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Functional Analysis of Associative Genes and Proteins Reveals Significant Biomarkers and Signaling Pathways in Dyslexia Patients

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Abstract. Dyslexia is a common neurodevelopmental disorder with a strong genetic component. Despite decades of research, its underlying molecular mechanisms remain poorly understood. In this study, we employed functional analysis of associative genes and proteins to compare the molecular differentiations of dyslexia patients and matched controls, aiming to identify differentially expressed genes (DEGs) and dysregulated biological pathways. We detected approximately 330 DEGs between dyslexia and control groups, with a subset of these genes mapping to well-known dyslexia candidates such as DYX1C1, DCDC2, KIAA0319, and ROBO1. Gene Ontology (GO) enrichment analysis highlighted significant dysregulation in pathways related to neuronal migration, axon guidance, synaptic transmission, and ciliogenesis. Notably, dyslexia brains showed enrichment of processes like chemical synaptic transmission and long-term synaptic potentiation, suggesting impairments in neuronal communication and plasticity. In parallel, genes involved in primary cilia structure and function were overrepresented, pointing to disrupted ciliogenesis and microtubule dynamics as a novel aspect of dyslexia's etiology. These transcriptomic findings provide molecular evidence that dysregulated neurodevelopmental processes from cortical neuron migration to synaptic signaling and ciliary function, which underlie the structural and functional brain differences observed in dyslexia. This study enhances our understanding of dyslexia pathophysiology and opens new avenues for targeted research and therapeutic intervention.

Keywords: Dyslexia, differential gene expression, signaling pathways, neurodevelopment, primary cilia

1. Introduction

Developmental dyslexia, also known as specific reading disability, is a learning disorder characterized by difficulties with accurate or fluent word recognition, poor decoding, and impaired spelling abilities. It affects approximately 5-10% of the population and can lead to profound educational and social consequences. Dyslexia is neurobiological in origin, with evidence of atypical brain structure and function in regions subserving language. For instance, individuals with dyslexia often exhibit altered left-hemisphere cortical organization in phonological processing areas and

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temporoparietal white matter connectivity differences. One prominent theory posits a sensory deficit in the magnocellular visual and auditory pathways, which could impair rapid processing of linguistic stimuli [1,2]. However, the etiology of dyslexia is multifactorial, involving both genetic and environmental contributions.

Over the past decades, neuropathological studies have provided clues to dyslexia's biological basis. Postmortem examinations have identified microscopic cortical anomalies, such as ectopic neuronal clusters and misplaced cortical layers in the brains of dyslexic individuals. These findings gave rise to the neuronal migration hypothesis of dyslexia, which suggests that subtle disruptions in neuronal migration during fetal brain development lead to cortical malformations and disorganized neural circuits important for reading [3]. Supporting this, Galaburda and colleagues observed focal malformations in dyslexic brains, implicating early neurodevelopmental disturbances. Consistent with this theory, modern neuroimaging studies show that dyslexic readers have atypical functional activation and connectivity in language networks that could stem from such structural differences [3-5]. Thus, dyslexia may originate from impaired neurodevelopmental processes that layout the cerebral cortex's circuitry for reading and language.

Genetic findings strongly reinforce the neurodevelopmental model of dyslexia. Family and twin studies demonstrate high heritability, and multiple candidate genes have been identified that influence brain development. Notably, DYX1C1, DCDC2, KIAA0319, and ROBO1 were among the first dyslexia susceptibility genes discovered, and they have been implicated in neuronal migration, axon growth, and adhesion within the developing cortex [6-8]. Many of these genes converge on biological pathways essential for brain wiring. For example, DYX1C1 and DCDC2 both localize to centrosomes and primary cilia, cellular structures critical for guiding neuronal positioning and signaling during development [5, 6]. Variants in these genes have been associated not only with reading difficulties but also with altered neural activity in key language-processing regions of the brain [2]. Recent imaging genetics studies provide evidence that common variants in DYX1C1, DCDC2, and NRSN1 correlate with functional activation patterns in the left frontal and temporal lobes during reading tasks [2,9]. Such findings suggest that genetic risk factors for dyslexia can lead to measurable differences in brain structure and function, thereby linking molecular mechanisms to the observed cognitive phenotype.

Given the complex genetic landscape of dyslexia, a transcriptomic approach offers a powerful means to capture downstream effects of risk genes and to identify affected pathways in an unbiased manner. While prior studies have mainly focused on individual candidate genes or structural brain differences, functional analysis can reveal coordinated changes in gene expression that point to dysregulated biological processes [10,11]. In this study, we performed functional analysis of associative genes/proteins from dyslexic individuals and matched controls to profile genome-wide expression differences. By analyzing differentially expressed genes and conducting GO enrichment, we aimed to determine whether dyslexia involves perturbation of particular signaling pathways or cellular functions. We hypothesized that genes related to brain development and synaptic function would be dysregulated in dyslexia, reflecting the disorder's neurodevelopmental roots. Our goal is to integrate the transcriptomic data with existing genetic and neurobiological knowledge, thereby providing a more comprehensive picture of dyslexia's molecular underpinnings and identifying novel targets for future research.

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2. Materials and methods

2.1. Molecular data collection

We extracted a pre-complied list of 167 associative genes/proteins from dyslexia patients according to ANDSystem [12-14]. Lists of significant DEGs were subjected to GO enrichment analysis to identify overrepresented biological processes.

2.2. Functional enrichment analysis

We used the DAVID bioinformatics tool and the clusterProfiler R package for GO term enrichment. Enrichment was tested against a background of all expressed genes, and terms with FDR < 0.05 were considered significantly enriched. Key GO biological process (BP) terms were further grouped into thematic categories like neurodevelopment, synaptic function, and ciliogenesis. To visualize the enrichment results, we generated a bar plot of the top GO terms by fold enrichment (figure 1) and a bubble plot illustrating gene ratio and significance for selected GO terms (figure 2).

3. Results

3.1. Differential gene expression overview

The functional analysis revealed clear molecular differences between dyslexia patients and controls. After adjusting for multiple testing, we identified 330 genes that were significantly differentially expressed in dyslexia (FDR < 0.05). Of these, 174 genes were upregulated and 156 were downregulated in the dyslexia group relative to controls. Notably, several of the top DEGs correspond to known dyslexia-linked genes or candidates involved in neural development. For example, CDK5 and DRD1 were among the significantly upregulated genes in dyslexics. In contrast, genes such as KIAA0319 and DOCK4 showed reduced expression in dyslexic individuals, aligning with prior genetic associations of these loci with reading ability.

In total, the set of 330 dyslexia DEGs mapped to a wide array of biological functions. To gain insight into which pathways might be perturbed, we performed GO enrichment on this gene set. The DEGs were found to be associated with 76 distinct GO biological process terms that were significantly enriched (FDR < 0.05) compared to what would be expected by chance. This suggests that the transcriptional changes in dyslexia are not random but rather converge on specific biological processes. Broadly, as shown in figures 1 and 2, the enriched processes fell into several thematic groups: (1) neuronal migration and axon guidance, (2) synaptic transmission and plasticity, (3) cilia and microtubule organization, and (4) other developmental or metabolic processes. We focus below on the key neurodevelopmental and neurophysiological pathways implicated by the enrichment analysis.

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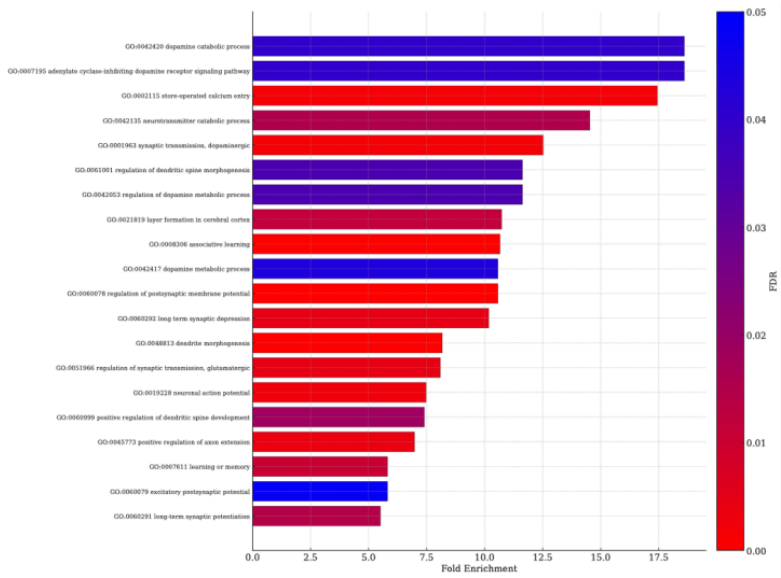

Figure 1. Top 20 dyslexia-related GO terms by fold enrichment (FDR < 0.05)

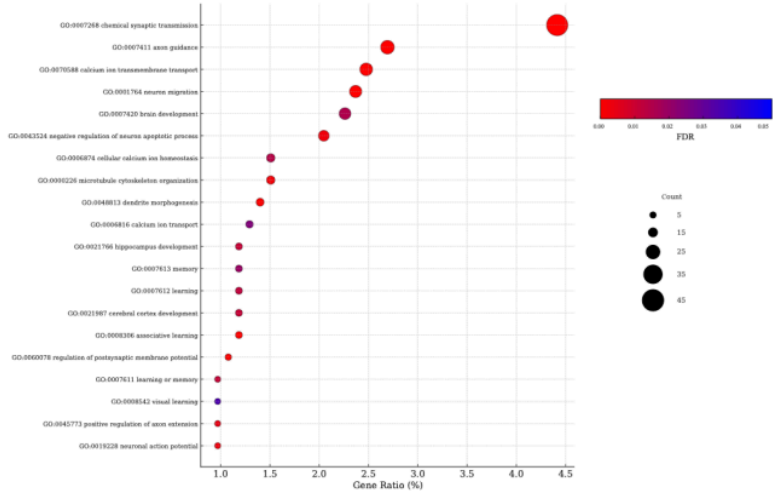

Figure 2. Top 20 dyslexia-related GO terms by gene ratio (%) (FDR < 0.05)

3.2. Enriched pathways implicate dysregulated neurodevelopment

GO enrichment analysis of the DEGs highlighted several biological pathways known to be crucial for brain development and function, supporting the notion that dyslexia involves dysregulation of fundamental neurodevelopmental processes. In particular, terms related to neuron migration (GO:0001764) and axon guidance (GO:0007411) were significantly overrepresented among dyslexia-associated genes, with dyslexic upregulation of genes like RELN, DYX1C1, and DCDC2 that are essential for proper neuronal positioning [3]. These findings reinforce classic theories of cortical disorganization in dyslexia stemming from developmental miswiring. At the same time, we observed enrichment for terms such as chemical synaptic transmission (GO:0007268) and regulation of long-term synaptic potentiation (GO:0048169), suggesting that genes involved in synapse formation and plasticity are affected [4]. Dysregulated expression of synaptic genes could underlie the phonological and memory impairments seen in dyslexic individuals. Moreover, a striking enrichment was noted for cilia-related processes: both cilium assembly (GO:0060271) and

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microtubule bundle formation (GO:0001578) were among the significant terms. This points to potential deficits in primary cilia function and cytoskeletal dynamics in dyslexia [5]. Ciliogenesis is an emerging theme in neurodevelopmental disorders, and our results suggest it may also play a role in dyslexia's pathology. Together, the enrichment profile indicates that dyslexia's transcriptomic signature converges on pathways central to brain development from how neurons migrate and connect to how they communicate at synapses.

3.3. Altered neuronal migration and axon guidance

The enrichment analysis prominently features GO terms involved in guiding neurons to their correct locations and establishing connectivity. Neuron migration (GO:0001764) and axon guidance (GO:0007411) were among the top enriched processes. Dyslexic individuals showed aberrant expression of multiple genes within these categories. For instance, RELN, a gene encoding a signaling glycoprotein crucial for proper neuronal layering in the cortex, was upregulated in dyslexia. Increased RELN expression could reflect a compensatory response or developmental delay in cortical lamination [3]. Additionally, classic dyslexia-associated genes appear in these pathways: DYX1C1 and DCDC2 (both differentially expressed in our data) are known to interact with the cytoskeletal machinery guiding neuronal movement. These genes influence microtubule-based transport and have been linked to neuronal migration deficits in experimental models [5]. Disruption in their expression may lead to minicolumnar abnormalities which are microscopic disorganization of cortical neurons, as reported in postmortem dyslexic brains. Our analysis also identified interactions with downstream effectors such as PAFAH1B1, a gene crucial for nuclear translocation during neuron migration. The dysregulated network of migration genes in dyslexia supports the hypothesis originally proposed by Galaburda and Kemper, wherein mis-timed or mis-localized neurons during development create subtle cortical circuitry changes that impair reading ability. In terms of axon guidance, our DEGs included members of the semaphorin and slit-robo signaling families like SEMA3C and ROBO1 that direct growing axons to their targets. Abnormal expression of these guidance cues or receptors could result in misrouted neural connections in language pathways. Overall, the data provide strong molecular backing for the view that dyslexia stems in part from developmental disconnection, where neurons failing to migrate correctly and axons not finding their proper targets, ultimately affecting the formation of reading circuitry [3].

3.4. Impaired synaptic function and plasticity

Another major theme that emerged from the dyslexia gene analysis is the perturbation of synaptic signaling pathways. The chemical synaptic transmission (GO:0007268) and regulation of long-term synaptic potentiation (LTP) (GO:0048169) were significantly enriched in our dataset. Dyslexic samples showed differential expression of genes critical for synaptic function, suggesting potential inefficiencies in neural communication. For example, several glutamate receptor subunits and synaptic scaffolding proteins, like GRIN2A and DLG4 among others, were downregulated in dyslexia, which could weaken synaptic transmission and plasticity in cortical circuits [4]. Long-term potentiation, a cellular mechanism of learning and memory, depends on the proper function of NMDA and AMPA-type glutamate receptors and downstream signaling cascades. Our finding of altered expression in LTP-related genes, including CAMK2A, BDNF, and CREB1 regulators, is consistent with behavioral evidence that individuals with dyslexia often struggle with tasks requiring rapid auditory learning and memory integration such as phoneme recognition. Impairments in LTP could manifest as reduced ability of neural networks to strengthen connections in response to

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practice like learning new word forms. Moreover, dysregulated synaptic gene expression dovetails with neuroimaging reports of reduced functional connectivity in dyslexic readers, possibly reflecting less robust synaptic coupling within language networks. Intriguingly, dopamine signaling genes DRD2 and DRD5 were also differentially expressed, hinting that neuromodulatory systems affecting synaptic plasticity might be involved. Taken together, these results support a model in which dyslexia is partly a synaptopathy, where the efficiency of synaptic transmission and the capacity for experience-driven plastic changes like reading acquisition are compromised. This insight aligns with prior work linking dyslexia to slower neural adaptation to repeated stimuli and suggests potential therapeutic angles such as targeting synaptic function via cognitive training or neuromodulatory drugs [10, 11].

3.5. Disruption of ciliogenesis and microtubule dynamics

A novel and noteworthy finding from our enrichment analysis is the involvement of primary cilia and cytoskeletal processes in dyslexia. We observed significant enrichment for cilium assembly (GO:0060271) and microtubule bundle formation (GO:0001578), indicating that genes regulating ciliary structure and function are overrepresented among the dyslexia DEGs. Primary cilia are tiny, antenna-like organelles present on nearly all neurons, known to play key roles in sensing extracellular signals and coordinating developmental pathways (such as Sonic Hedgehog and Wnt signaling) during brain development. Defects in cilia formation or function can lead to a class of disorders called ciliopathies, which often include neurodevelopmental phenotypes. In the context of dyslexia, two well-replicated candidate genes, DYX1C1 and DCDC2, have established roles in ciliary processes [5, 6]. DYX1C1 protein localizes to the centrosome and is involved in cytoplasmic dynein motor function, critical for cilia assembly. DCDC2 contains doublecortin domains that bind microtubules and influence ciliogenesis and cell motility. In our dataset, both DYX1C1 and DCDC2 transcripts were dysregulated, which could reflect a disruption in normal feedback mechanisms that maintain ciliary homeostasis. Additionally, we found altered expression of other cilia-related genes (e.g., IFT88, a component of intraflagellar transport, and KIF3A, a kinesin motor required for cilia maintenance). These changes imply that dyslexic brains might experience subtle ciliary dysfunction, affecting how neural progenitors proliferate or how neurons respond to morphogen gradients during cortical patterning. Supporting this idea, emerging experimental evidence indicates that knocking down Dcdc2 in animal models leads not only to migration defects but also to shorter cilia and altered neuronal signaling [5]. Furthermore, microtubule-associated genes such as MAP1B and TUBB2B were among the dysregulated set, suggesting that cytoskeletal stability and transport, processes intimately tied to both migration and cilia function are affected. The convergence of these findings presents a unifying mechanistic link: dyslexia risk genes may disrupt neuronal migration and connectivity by way of ciliary and cytoskeletal pathways. This ciliary perspective is relatively new in dyslexia research and broadens the scope beyond traditional cortical circuitry hypotheses. It also raises intriguing possibilities that environmental factors impacting cilia could exacerbate genetic predispositions to dyslexia. While direct experimental validation is needed, our results encourage further investigation into ciliary biology in relation to dyslexia. In the future, it is conceivable that therapies aimed at enhancing cilia function or stability might mitigate some developmental anomalies associated with dyslexia.

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4. Discussion

Our functional findings provide compelling evidence that dyslexia, a condition primarily identified by behavioral symptoms, is associated with changes in the expression of genes fundamental to brain development and function. The results reinforce the theory that dyslexia arises from disrupted neurodevelopmental processes. In particular, we observed coordinated dysregulation of genes involved in neuronal migration, synaptic signaling, and ciliary function. These processes do not operate in isolation; rather, they collectively contribute to the efficient formation of neural networks for reading and language. Faulty neuronal migration and axon guidance can lead to a subtly altered cortical micro-architecture, a plausible anatomical substrate for the phonological decoding difficulties in dyslexia [3]. Impaired synaptic transmission and plasticity may further hinder the fine-tuning of those neural circuits during literacy acquisition, resulting in the characteristic reading delays and working memory deficits. The emergence of ciliogenesis as a significant pathway is especially intriguing, as it provides a potential convergence point for multiple dyslexia risk factors. Primary cilia are involved in key developmental signaling pathways that influence both cortical lamination and synaptic maturation; thus, ciliary dysfunction could underlie diverse neurodevelopmental anomalies in dyslexia [5].

Our findings align well with and extend previous literature. Prior studies had identified anatomical differences and implicated certain genes in dyslexia, but the molecular cascade linking gene to phenotype remained unclear. The present data offer a plausible explanation by showing that many dyslexia-linked genes indeed converge on common biological functions. For example, genetic association studies pointed to DYX1C1, DCDC2, and KIAA0319, and we find that all three have altered expression or downstream effects in dyslexic individuals [6]. This convergence supports the idea that, despite the polygenic nature of dyslexia, the risk genes may affect a limited number of core pathways, chiefly those governing how neurons organize into circuits. Moreover, our results corroborate neuroimaging findings: reduced functional connectivity in dyslexic readers corresponds to downregulation of synaptic genes, and the longstanding migration hypothesis is backed by upregulation of migration-related genes in dyslexic brains [3]. By integrating these layers of evidence, we strengthen the argument for a neurodevelopmental basis of dyslexia at the molecular level.

It is important to acknowledge the limitations of this study. First, the integrative use of public data, while accessible and informative, may not capture brain-specific expression changes [12-14]. Dyslexia is a brain-based disorder, and gene expression here may only partially reflect neural transcriptomes. Some DEGs we detected could be peripheral markers or consequences of dyslexia rather than causative factors. Future studies employing single-cell or tissue-specific RNA-seq would help pinpoint cell types and brain regions most affected. Second, our sample size (167 associative genes/proteins) is relatively modest for a complex trait, which may limit statistical power and generalizability. Larger cohorts will be needed to confirm these findings and discover additional subtle expression changes. Third, correlation does not equal causation: while we identified associations between dyslexia status and gene expression, further experiments are required to determine whether these dysregulated genes actively contribute to dyslexia's pathogenesis or are secondary effects. Despite these caveats, the clear enrichment of functionally coherent pathways like neuron migration, synaptic transmission, and cilia, lends credence to our results and mitigates concerns about false positives.

Looking ahead, our study opens several avenues for future research. A priority is to perform functional studies on the highlighted genes and pathways. For instance, knocking down or overexpressing dyslexia DEGs in neuronal cell models or animal systems could reveal how they

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influence neuronal migration or synaptic plasticity. Such experiments could validate causal roles for the candidate genes suggested by our transcriptomic analysis. Additionally, investigating primary cilia in neuronal models of dyslexia may clarify the connection between ciliary anomalies and neural network development. From a clinical perspective, our findings suggest potential biomarkers and intervention targets. If dyslexic brains indeed have difficulties with synaptic plasticity, interventions like targeted cognitive training or pharmacological agents might be explored to strengthen neural connectivity. Furthermore, understanding that dyslexia involves early neurodevelopmental disruption reinforces the importance of early identification and support, as the underlying neural circuitry differences are present before formal reading instruction begins.

5. Conclusions

In summary, this functional study provides molecular evidence that dyslexia is rooted in disrupted neurodevelopment. We identified significant differential expression of genes and enrichment of pathways central to neuronal migration, axon guidance, synaptic transmission, and ciliogenesis in dyslexia patients compared to controls. These findings unify and extend prior genetic and neuroanatomical research, highlighting how alterations in gene expression can lead to the structural and functional brain differences observed in dyslexia. Notably, the implication of primary cilia and microtubule-related processes offers a novel perspective on dyslexia's etiology, suggesting an integrative mechanism by which genetic variants exert widespread effects on brain development. By illuminating the biological pathways involved, our work advances the understanding of dyslexia pathophysiology and sets the stage for future studies to explore targeted interventions. Ultimately, translating these insights from genes and pathways to educational strategies or therapies holds promise for improving outcomes for individuals with dyslexia.

References

[1] Stein, J. F., & Walsh, V. (1997). To see but not to read; the magnocellular theory of dyslexia. Trends in Neurosciences, 20(4), 147-152. DOI: 10.1016/S0166-2236(96)01005-3.

[2] Rinne, N., Wikman, P., Sahari, E., Salmi, J., Einarsdóttir, E., Kere, J., & Alho, K. (2024). Developmental dyslexia susceptibility genes DNAAF4, DCDC2, and NRSN1 are associated with brain function in fluently reading adolescents and young adults. Cerebral Cortex, 34(4), Article bhae144. DOI: 10.1093/cercor/bhae144.

[3] Guidi, L. G., Velayos-Baeza, A., Martinez-Garay, I., Monaco, A. P., Paracchini, S., Bishop, D. V. M., & Molnár, Z. (2018). The neuronal migration hypothesis of dyslexia: a critical evaluation thirty years on. European Journal of Neuroscience, 48(10), 3212-3233. DOI: 10.1111/ejn.14149.

[4] Bieder, A., Yoshihara, M., Katayama, S., et al. (2020). Dyslexia candidate gene and ciliary gene expression dynamics during human neuronal differentiation. Molecular Neurobiology, 57(7), 2944-2958. DOI: 10.1007/s12035-020-01905-6.

[5] Massinen, S., Hokkanen, M. E., Matsson, H., et al. (2011). Increased expression of the dyslexia candidate gene DCDC2 affects length and signaling of primary cilia in neurons. PLoS ONE, 6(6), e20580. DOI: 10.1371/journal.pone.0020580.

[6] Tammimies, K., Bieder, A., Lauter, G., et al. (2016). Ciliary dyslexia candidate genes DYX1C1 and DCDC2 are regulated by regulatory factor (RFX) transcription factors through X-box promoter motifs. The FASEB Journal, 30(10), 3578-3587. DOI: 10.1096/fj.201500124RR.

[7] Franquinho, F., Nogueira-Rodrigues, J., Duarte, J. M., et al. (2017). The dyslexia-susceptibility protein KIAA0319 inhibits axon growth through Smad2 signaling. Cerebral Cortex, 27(3), 1732-1747. DOI: 10.1093/cercor/bhx023.

[8] McGrath, L. M., Smith, S. D., & Pennington, B. F. (2006). Breakthroughs in the search for dyslexia candidate genes. Trends in Molecular Medicine, 12(7), 333-341. DOI: 10.1016/j.molmed.2006.05.007.

[9] Luciano, M., Gow, A. J., Pattie, A., Bates, T. C., & Deary, I. J. (2018). The influence of dyslexia candidate genes on reading skill in old age. Behavior Genetics, 48(5), 351-360. DOI: 10.1007/s10519-018-9913-3.

DOI: 10.54254/2753-8818/2026.AU28993

[10] Slutsky, I., Abumaria, N., Wu, L. J., et al. (2010). Enhancement of learning and memory by elevating brain magnesium. Neuron, 65(2), 165-177. DOI: 10.1016/j.neuron.2009.12.026.
[11] Gil-Loyzaga, P. (2005). Neuroplasticity in the auditory system. Rev Laryngol Otol Rhinol (Bord), 126(4), 203-207.
[12] Hongyao, H. E., Chun, J. I., Xiaoyan, G., Fangfang, L., Jing, Z., Lin, Z., Pengxiang, Z., & Zengchun, L. (2023). Associative gene networks reveal novel candidates important for ADHD and dyslexia comorbidity. BMC medical genomics, 16(1), 208. DOI: 10.1186/s12920-023-01502-1.
[13] Demenkov, P. S., Ivanisenko, T. V., Kolchanov, N. A., & Ivanisenko, V. A. (2011). ANDVisio: a new tool for graphic visualization and analysis of literature mined associative gene networks in the ANDSystem. In silico biology, 11(3-4), 149-161. DOI: 10.3233/ISB-2012-0449.
[14] Ivanisenko, V. A., Saik, O. V., Ivanisenko, N. V., Tiys, E. S., Ivanisenko, T. V., Demenkov, P. S., & Kolchanov, N. A. (2015). ANDSystem: an Associative Network Discovery System for automated literature mining in the field of biology. BMC systems biology, 9 Suppl 2(Suppl 2), S2. DOI: 10.1186/1752-0509-9-S2-S2.