process. Such an interactive signaling pathway may confer new state to neural cells to modify intelligence. To explore the putative signaling pathway(s) and interaction network associated with intelligence, pathway analyses were performed by PANTHER web server. Thirteen signaling pathways were statistically significant, and the Wnt signaling pathway was involved by most genes of the study, indicating association of the Wnt pathway in intelligence (Fig. 2b).

Pathway significance is partly dependent on if the number of IRGs observed in a pathway is larger than that observed by random chance. Therefore, first, we investigate the enrichment by well-documented Wnt pathway-related genes, as a positive control for the PANTHER database. Expectedly, this database detected an enrichment for the Wnt signaling pathway

Table 1. Top 5 protein classes for the studied IRGs, categorized by PANTHER

Protein class (ID)	Gene count	Genes/total genes, %	Contribution in pathways, %	Genes
Nucleic acid binding (PC00171)	13	8.60	10.20	*MTOR*, *UHMK1*, *GDA*, *ATXN2*, *NR3C2*, *PHOX2B*, *FOXO4*, *LHX5, NPAS3*, *MAP2*, *FOXF2*, *BCL11A*, *TCF3*
Signaling molecule (PC00207)	13	8.60	10.20	*VAV3*, *SEMA3A*, *DAB1*, *BDNF*, *BAX*, *NPPB*, *BCL2*, *NRG1*, *PROK2*, *NPPA*, *VAV2*, *GHR*, *IL6R*
Receptor (PC00197)	13	8.60	10.20	*DRD2*, *NFASC*, *IL1RAPL1*, *CNR1*, *DRD5*, *GRM7*, *SLIT2*, *ADRB2*, *SLIT3*, *PTPRM*, *ALCAM*, *LAMB1*, *SLIT1*
Transferase (PC00220)	12	7.90	9.40	*COMT*, *EXT1*, *SGK1*, *DMPK*, *PRKCA*, *SGK2*, *DGKE*, *MTOR*, *RPS6KA3*, *B3GAT1*, *HIPK2*, *MAPK8*
Enzyme modulator (PC00095)	12	7.90	9.40	*ITSN1*, *CCND2*, *GNAS*, *CABIN1*, *VAV3*, *KNDC1*, *Rac2*, *RAC2*, *RIT2*, *CDKN2D*, *RND1*, *RGS3*, *VAV2*

Table 2. PANTHER enrichment of GO biological process for the studied IRGs. Many neural system-related biological processes were identified and the top 5 are represented here

Rank	GO biological process	Gene count	*p*-value
1	Neurogenesis (GO:0022008)	79	3.75E-45
2	Generation of neurons (GO:0048699)	77	5.92E-45
3	Nervous system development (GO:0007399)	88	3.53E-42
4	Neuron differentiation (GO:0030182)	59	3.27E-35
5	Neuron development (GO:0048666)	52	3.94E-32

for 46 Wnt signaling components which are mostly listed in Wnt signaling home page (Fig. 2a).

Brain-enriched IRGs mostly play role in g-protein- and dopamine-mediated signaling pathways. Among all IRGs, a list of brain-enriched genes was selected and pathway analysis was followed by limiting the input to these brain-enriched genes (48 genes). To this end, all IRGs (181 genes) were passed through the Gene Enrichment Profiler (http://xavierlab2.mgh. harvard.edu/EnrichmentProfiler/) and only the brain-enriched genes were selected (S3 file). Afterward, to achieve closest signaling pathway(s) for this gene set, PANTHER software was used. As the result, PANTHER Gene Annotation categorized these brain-enriched genes in three protein classes: signaling molecules, enzyme modulators, and receptors (Table 3).

In another analysis, all brain-enriched IRGs (48 genes) were included in the PANTHER database for signaling pathway enrichment. Significant PANTHER signaling pathway enrichment showed that the majority of IRGs are enriched in G-protein- and dopamine receptor-mediated signaling pathways (total contribution = 40.90%) (Fig. 3).

Consistent with this data, PANTHER analysis of the biological process revealed that the brain-enriched IRGs mostly contribute to signal transduction and signaling pathways related to G-protein- and dopamine-receptors (Table 4).

An integrated molecular model for human intelligence using the resultant signaling pathways. To construct an integrative genetics network of human intelligence, the common gene set of human cell types (181 genes) together with brain-enriched genes were analyzed by three additional pathway-based online software (GeneMANIA, KEGG and Reactome). In most cases, these software confirmed the results of PANTHER pathway predictor (Table 3). Finally, the data of all prediction results were incorporated in a suggested model (Fig. 4). In this model, two distinct types of signaling pathways are playing role in two different developmental stages of neurons: (1) maturation from progenitor cells, (2) neural cell survival and functioning. Growing evidence indicates that canonical Wnt signaling pathway is essential for development of the central nervous system from neural progenitor or stem cells [16, 17]. Nevertheless, at the late stages of neuronal cell life, other routs of the Wnt pathway (termed as non-canonical pathways) are functioning [18]. In addition, the canonical Wnt signaling pathway has an interplay between stem cells and neural progenitor cells [19].

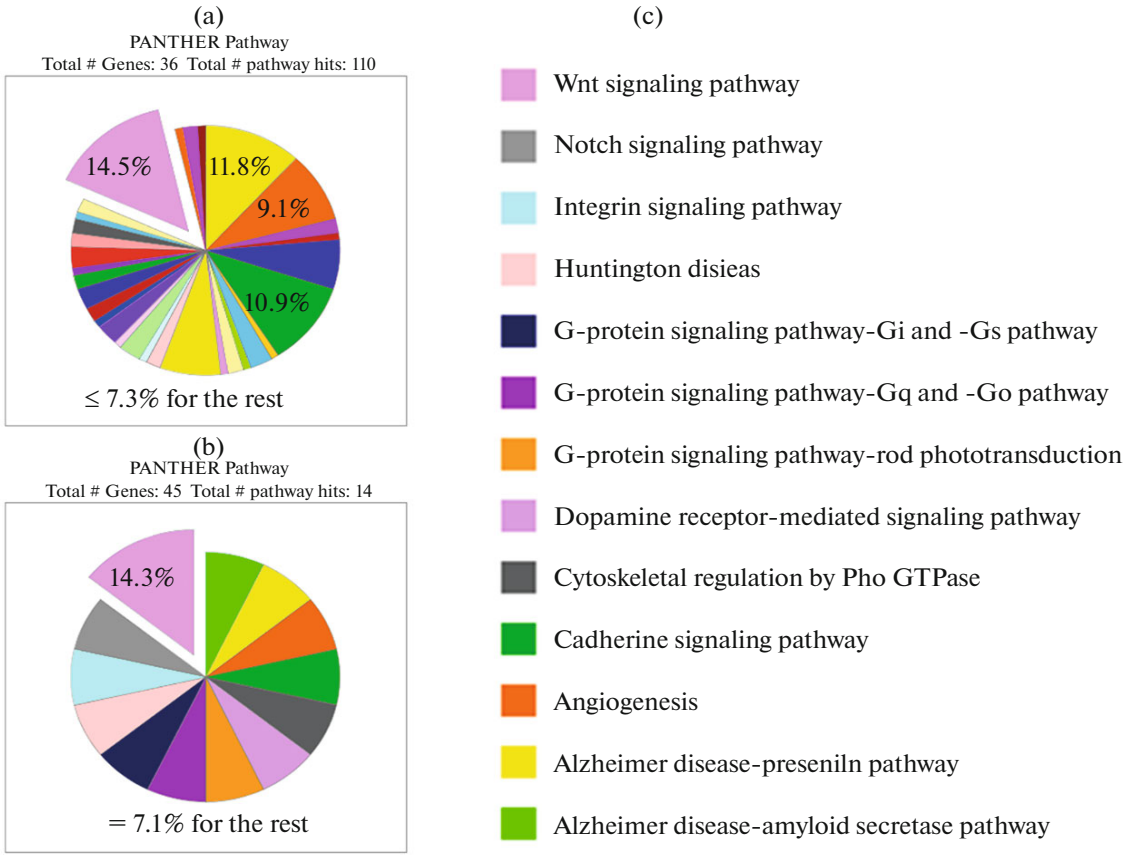

Fig. 2. Pie chart of the pathway enrichment for Wnt signaling pathway genes as control (a) and for intelligence-related genes (b). Each signaling pathway is denoted as colors (c).

G-protein- and dopamine-mediated signaling pathways act in neuronal networks where the fully-differentiated neural cells (such as dopaminergic neural cells) are existed. A simple explanation for this process is represented in Fig. 4.

DISCUSSION

Although the intelligence is considered as complex trait and many genes are known to be involved [10], little is known about the underlying biological mechanisms that lead to the differences in human [10]. Modeling the signaling pathways contributed in human intelligence provides potential detailed understanding for its complex genotype-to-phenotype relationships [20]. More importantly, these results enable us to generate a concrete molecular mechanism underlying behind intelligence which can be used as intelligence molecular measuring tools [21, 22]. While a myriad numbers of genes previously were attributed to human intelligence [23], little is known about a comprehensive molecular system for this trait.

Table 3. The PANTHER protein classes in which the brain-enriched IRGs were primarily categorized

Protein class (ID)	Gene count	Genes/total genes, %	Contribution in pathways, %	Genes
Signaling molecule (PC00207)	13	29.5	31	*VAV3*, *SEMA3A*, *DAB1*, *BDNF*, *BAX*, *NPPB*, *BCL2*, *NRG1*, *PROK2*, *NPPA*, *VAV2*, *GHR*, *IL6R*
Enzyme modulator (PC00095)	12	27.3	28.6	*NPPB*, *VAV3*, *NRG1*, *IL6R*, *DAB1*, *BDNF*, *BCL2*, *NPPA*, *PLXNA2*, *CNTNAP2*, *PROK2*, *BAX*, *GHR*, *SEMA3A*, *VAV2*
Receptor (PC00197)	10	22.8	23.8	*CNR1*, *ADRB2*, *DRD2*, *IL1RAPL1*, *DRD5*, *GRM7*, *PTPRM*, *ALCAM*, *LAMB1*, *NFASC*

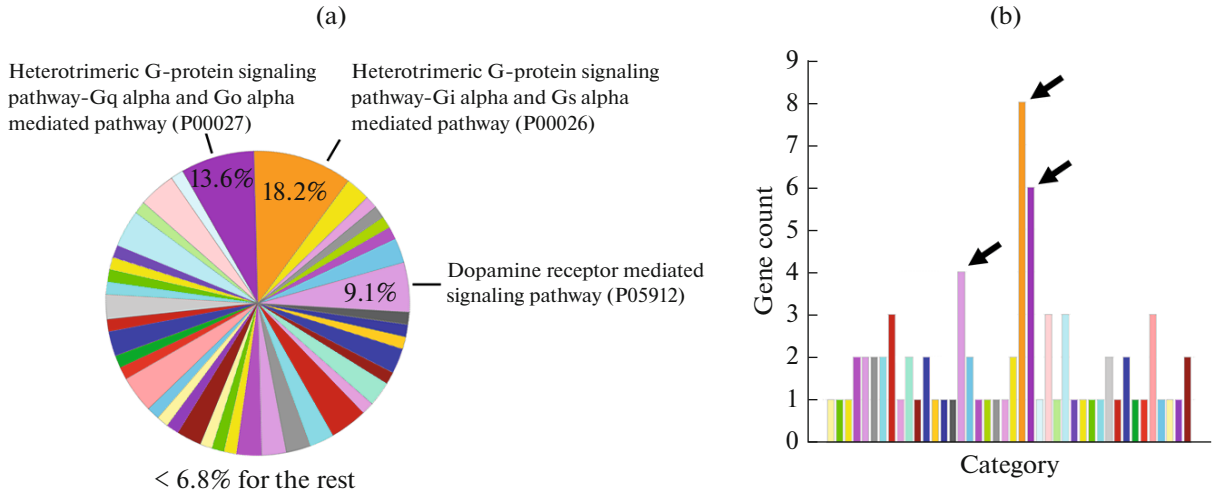

Fig. 3. Pie chart of the pathway enrichment results for brain-specific IRGs from PANTHER gene classifier tool. The top three signaling pathways (a) had the highest gene count (b). Contributions of other pathways were < 6.8%. The number of genes of each category (signaling pathway) is represented in part b. The arrow-heads show the most relevant pathways G-protein and dopamine pathways.

In this study, we aimed to identify a comprehensive gene network with functional insight associated with intelligence using protein-network-based approaches. The genes selected to be analyzed in our study were those which have previously been verified by original researches. We prepared the gene dataset by seeking into review or original articles. Therefore, the associations of signaling pathways described here are based on our literature-based database, which currently represents the best available depository of IRGs.

Since the analysis of these genes by STRING database resulted in a giant PPI network with a very complicated complex, we initially classified them based on their subcellular locations. Thereafter, computational pathway analyses were undertaken. Such a gene classification not only aids to focus on the biological function of the genes [24], but to clarify their mode of actions [25]. Besides, to deduce a *bona fide* signaling network for a set of proteins we ought to consider the proteins which are co-located in the same cellular compartments (e.g. cytoplasm) or in the same cell types (e.g. in neurons).

In a general cell type model, we uncovered importance of Wnt signaling pathway and the signaling pathways related to Alzheimer's disease (contribution = 14.1%) (Fig. 2) in human intelligence. However, the functional enrichment of normal state highlighted the Wnt signaling pathway (contribution = 14.3%) whose activity is necessary for neurogenesis [26, 27], specifically dopaminergic neurons [28]. For positive controls, we test the results of PANTHER pathway analysis for previously-confirmed components of Wnt signaling pathway as input (Fig. 2). As expected, the most portion of the pie graph of this positive control fell into the Wnt signaling pathway. However, co-occurrence of Alzheimer disease-related pathways in the two results might be due to multi-functionality of the Wnt signaling pathway genes [29, 30]. This data also adds extra evidence for linking cancer to cognitive traits, including intelligence [31].

Table 4. PANTHER GO biological process for brain-enriched IRGs. Several biological processes were identified and the top 5 are represented here

Rank	GO biological process	Gene count	*p*-value
1	Signal transduction (GO:0007165)	35	5.37E-11
2	G-protein coupled receptor signaling pathway (GO:0007186)	12	4.09E-02
3	G-protein coupled receptor signaling pathway, coupled to cyclic nucleotide second messenger (GO:0007187)	8	3.52E-05
4	Adenylate cyclase-modulating G-protein coupled receptor signaling pathway (GO:0007188)	8	1.01E-05
5	Adenylate cyclase-activating dopamine receptor signaling pathway (GO:0007191)	3	1.21E-02

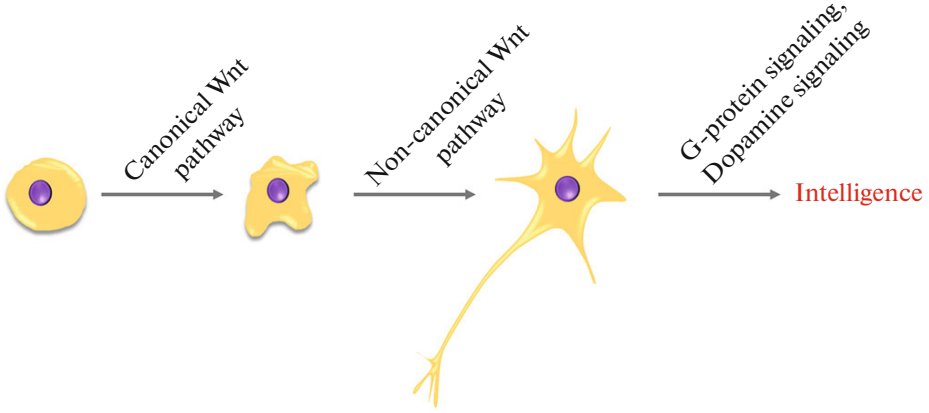

Fig. 4. Main signaling pathways proposed to be functioning during neural cell development. While, the main predicted molecular signaling in the neural maturation process was the Wnt signaling pathway, G-protein- and dopamine-mediated pathways was predicted to be regulating the differentiated neuron activity.

In our constructed pathway models, numerous genes were involved in cancers (Fig. 2). Consistently, previous studies showed that there is an extensive connection between cancer and intelligence [32, 33]. For example, one of most well-known Parkinson's causal gene (named PARKIN) has been reported as a tumor suppressors in several cancer types [34, 35]. Though there is no direct evidence to associate cognitive processes with cancer, previous studies showed that IRGs were highly related to neuron disorders such as schizophrenia [36, 37], autism [38], and bipolar disorder [39]. Consistently, our data showed that in addition to Wnt signaling pathway whose aberration is hallmark of many cancers [40], the signaling pathways related to Alzheimer's disease was the most relevant pathways in human intelligence (Fig. 2).

A possible problem with pathway analysis of intelligence would be the mixing all IRGs. That is some genes might not function in intelligence but due to their indirect effects were included in model development. To rule out this problem, another pathway analysis was performed by using only brain-enriched IRGs. Results showed that the most relevant cellular processes were G-protein- and dopamine-related signaling pathways (Fig. 3).

As mentioned, the most relevant signaling pathways in the case of brain-specific genes were G-protein-coupled receptor- and dopamine-mediated signaling pathways (Fig. 3); G-protein-coupled receptors (GPCRs) comprise the largest family of transmembrane signaling molecules with 600–1000 protein members [41]. A microarray profiling GPCRs in human and mice showed that over 90% of GPCRs are mainly expressed in central nervous system; the most notably expressed in the neuronal tissues was a cluster of 67 GPCRs [42].

GPCRs found to be expressed in adult neural stem/progenitor cells as well as the adult differentiated neurons [43], and regulate adult neurogenesis. They exert this function mainly by binding to the neuromodulators such as norepinephrine, dopamine, glutamate, and serotonin [44]. For example, GPRC5B, which encodes an orphan GPCR, is present in the ventricular surface of cortical progenitors in the mouse developing neocortex and is required for their neuronal differentiation [45]. Furthermore, GPRC5B is associated with Wnt signaling pathway which is crucial for neural cell development [45]. Besides involvement in neural development, GPCRs are also functioning in neuronal responses, synapse formation and function. For example, BAI3 (a brain-specific GPCR) is present in biochemical preparations of brain synapses, supporting the role of GPCRs in synapse formation and maintenance [46, 47].

In addition, there are GPCRs that displayed ubiquitous expression with nominal tissue specificity [48]. However, the pancreas, followed by CNS tissues, had the greatest number of GPCRs, suggesting a high degree of cellular regulation by GPCR signal transduction [49]. Therefore, it is of great importance to discriminate which GPCRs are specifically expressed in brain.

Another predicted intelligence-related pathway in our study was dopamine-mediated signaling pathway (Fig. 3). Interestingly, all dopamine receptors are also belonging to a large superfamily of GPCRs [50]. Dopamine has a tight link with GPCR-mediated pathways [51]. In fact, once released, dopamine activates members of GPCRs; they binds to two distinct classes of GPCRs (termed D1 and D2 receptors) [52, 53] in which the D1 receptors are exclusively expressed in postsynaptically on dopamine-receptive cells (such as GABAergic medium spiny neurons) while D2 dopamine receptors are expressed both postsynaptically (on dopamine target cells) and presynaptically (on dopaminergic neurons) [54]. The most recognized

Table 5. Pathway analysis by three extra signaling pathway analyzers. Consistent with PANTHER predictions, Wnt signaling pathway is enriched in progenitor cells, while to other signaling pathways are mostly enriched in fully-differentiated neural cells. p-value < 0.05 was considered as the statistical significance level

Cells	Bioinformatics tools	Wnt signaling pathway	G-protein-mediated signaling pathway	Dopamine-mediated signaling pathway
Progenitor cells	GeneMANIA	p-value < 0.05	Not predicted	Not predicted
	KEGG	Not predicted	Not predicted	Not predicted
	Reactome	p-value = 3.24E-3	Not predicted	Not predicted
Fully-differentiated neural cells	GeneMANIA	Not predicted	p-value < 0.05	p-value < 0.05
	KEGG	Not predicted	Not predicted	p-value = 7.1E-3
	Reactome	Not predicted	p-value = 1.91E-1	Not predicted

dopamine-related disorder is Parkinson's disease [55]. According to many lines of evidence for known function of dopamine in neural physiology [56, 57] and our pathway enrichment data, we conclude that dopamine-mediated signaling pathway is expected to be functioning in intelligence.

Differences in intelligence-related signaling pathways in two different IRG sets may justify the variable heritability of intelligence in different period of human lifetime (inheritance of 20 and 80% for childhood and late adulthood, respectively) [58]. This may be due to contribution of distinct signaling pathways during different developmental stages of human neural system (Fig. 4). On the other hand, PANTHER classification of "protein class" for all studied IRGs (181 genes) showed many significant (p-value < 0.05) enrichment category (Table 1), but only three protein classes for the brain-enriched IRGs (48 genes) (Table 3). This data suggest that these gene sets include "transferases", "receptors", "signaling molecules", "enzyme modulators, etc. (Tables 1 and 3) and hence can mediate biological processes. Therefore, for determination of the biological processes associated with the IRGs and also with brain-enriched IRGs, the PANTHER classification of "GO-biological process" was applied. Interestingly, we found that significantly enriched biological processes (p-value < 0.05) are associated with neural systems, and the top 5 are "neurogenesis", "generation of neurons", 'nervous system development", "neuron differentiation" and "neuron development" (Table 2). This data suggest that since the expression of the 181 genes is not restricted to neural cells, they may conduct biological processes in non-neuronal cells (for example stem or progenitor cells) enabling them to be developed into neurons. When the brain-enriched IRGs were analyzed in the same way, the biological processes of G-protein- and dopamine-receptors are enriched (Table 4) which again emphasizes the crucial role of the G-protein- and dopamine-receptor signaling pathways in neural cells' activity.

Complementary to the dissection of signaling pathways, we surveyed the function of brain-enriched IRGs individually and found that these genes contribute to neuronal development or function. The main characteristics of the brain-enriched IRGs which may link them to the human intelligence include:

SEMA3A. This secreted protein can either inhibit axonal outgrowth or stimulate the growth of apical dendrites [59]. Aberrant release of this protein is associated with the progression of Alzheimer's disease [60].

DAB1. An adaptor protein that is an obligate effector of the Reelin signaling pathway, and is essential for laminar organization of multiple neuron types of the cerebral cortex [61]. Increased activation of DAB1 by Reelin signaling pathway is correlated with increased dendritic spine density and enhanced performance in associative and spatial learning and memory [62].

BDNF. Several variations in the BDNF gene has been studied as a source of individual differences in intelligence [63] and personality [64, 65]. For example, most studies report significant effects of a polymorphism (Val66Met) in the BDNF gene on intelligence [66, 67].

NRG1. Neuregulin 1 (NRG1) is a schizophrenia-susceptible gene whose polymorphisms (including rs35753505) correlate with differences in frontal brain activation in working memory tasks of healthy individuals [68, 69].

CNR1. This gene encodes for the type 1 cannabinoid receptor, a presynaptically expressed Gi/Go-protein-coupled receptor that is densely localized to the hippocampus, amygdala, prefrontal cortex, striatum, and cerebellum [70]. It binds and reacts to both natural and synthetic cannabinoids. Several polymorphisms in this gene affect the efficiency of memory [71, 72] and procedural learning in human [73, 74]. For example, a variant on promoter of the CNR1 (rs2180619) moderates the effect of valence on working memory [70].

ADRB2. It encodes beta-2-adrenergic receptor which is a member of the G protein-coupled receptor superfamily. There is evidence that the β2-adrenergic receptors might have a role in memory and learning formation [75]. Noradrenalin which is the ligand for these receptors exerts a set of functions in cognition, behavior and emotion [76]. Reduction in the activity

of ADRB2 gene causes impairment of memory and learning [77], while its upregulation increases long-term memory and learning [78]. Therefore, because of its causative role, they appear to have significant potential in managing disorders of CNS, such as Parkinson, Alzheimer's, etc. [79]. Genetic association study was performed for this gene and human intelligence using two non-synonymous coding SNPs (rs1042713 and rs1042714). It was found that polymorphisms in ADRB2 and DRD2 are directly linked to intelligence [80].

DRD2. It encodes the D2 subtype of the dopamine receptor. A study found that individuals with the DRD2 A1/A1 genotype had a significantly higher intelligence than A2/A2 carriers [81]. In addition, a relationship between the striatal dopamine receptor D2 and verbal intelligence quotient was found [82].

IL1RAPL1. This gene is a member of the interleukin 1 receptor family. It is expressed in various parts of the human brain, and is closely associated with memory and concentration abilities [83]. IL-1 signaling pathway modulates the activity of hippocampus which suggests a specialized role in the physiological processes underlying memory and learning abilities as well as synapse formation and stabilization. A study on different population groups with different intelligence quotient (IQ) levels showed a link between the activity of this gene and IQ [84]. Deletion, inversion and mutations were reported for this gene and intellectual disabilities in patients [85–88]. IL-6R is another class of interleukin receptors which is associated with human intelligence [89].

NFASC (neurofascin). This protein functions in neurite outgrowth, neurite fasciculation, and organization of the axon initial segment and nodes of Ranvier on axons during neuronal development [90]. However, NFASC functions in mature neurons as a switch between neuronal plasticity and stability [91] which strongly influence intelligence [92]. Genome-wide high-throughput transcriptome analyses reveal that NFASC is one of the most differentially expressed transcript in manic episode of bipolar disorder (dataset: GSE46416) [14].

A fundamental follow up work on our built biological system would be discovering new regulators of the described signaling pathways. For example, a major group of such regulators are microRNAs (miRNAs) which regulate gene expression at post-transcriptional and/or translational levels [93]. It would be of great importance to include the miRNAs in future model designing studies. Such studies can provide a more comprehensive insight to the molecular mechanism(s) behind the intelligence trait. Transcription factors (TFs) can also influence gene expression through transcription activation or suppression of their target genes [94]. Therefore, the genes under the regulation of such TFs may be included in intelligence-related signaling pathways. This works adds complexity not only on our molecular model but any types of pathway-based modeling of other multifunctional traits. By identification of potential upstream miRNAs and/or TFs, as possible regulators of the suggested molecular networks, we can used them as more promising intelligence determinant factors than the genes itself [89]. Moreover, the study of changes in PPI network among different individuals (who have different intelligence quotient) can also assist the identification of biomarkers or modules for molecular assessment of IQ [95]. Besides, our molecular model of intelligence may advance the understanding cellular factors which modulate human intelligence, which may elucidate novel pathways for future drug development on intelligence-related mental disorders [96, 97].

CONCLUSIONS

Taken together, in spite of many studies about the genes whose functions are related to brain activity, a comprehensive study bearing integrated data of molecular signaling pathways underlying the human intelligence was obscure. In the current study, we collect the genes which were potentially linked to brain function and then we have drawn a molecular model responsible for human intelligence. The results highlighted two signaling pathways, respectively mediated by G-protein coupled receptors and dopamine receptors, in human intelligence. In addition, the data of this study will provide an opportunity to use the regulators of these two pathways as identifiers of human intelligence which confer a novel IQ assessment method on the basis of genetic markers.

COMPLIANCE WITH ETHICAL STANDARDS

Funding. No external funding was received.

Conflict of interest. The authors declare that they have no conflict of interest.

Ethical approval. This article does not contain any studies with human participants or animals performed by any of the authors.

ACKNOWLEDGMENTS

We thank Dr. Ali Fasihi for his kind advices during statistical analyses of the work.

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