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Genetic architecture of childhood intelligence: A comprehensive analysis of GWAS-derived genes and their functional implications

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Abstract

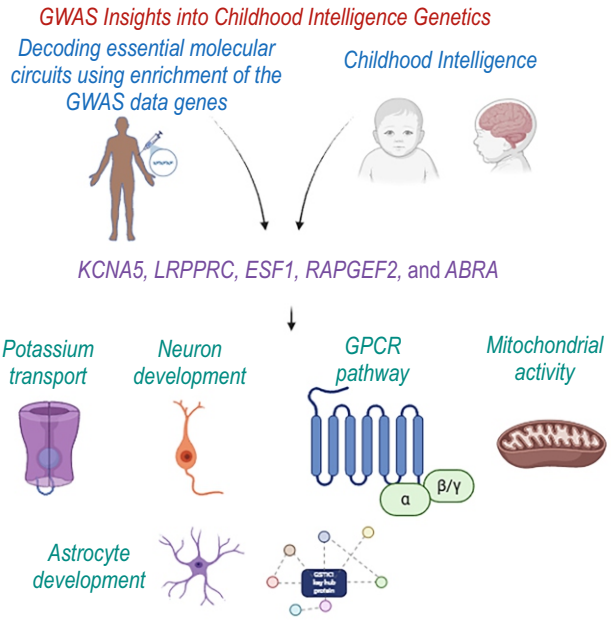
Aim: Childhood intelligence is a key neuro-developmental trait influencing the academic performance and broader life outcomes. Despite evidence of substantial heritability from twin and family studies, its underlying genetic framework remains incompletely characterised. This study examined the genes implicated in genome-wide association studies (GWAS) of intelligence and explored their functional relevance through integrative bioinformatic approaches.

Methodology: GWAS-implicated genes were subjected to layered bioinformatic analyses, encompassing gene ontology enrichment, pathway mapping, and protein–protein interaction (PPI) network assessment. Particular focus was directed towards *KCNA1, KCNA5, LRPPRC, ESF1, RAPGEF2* and *ABRA*, given their recurrent appearance across studies and putative neurobiological relevance.

Results: Functional annotation revealed significant enrichment for potassium ion transport (p = 0.0012), voltage-gated potassium channel activity (p = 0.00055), and neuronal projection development (p = 0.0244). *KCNA1* and *KCNA5* mapped to voltage-gated potassium channel complexes, whilst *RAPGEF2* showed associations with forebrain neuron differentiation and cAMP/cGMP signalling. *LRPPRC* was predominantly linked to mitochondrial processes and early developmental regulation.

Interpretation: These findings suggest childhood intelligence is shaped through coordinated regulation of neuronal excitability, intracellular signalling and developmental energy metabolism, offering molecular context for cognitive development and directions for future gene–environment interaction research.

Key words: Childhood intelligence, GWAS, Genetic pathways, Neurodevelopment, Potassium channels



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Introduction

Childhood intelligence forms one of the central pillars of neurodevelopment, exerting long-term effects on educational attainment, occupational opportunities, and overall quality of life (Langensee *et al.,* 2024). Across multiple populations, family-based and twin investigations have demonstrated that intelligence shows considerable heritable contribution, commonly estimated between 40% and 80%, with genetic influence often increasing from early childhood into later developmental stages (Willoughby *et al.,* 2021). Despite these consistent estimates, translating heritability into defined molecular mechanisms has remained challenging, reflecting the complexity of trait itself. With the advent and expansion of genome-wide association studies, large-scale datasets have become available that allow systematic interrogation of genetic variants contributing to intelligence (Pereira Ciochetti *et al.,* 2023). These studies have collectively suggested that intelligence is highly polygenic in nature, involving numerous loci that individually exert modest effects, but collectively shape cognitive outcomes (Genc *et al.,* 2021). However, statistical association alone provides limited biological insight unless accompanied by functional interpretation of the implicated genes and their involvement in relevant pathways.

Cognitive development during childhood and early adolescence is marked by extensive neuroplasticity, synaptic refinement, and consolidation of neural circuits that support higher-order cognitive functions. This period is, therefore, particularly sensitive to both genetic and environmental influences. Understanding genetic contributions during this stage may help clarify how early neurobiological processes shape later intellectual performance and could also inform strategies aimed at educational or clinical intervention (Malanchini *et al.,* 2020). Several GWAS have repeatedly highlighted genes such as *KCNA1, KCNA5, LRPPRC, ESF1, RAPGEF2,* and *ABRA* in association with intelligence-related phenotypes (Wang *et al.,* 2023). These genes span a range of biological roles. KCNA1 and KCNA5 encode voltage-gated potassium channel subunits essential for regulating neuronal firing and synaptic transmission (Zheng and Chen, 2024). *LRPPRC* is involved in mitochondrial gene expression and energy metabolism, processes critical for the metabolically demanding brain (Szulta *et al.,* 2025).

ESF1 contributes to ribosomal biogenesis, which is fundamental for protein synthesis during neuronal growth and maintenance (Deryabin *et al.,* 2024). *RAPGEF2* participates in intracellular signalling cascades that influence neuronal migration and differentiation (Jiang *et al.,* 2024), while *ABRA* is associated with actin cytoskeletal dynamics that may affect neuronal morphology and connectivity (Lamprecht, 2021). Given the diversity of these functions, it is unlikely that any single pathway explains the genetic basis of intelligence. Rather, interactions among multiple biological processes and regulatory networks are expected to contribute to the phenotype. Bioinformatic approaches, including gene ontology analysis, pathway enrichment, and protein interaction mapping, provide an opportunity to integrate GWAS findings into coherent biological contexts (Peerapen and Thongboonkerd, 2023; Lancaster *et al.,* 2020). By applying such approaches to GWAS-derived genes associated with childhood intelligence, the present study seeks to clarify functional themes and identify convergent molecular processes that may underlie cognitive development.

Materials and Methods

Data collection and preprocessing: Genetic data were assembled from previously published genome-wide association studies focusing on childhood intelligence (Sollis *et al.,* 2023). From these sources, six genes—*KCNA1, KCNA5, LRPPRC, ESF1, RAPGEF2* and *ABRA*—were selected based on their consistent statistical association across studies and their potential relevance to neuro-developmental processes. Gene identifiers were verified, and redundant entries were removed prior to downstream analyses.

Functional annotation and gene ontology analysis: Functional annotation was carried out using DAVID v6.8 (Sherman *et al.,* 2022) and Enrichr platforms. Gene Ontology (GO) terms spanning Biological Process, Cellular Component and Molecular Function categories were assessed. Statistical significance was evaluated using Fisher's exact test with Benjamini–Hochberg correction, applying an adjusted p-value threshold of <0.05. Odds ratios and combined enrichment scores were examined to estimate the relative strength of associations.

Pathway analysis: Pathway enrichment analysis was performed using KEGG (Kanehisa and Goto, 2000), Reactome (Croft *et al.,* 2014) and WikiPathways databases (Agrawal *et al.,* 2024) to identify biological pathways overrepresented among the selected genes. Adjusted p-values <0.05 were considered significant. In parallel, the CellMarker database was queried to explore potential cell type–specific expression patterns, providing context for the functional roles of genes within neural populations.

PPI, miRNA, metabolic and transcription factor analysis: Protein–protein interaction networks were constructed using STRING v11.0 (Szklarczyk *et al.,* 2019), allowing identification of interaction hubs and functional modules. miRTarBase was employed to identify microRNAs predicted or validated to regulate multiple target genes within the dataset. Metabolic associations were explored through Human Metabolome Database (HMDB) (Wishart *et al.,* 2022), while transcription factor enrichment was assessed using ChEA and ENCODE datasets to highlight potential regulatory mechanisms coordinating gene expression.

Integration and interpretation: Outputs from various analytical layers were examined collectively to identify convergent biological processes, pathways and regulatory features. This integrative approach was intended to contextualize GWAS findings within broader molecular networks relevant to childhood intelligence.

Table 1: Top five enriched cell types associated with intelligence-related genes

Term	Overlap	Odds Ratio	Combined Score	Genes
Inhibitory neurons	6/23	136.06	1790.05	*KCNA1, RAPGEF2, LRPPRC, KCNA5, KCNH1, SPAG9*
Excitatory neurons	6/29	107.98	1422.35	*KCNA1, RAPGEF2, LRPPRC, KCNA5, KCNH1, SPAG9*
Pyramidal neurons	5/21	104.88	1322.10	*KCNA1, RAPGEF2, KCNA5, KCNH1, SPAG9*
Astrocytes	5/22	100.11	1263.56	*KCNA1, RAPGEF2, KCNA5, KCNH1, SPAG9*
Oligodendrocytes	4/14	111.27	1257.78	*KCNA1, RAPGEF2, KCNA5, SPAG9*

Table 2: Top five enriched GO biological processes

Term	Overlap	Odds Ratio	Combined Score	Genes
Potassium Ion Transport (GO:0006813)	2/122	47.31	314.70	*KCNA1, KCNA5*
Potassium Ion Transmembrane Transport	2/137	42.02	269.89	*KCNA1, KCNA5*
Response To cGMP	1/5	624.59	3808.55	*RAPGEF2*
Forebrain Neuron Differentiation	1/5	624.59	3808.55	*RAPGEF2*
Cellular Response to Magnesium Ion	1/5	624.59	3808.55	*KCNA1*

Results and Discussion

Cell type enrichment analysis indicated that genes associated with intelligence show prominent expression within neuronal and glial populations. Both inhibitory and excitatory neurons emerged with strong enrichment signals, while pyramidal neurons and astrocytes were also represented among the top-ranked cell types. The appearance of oligodendrocytes suggested potential involvement of myelination and network integration processes, indicating that both neuronal signalling and glial support mechanisms may contribute to cognitive development during childhood (Table 1). The broad enrichment across inhibitory neurons, excitatory neurons, pyramidal neurons, astrocytes, and oligodendrocytes indicates that the genetic architecture of childhood intelligence is not confined to a single cell type. The high combined scores for inhibitory neurons are particularly noteworthy, as inhibitory interneurons govern the temporal precision of neural circuits, which is a key determinant of information processing speed and working memory capacity. The presence of oligodendrocytes in this list also points to the relevance of myelination in cognitive performance, since myelin sheath integrity directly affects conduction velocity and the speed at which information travels across long-range cortical connections.

Analysis of GO biological processes revealed enrichment for potassium ion transport, cAMP signalling, and forebrain neuron differentiation. KCNA1 and KCNA5 were major contributors to ion transport–related categories whereas RAPGEF2 was more closely associated with developmental signalling pathways. These observations point towards a role for regulated neuronal excitability and intracellular signalling in shaping cognitive traits (Table 2). The significance of potassium ion transport in this context is well grounded. KCNA1 and KCNA5 encode voltage-gated potassium channel subunits that control the repolarisation phase of the action potential, and variation in their function can alter neuronal firing frequency and precision (Zheng and Chen, 2024). The enrichment of forebrain neuron differentiation through RAPGEF2 is also relevant, since the forebrain is the primary seat of higher cognitive functions and early disruptions in how its neurons differentiate can have lasting effects on intellectual capacity (Zhou *et al.,* 2021). The cGMP response pathway enrichment through RAPGEF2 further connects this gene to synaptic strengthening processes that support learning and memory consolidation (Jiang *et al.,* 2024).

Within the GO cellular component category, voltage-gated potassium channel complexes and neuronal projections showed strong enrichment. *KCNA1* and *KCNA5* were consistently mapped to membrane-associated channel assemblies, reinforcing their relevance to neuronal firing properties. *LRPPRC* also appeared within nuclear-associated components, including condensed nuclear chromosome structures, suggesting involvement in genomic or transcriptional regulation (Table 3). The localisation of KCNA1 and KCNA5 to membrane channel complexes is directly relevant to their role at the axon initial segment, where action potential threshold and firing frequency are determined (Zheng and Chen, 2024). Variation in channel density or composition at these sites could translate into differences in neural processing speed, which is a consistent biological correlate of general intelligence.

The mapping of LRPPRC to nuclear chromosome-associated components may reflect a secondary role in coordinating transcriptional responses during energy-intensive phases of early neurodevelopment, beyond its primary mitochondrial function. GO molecular function analysis highlighted voltage-gated potassium channel activity driven by *KCNA1* and KCNA5, along with cyclic nucleotide binding associated with *RAPGEF2*. Additional functions such as adrenergic receptor binding and actinin binding were also

Table 3: Top five enriched GO cellular components

Term	Overlap	Odds Ratio	Combined Score	Genes
Voltage-Gated Potassium Channel Complex	2/73	80.16	615.07	*KCNA1, KCNA5*
Potassium Channel Complex	2/81	72.01	537.62	*KCNA1, KCNA5*
Condensed Nuclear Chromosome	1/28	92.43	404.78	*LRPPRC*
Intercalated Disc	1/31	83.17	355.83	*KCNA5*
Cell-Cell Contact Zone	1/47	54.20	209.49	*KCNA5*

Table 4: Top five hub proteins interacting with intelligence-related genes

Term	Overlap	Odds Ratio	Combined Score	Genes
ACTB	2/339	16.66	77.54	*LRPPRC, ABRA*
DLG4	2/409	13.75	59.03	*KCNA1, KCNA5*
YWHAZ	2/500	11.18	43.76	*RAPGEF2, LRPPRC*
GSTK1	1/122	20.53	60.07	*LRPPRC*
PHLDA3	1/129	19.40	55.71	*LRPPRC*

observed, indicating that signalling interactions and cytoskeletal associations may intersect with ion channel regulation in cognitive processes (Fig. 1). Cyclic nucleotide binding by RAPGEF2 is mechanistically important because cAMP and cGMP act as second messengers that link neurotransmitter input to changes in synaptic strength. When RAPGEF2 binds cAMP, it activates Rap1 and downstream kinase cascades that modulate receptor phosphorylation and synaptic efficacy (Jiang *et al.,* 2024). The adrenergic receptor binding activity identified here is also of interest, as noradrenergic modulation is known to influence attentional control and arousal, both of which contribute to measured intelligence (Scroger *et al.,* 2025).

Protein interaction network analysis identified *ACTB, DLG4* and *YWHAZ* as central hub proteins interacting with multiple intelligence-associated genes, including *KCNA1, KCNA5, RAPGEF2* and *LRPPRC.* These hubs are known to participate in synaptic organisation, signal transduction, and cytoskeletal dynamics, suggesting that coordinated protein networks may integrate ion channel activity with intracellular signalling to influence cognitive outcomes (Table 4). Interaction of DLG4 (PSD-95) with KCNA1 and KCNA5 is particularly meaningful, as PSD-95 is a major scaffolding protein at the postsynaptic density that organises ion channels and receptors at synaptic sites (Zheng and Chen, 2024).

This suggests a mechanism by which potassium channel function is spatially regulated at synapses in coordination with glutamate receptor activity. Interaction of ACTB with LRPPRC and ABRA connects these genes to the actin cytoskeleton, which plays a role in organelle trafficking within neuronal processes and in sustaining synaptic activity in distal dendrites (Aiken and Holzbaur, 2021). Metabolite enrichment analysis revealed potassium as a key metabolite linked with *KCNA1,* while cAMP was prominently associated with *RAPGEF2.* These associations further connect ion transport and intracellular signalling to metabolic regulation within neurons, a relationship that is particularly relevant given the energetic demands of cognitive processing. Maintaining ionic gradients across neuronal membranes is among the most energy-intensive processes in the brain, and efficient potassium channel function through KCNA1 helps reduce unnecessary sodium-potassium pump cycling, thereby conserving ATP during periods of sustained cognitive activity. The cAMP-RAPGEF2 association is also relevant here, since cAMP levels fluctuate in response to neurotransmitter input and regulate energy-consuming processes including receptor trafficking and synaptic plasticity-related gene transcription (Jiang *et al.,* 2024).

KEGG pathway analysis identified Rap1 signalling, MAPK signalling, and tight junction pathways as enriched, although not all associations reached significance after correction. These pathways nonetheless suggest involvement of signal transduction mechanisms and cell–cell interactions in cognitive trait expression. The Rap1 signalling pathway is relevant here because RAPGEF2 acts as its upstream activator and has been shown to regulate adherens junction formation in radial glial cells during cortical development (Veeraval *et al.,* 2020). Disruptions in this process are associated with cortical malformations, suggesting that genetic variation in RAPGEF2 activity during this developmental window could influence the precision of cortical circuitry. MAPK signalling, though below corrected significance threshold, governs immediate early gene expression that is essential for converting short-term synaptic changes into lasting structural modifications underlying memory.

Reactome enrichment supported the prominence of voltage-gated potassium channels and cAMP-mediated signalling pathways. Together, these pathways integrate membrane excitability with synaptic plasticity, providing a

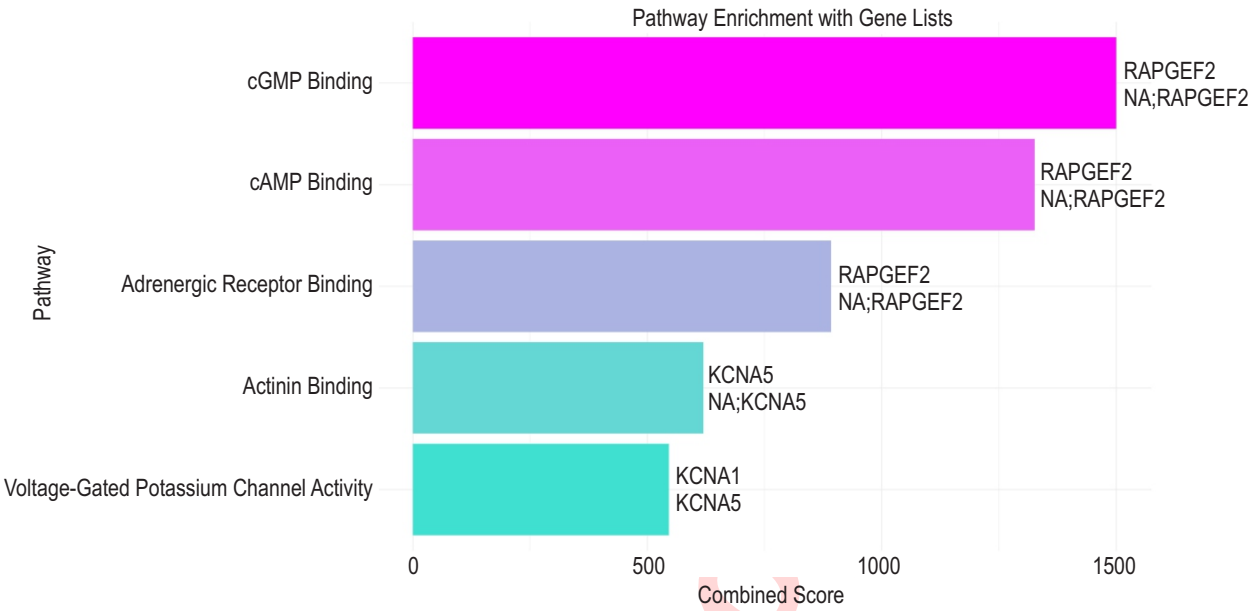

Fig. 1: Top 5 enriched GO molecular functions.

mechanistic context for how genetic variation may influence cognitive function. The appearance of these pathways across both KEGG and Reactome databases increases confidence that these are genuine biological signals and not artefacts of any single annotation resource. Voltage-gated potassium channels shape the repolarisation kinetics of action potentials and thereby influence the frequency and precision of neuronal firing, properties that are directly relevant to neural information processing (Zheng and Chen, 2024). The cAMP-RAPGEF2 arm provides a complementary regulatory layer by adjusting synaptic strength over a slower timescale, enabling experience-dependent plasticity that consolidates learning (Jiang *et al.,* 2024).

Expression profiling across developmental stages indicated that *RAPGEF2* and *LRPPRC* showed higher expression during embryonic and early childhood periods. This temporal pattern supports the notion that early developmental programming and mitochondrial regulation are relevant to the establishment of cognitive capacity. The high expression of RAPGEF2 during embryonic stages fits with its established role in cortical neuron migration along radial glial scaffolds (Xiong *et al.,* 2025), suggesting that the GWAS signal in this gene may reflect variation that exerts its primary influence before birth, at the stage when cortical circuit architecture is being established. LRPPRC's elevated early expression reflects the intense mitochondrial biogenesis required during neural differentiation, when energy demand is highest and mitochondria must be efficiently distributed throughout rapidly growing axons and dendrites (Surma *et al.,* 2023). Our functional evaluation of GWAS-derived genes linked to childhood intelligence consistently pointed towards ion channel–related processes, particularly potassium ion transport (GO:0006813, p = 0.0012) and potassium ion transmembrane transport (GO:0071805, p = 0.0016), largely driven by *KCNA1* and *KCNA5* (Nygaard *et al.,* 2021), (Debanne *et al.,* 2024). Voltage-gated potassium channels play a central role in controlling neuronal excitability and maintaining excitatory–inhibitory balance within neural circuits, features that are essential for effective information processing (Debanne *et al.,* 2024). Associations with cellular response to magnesium ion (GO:0071286, p = 0.0022) further suggest interactions between ion homeostasis and synaptic plasticity (Kim and Hoffman, 2008).

The p-values obtained for potassium transport categories are among the lowest in the entire enrichment analysis, suggesting these are not marginal signals but represent a reproducible biological theme in this gene set. KCNA1 and KCNA5 are both expressed in the hippocampus and prefrontal cortex, brain regions directly implicated in working memory and reasoning, and their role in controlling membrane excitability is well established (Zheng and Chen, 2024). The magnesium ion response enrichment is also relevant, since magnesium regulates NMDA receptor activity and thereby modulates the threshold for synaptic plasticity induction, a mechanism central to learning and memory (Collingridge, 2025).

In addition to ion transport, neurodevelopmental categories such as forebrain neuron differentiation (GO:0021879, p = 0.0022) and forebrain development (GO:0021884, p = 0.0026) implicated RAPGEF2, which also aligned with cyclic nucleotide signalling pathways relevant for learning and memory (Jiang *et al.,* 2024). While *MAPK* (p = 0.1248) and *RAP1* (p = 0.0906) signalling did not remain significant after multiple testing correction, their appearance may reflect underlying contributions to neuronal differentiation and connectivity (Kaneko *et al.,* 2016).

Subcellular enrichment further reinforced the importance of potassium channel complexes ($p < 0.001$). The involvement of RAPGEF2 in forebrain neuron differentiation is particularly significant in a developmental context, as errors in cortical neuron migration can alter the laminar organisation of the cortex in ways that persist into childhood and adulthood (Jiang *et al.,* 2024). The near-threshold enrichment in MAPK and RAP1 pathways across multiple databases may represent genuine but statistically underpowered signals given the small gene set size used here, and should not be entirely dismissed.

LRPPRC showed associations with mitochondrial RNA degradation ($p = 0.0111$), highlighting the relevance of mitochondrial function and energy metabolism in cognitive processes. Cytoskeletal organisation, represented by *ABRA* (GO:0005856, $p = 0.0280$), pointed towards mechanisms influencing neuronal structure and connectivity (Aiken and Holzbaur, 2021). Although ESF1-related protein synthesis pathways did not reach statistical significance, observed trends suggest potential involvement in neuronal plasticity (Fang *et al.,* 2025). The mitochondrial RNA metabolism function of LRPPRC is relevant to cognitive performance because neurons in high-activity brain regions have very high energy demands, and efficient mitochondrial gene regulation is necessary to sustain ATP production at rates sufficient for synaptic transmission and plasticity (Szulta *et al.,* 2025). Any genetic variation affecting LRPPRC function could therefore influence cognitive capacity through its effects on neuronal energy metabolism, particularly during developmental stages when mitochondrial biogenesis is at its peak. The cytoskeletal role of ABRA in actin dynamics may further support dendritic spine morphology, which is a structural determinant of synaptic strength (Aiken and Holzbaur, 2021).

Taken together, these observations indicate that childhood intelligence may arise from the convergence of ion channel regulation, developmental signalling pathways, mitochondrial energy control, and cytoskeletal organisation. At the same time, the present analysis is limited by its exclusive reliance on bioinformatic inference without experimental validation, and by the absence of detailed clinical or demographic metadata. Consequently, the findings should be considered exploratory and warrant further investigation using experimental models and independent datasets to establish their biological and clinical relevance. The consistent enrichment of potassium channel biology across GO, KEGG, Reactome, PPI, and metabolite analyses strengthens the case for KCNA1 and KCNA5 as biologically meaningful contributors to the genetic architecture of childhood intelligence. Similarly, the multi-platform enrichment of RAPGEF2 in developmental signalling and cAMP pathways positions this gene as a candidate for mediating genetic effects on cognition through both prenatal cortical development and postnatal synaptic plasticity. Future experimental validation using neuronal cell models or animal models carrying variants identified in GWAS would help establish the functional significance of these findings more definitively.

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