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"GENETIC VARIANTS LINKED TO DYSLEXIA CO-MORBID ADHD: A CASE STUDY OF A PAKISTANI OUTPATIENT"

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Abstract:
Developmental Dyslexia (DD) and Attention-deficit/hyperactivity disorder (ADHD) are neurodevelopmental disorders that often coexist and share complex genetic underpinnings. Our case study integrates psychological assessments and whole exome sequencing to explore the genetic basis of DD and ADHD co-occurrence in a single proband (a nine-year-old female born to healthy) from a consanguineous Pakistani family. We present a proband with symptoms of impulsivity, inattention, and severe hyperactive behavior, along with speech impairment and moderate learning disabilities. The study identified non-synonymous de novo variations in genes associated with both disorders, such as *COMT*, *ADRA1A*, and *HTR2A*, *DNAAF4*, *DCDC2*, *KIAA0319*, *LRRC56*, and *PHRF1*. Network analysis revealed key pathways like *S100 Family Signaling*, *G-Protein Coupled Receptor Signaling*, and *Dopamine Receptor Signaling* shedding light on potential mechanisms underlying the observed phenotypes. The study emphasizes the complexity of these conditions and underscores the need for personalized interventions to address diagnosis challenges.

Keywords: Dyslexia; ADHD; Whole Exome sequencing; Pathway analysis

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder marked by persistent inattention, hyperactivity, and impulsivity, often continuing from childhood into adulthood and attributed to a blend of genetic, environmental, and neurological factors [1]. Conversely, developmental dyslexia (DD) is a learning disability mainly impacting reading and language processing, stemming from difficulties in efficiently processing speech sounds (Phonetics) in the brain, despite normal intelligence [2]. Both the disorders are typically diagnosed in childhood and continue into adulthood. The possible causes are the combinations of genetics, environment, and neurological factors. ADHD and DD are distinct neurodevelopmental disorders that can also coexist in same individuals [2]. Both conditions have neurological origins, but dyslexia are primarily linked to difficulties in processing languages [3]. Research shows that the presence of one disorder does not exclude the possibility of having other when they coexist and they can complicate the learning and behavioral challenges deteriorating the conditions [2,4]. Prevalence of ADHD and DD can also vary

between countries and regions due to different diagnostic criteria, cultural factors, socio-economic, and healthcare access [5].

Globally, ADHD prevalence in children and adolescents is estimated to be around 7.6% and rates varies widely across the populations [1]. Dyslexia affects approximately 15% of the world's population, but specific prevalence rates can differ across the studies and the regions [6]. In Pakistan, there is a limited data available on the prevalence of ADHD and DD. However, studies suggest that both are significant concerns [7,8]. A 2015 regional study published in the Journal of the Pakistan Medical Association reported a prevalence rate of 11.2% for ADHD among school-going children in Karachi [9]. Diagnosing ADHD and DD can be challenging and are often relies mostly on physiological behavioral tests in children, which can also exhibit variations. Limited information exists on how genetic diagnosis could potentially enhance our understanding of these distinctions.

Investigation by whole-exome sequencing (WES) focuses on coding regions which comprise of only about 2% of the human genome but include approximately 80% of known Mendelian disease-associated variants [11]. When combined with computational bioinformatics tools, WES offers a rapid, unbiased, and cost-effective approach in identifying genetic variants responsible for human diseases [12]. This approach facilitates an efficient filtering of significant variants clustered in the family, identification of de novo mutations, and prioritization of candidate variants based on established inheritance patterns. Utilizing WES to identify non-synonymous single nucleotide variants (SNVs) within conditions like DD comorbid ADHD can serve a critical role in elucidating the intricate genetic foundation of these disorders [13, 14]. Our study uses exome sequencing and comprehensive bioinformatics analyses in a single proband to identify the genetic variants and understand the associated gene pathways for such physiological conditions as ADHD comorbid DD. Our primary objective encompassed the identification of potential non-synonymous SNVs within the 28 genes (selected with priory information) that are associated with ADHD and DD phenotypes (Supplementary Table 1). Information about them was gathered from reputable sources such as OMIM (Online Mendelian Inheritance in Man), PubMed, and NCBI (National Center for Biotechnology Information) databases (Supplementary Table 1). The present report is aimed at to check the potential implications of these variants and their contributions towards the development of intricate neurodevelopmental phenotype observed in the proband investigated with a possible implication in future clinical and diagnostic studies in the Pakistani pediatric population.

2. Case Presentation

The proband, a nine-year-old female born to healthy consanguineous parents in Islamabad, Pakistan, demonstrated a slow academic progression in her 3rd-grade (currently at 11 years of age). She was referred to the Neurology and Child Psychiatry Outpatient Department at the Pakistan Institute of Medical Sciences Hospital in Islamabad (ERB No. CUI/BIO/ERB/2022/11). The primary clinical assessment revealed symptoms of impulsivity, inattention, and severe hyperactive behavior, along with reported speech impairment and learning disabilities. Notably, there were no indications of visual or hearing impairment or any significant neurological disorders at the time of diagnosis (at the 9-year of age). There were no complications during the proband's prenatal period or at birth (normal vaginal delivery). The family pedigree indicated that the proband and her eight-year-old younger sister, both experiencing hyperactivity and learning disabilities, were the first affected individuals in three generations (Figure 1).

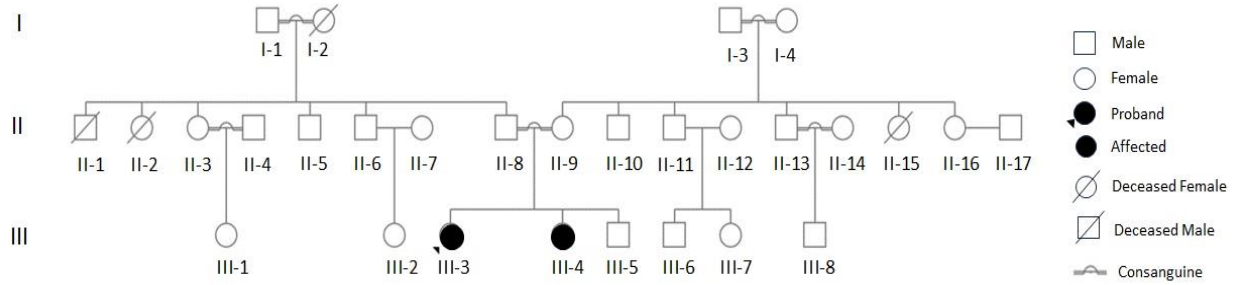

Figure 1. The pedigree of the proband shows that the affected family have a recessive inheritance pattern of three generations. The black arrow with a filled circle is pointed towards a 9-year-old female proband (DD comorbid ADHD phenotypes) selected for biochemical examination and WES analysis.

2.1 Clinical evaluation of the proband

The neuroadaptive profile was evaluated using standardized psychological methodologies, following the criteria of DSM V [15]. The assessments were conducted in accordance with internationally recognized standard protocols, which included the use of Urdu-translated layperson understandable local language questionnaires [15]. Nonverbal assessment was conducted using the *Standard Progressive Matrices* (SPM) [16]. To evaluate learning ability, problem-solving skills, issue comprehension, reasoning, judgment, and knowledge retention, the Urdu version of the *Slosson intelligence test* (SIT R3) was utilized [17]. Reading-writing ability, quantitative knowledge, and cognitive processing speed were measured using the *Woodcock–Johnson Tests* of Cognitive Abilities (WJ-IV) and the *Bangor Dyslexia test* [18,19]. Additionally, for a comprehensive evaluation of potential behavioral markers of ADHD in children aged 6-18 years, the *Conners Parent Rating Scale-Long Version* (CPRS-R: L) was employed. This scale assesses various aspects, including inattention, hyperactivity/impulsivity, learning problems, executive functioning, and aggression (Table 1) [20,21].

The *Standard Progressive Matrices* test for nonverbal intelligence showed a test score of 75%. The *Slosson Intelligence Test* (SIT R3) yielded a normal score of 71. The *Woodcock–Johnson Test (WJ-IV)* for cognitive abilities score was 88. Additionally, the adapted version of the *Bangor Dyslexia Test* revealed seven positive indicators, suggesting the presence of dyslexic features in the Proband. Lastly, the *Conners Parent Rating Scale-Long Version* for ADHD (CPRS-R: L) recorded a test score of 75, indicating a severe deficiency in subtypes of hyperactive and impulsive behavior issues. The standard procedures and multiple evaluation tests yielded the following results which were summarized in Table 1.

Clinical biochemistry parameters were retrieved from the patient medical records at Islamabad Diagnostic Laboratory (IDC) in Islamabad, Pakistan. The blood biochemical profile observed within the normal reference range. Interestingly, vitamin D3 and Valproic acid were both observed to be in the normal range with readings of 56.2ng/ml and 36.6ng/ml, respectively (Table 1).

Table 1. Psychological and blood biochemistry evaluation of proband with DD comorbid ADHD phenotype

Psychological instruments	Test score	Reference range
Standard Progressive Matrices (SPM)	75%	95% or above= Intellectual superior 75% to 94% = Above the average 25% to 75% = Intellectual average Below 25% = Below intellectual capacity
Slosson Intelligence Test (SIT R3)	71	130 or above= Bright 120 to 129= Superior high 80 to 119= Average 70 to 79= Borderline 69 and below= Intellectual deficient.

Woodcock–Johnson Tests of Cognitive Abilities for Cognitive AbilitiesTest (WJ-IV)	88	130 or above= Very Superior 120 to 129= Superior 110 to 119= High Average 90 to 109= Average 80 to 89= Low Average 70 to 79=Borderline 69 and below= Extremely Low
Bangor Dyslexia Test	07	At least 5 positive indicators or above
Conners Comprehensive Behavior Rating Scale Parents ADHD	75	59 or below= Normal 60 to 69= mild to moderate 70 or above= Severe
Biochemistry profile		
Biochemical indexes	Results	
Serum Glucose random (ref < 160 mg/dL)	92	
WBCs (ref 4.0-10.0*10^9/L)	9.7	
RBCs (Ref 3.8-5.8*10^{12}/L)	4.7	
Hemoglobin (ref 12-14 g/dL)	12.6	
PVC (Ref 40-50%)	39	
MCV (Ref 76-96fl)	81	
MCH (Ref 27-31pg)	26	
MCHC (Ref 32-34 g/dL)	32	
Platelets (ref 150-400*10^9/L)	321	
Polymorph (Ref 40-75%)	41	
Lymphocytes (Ref 20-45%)	55	
Monocytes (Ref 01-06%)	02	
Eosinophils (Ref 01-06%)	02	
Serum Bilirubin total (ref < 1.3 mg/dL)	0.50	
Serum ASAT (ref <31 U/L)	21	
Serum alkaline Phosphate (Ref M/F 100-290U/L, Child: 180-615 U/L)	258	
Serum creatinine (ref 0.6-1.1mg/dL)	0.6	
Serum Sodium (Ref 136-149 mmol/L)	139	
Serum Potassium (Ref 3.2-5.2 mmol/L)	4.31	
Serum Chloride (ref 95-105 mmol/L)	99	
Hydroxy vit. D3 Level (Ref: Sufficient 30-100ng/ml)	36.6	
S. Valproic acid (Ref: 50-100 ng/ml)	56.2	
S.T4 (Ref 4.50-11.7 ug/dL)	8.46	
S.TSH (Ref 0.4-4.2 ulU/mL)	0.96	
S. Cholesterol (Without known coronary artery disease, less than or equal to 200mg/dl)	186	
S. Triglycerides (ref 46-236 mg/dl)	157	
HDL- Cholesterol (Without known coronary artery disease, less than or equal to 35 mg/dl)	37	
LDL- Cholesterol (Without known coronary artery disease, less than or equal to 130 mg/dl)	116	
Aldolase (ref: Up to 8 U/L)	6.0	
CPK (ref male: up to 190, female: Up to 165 U/L)	52	
Anti TTG Ab IgA (ref Negative: < 20 U/ml)	8.975	
Anti TTG Ab IgG (ref Negative: < 20 U/ml)	4.049	

*Clinical biochemistry parameters were retrieved from the patient medical records to investigate associated risk factors, which included Blood profile, Random glucose, Liver Function tests, Renal Function tests, Serum lipid profile, Valproic acid, and vitamin D3 Level. These tests were carried out using the Cobas 6000 Modular System from Roche Diagnostics, Germany. Additionally, Thyroid Function tests and Anti TTG Ab tests were performed on the TOSOH AIA 600, TOSOH Bioscience, Japan, using immune-fluorescence Assay at Islamabad Diagnostic Laboratory (IDC) in Islamabad, Pakistan.

Table 2. WES data for proband with pathogenic variant reported in ADHD comorbid DD phenotype

Disorder	Chr	Start	Ref	Alt	Ref Gene	Amino Acid Change of Ref: Gene	Cytoband	Zygosity	Function	Variation Type
ADHD	chr22	19963748	G	A	*COMT*	COMT:NM_007310:exon2:c.G322A:p.V108M,COMT:NM_000754:exon4:c.G472A:p.V158M,COMT:NM_001135161:exon4:c.G472A:p.V158M,COMT:NM_001135162:exon4:c.G472A:p.V158M,COMT:NM_001362828:exon4:c.G472A:	22q11.21	Heterozygous	Exonic	Non-synonymous SNV
ADHD	chr8	26770511	A	G	*ADRA1A*	ADRA1A:NM_033302:exon2:c.T1039C:p.C347R,ADRA1A: NM_033303:exon2:c.T1039C: p.C347R,ADRA1A:NM_033304:exn2:c.T1039C:p.C347R,ADRA1A:NM_000680:exon3:c. T1039C:p.C347R	8p21.2	Heterozygous	Exonic	Non-synonymous SNV
ADHD	chr8	26779389	T	A	*ADRA1A*	ADRA1A:NM_001322504:exon2:c.A925T:p.S309C	8p21.2	Heterozygous	Exonic	Non-synonymous SNV
ADHD	chr13	46896689	C	T	*HTR2A*	HTR2A:NM_001165947:exon1:c.G145A:p.D49N	13q14.2	Homozygous	Exonic	Non-synonymous SNV
DD	chr15	55466995	T	C	*DNAAF4*	DNAAF4:NM_001033559:exon5:c.A572G:p.E191G, DNAAF4:NM_001033560:exon5:c.A572G:p.E191G, DNAAF4:NM_130810:exon5:c.A572G:p.E191G	15q21.3	Homozygous	Exonic	Non-synonymous SNV
DD	chr15	55497712	C	T	*DNAAF4*	DNAAF4:NM_001033559:exon3:c.G271A:p.V91I,DNAAF4:NM_00133560:exon3:c.G271A:p.V91I,DNAAF4:NM_1 30810:exon3:c.G271A:p.V91I	15q21.3	Heterozygous	Exonic	Non-synonymous SNV
DD	chr6	24290975	T	C	*DCDC2*	DCDC2:NM_016356:exon5:c.A661G:p.S221G, DCDC2:NM_00119561 0:exon6:c.A661G:p.S221G	6p22.3	Homozygous	Exonic	Non-synonymous SNV
DD	chr6	24588656	C	T	*KIAA0319*	KIAA0319:NM_001168376:exon3:c.G796A:p.A266T, KIAA0319:NM_001350404:exon3:c.G913A:p.A305T, KIAA0319:NM_001350406:exon3:c.G796A:p.A266T, KIAA0319:NM_001168375:exon4:c.G931A:p.A311T, KIAA0319:NM_001168377:exon4:c.G931A:p.A311T, KIAA0319:NM_001350403:exon4:c.G931A:p.A311T, KIAA0319:NM_001350405:exon4:c.G931A:p.A311T, KIAA0319:NM_001350407:exon4:c.G931A:p.A311T, KIAA0319:NM_001350408:exon4:c.G931A:p.A311T, KIAA0319:NM_014809:exon4:c.G931A:p.A311T,KIAA0319:NM_001168374:exon5:c.G904A:p.A302T,KIAA0319:NM_001350409:exon5:c.G475A:p.A159T,KIAA0319:NM_0013541 0:exon5:c.G475A:p.A1 59T	6p22.3	Heterozygous	Exonic	Non-synonymous SNV
DD	chr6	24596250	T	G	*KIAA0319*	KIAA0319:NM_001168376:exon2:c.A289C:p.T97P,KIAA0319:NM_001350404:exon2:c.A406C:p.T136P,KIAA0319:NM_001350406:exon2:c.A289C:p.T97P,KIAA0319:NM_001168375:exon3:c.A424C:p.T142P,KIAA0319:NM_0011 68377:exon3:c.A424C:p.T142P,KIAA0319:NM001350403:exon3:c.A424C:p.T142P,KIAA0319:NM_001350405:exon3:c.A424C:p.T142P,KIAA0319:NM_001350407:exon3:c.A424C:p.T142P,KIAA0319:NM_001350408:exon3:c.A424C:p.T142P,KIAA0319:NM_014809:exon3:c.A424C:p.T142P,KIAA0319:NM_001168374:exon4:c.A397C:p.T133P	6p22.3	Homozygous	Exonic	Non-synonymous SNV
DD	chr11	5542 14	G	C	*LRRC5 6*	LRRC56:NM_198075:exon14:c.G1567C:p.D523H	11p15.5	Homozygous	Exonic	Non-synonymous SNV
DD	chr11	6102 77	T	C	*PHRF1*	PHRF1:NM_001286581:exon15:c.T4346C:p.V1449A, PHRF1:NM_001286582:exon15:c.T4340C:p.V1447A, PHRF1:NM_001286583:exon15:c.T4334C:p.V1445A, PHRF1:NM_020901:exon15:c.T4343C:p.V1448A	11p15.5	Homozygous	Exonic	Non-synonymous SNV

2.2 Whole Exome Sequencing and Variant Calling Analysis

DNA from the proband and her parents peripheral blood lymphocytes was subjected to whole exome sequencing and variant calling analysis (Supplementary list 2). The sequencing was performed by Macrogen Inc., Korea, and the data underwent quality checking using the FASTQC (http://www.bioinformatics.babraham.ac.uk/projects/fastqc, date of last visit March 14, 2023) web

program. The reads were aligned to the reference human genome (GRCh38) using the Burrows Wheeler Aligner (BWA). Duplicate copies were identified and removed from the data using the Picard tool (version 2.18.20). The Genome Analysis Tool Kit (GATK) was utilized, and its Haplotype Caller tool filtered the variant calls. It utilizes annotation databases and algorithms to provide comprehensive information about the variants detected in the sequencing data [22,23].The quality of sample mapping was assessed using the Qualimap v2.2.1 tool, and it was ensured that the samples had an average coverage of over 45X. Evaluation of the variants was conducted following the American College of Medical Genetics (ACMG) criteria [24].We utilized an in-house pipeline that incorporates SIFT, PolyPhen2, Mutation Taster, Mutation Assessor, and FATHMM software (date of last visit March 12, 2023) for variant filtration, allowing us to classify variants as either deleterious or pathogenic. The frequency of alleles was assessed in control population databases, including gnomAD (https://gnomad.broadinstitute.org; date of last visit March 15, 2023), and ESP6500 (http://evs.gs.washington.edu/EVS/; date of last visit March 15, 2023). Genomic data analysis was conducted with a specific focus on 28 genes that are associated with ADHD and DD phenotypes (Supplementary Table 1). Among the 28 genes examined, 19 genes (*DRD5, DAT1 (SLC6A3), HTR1B, ADRA2A, DRD4, SCN8A, SNAP25, COMT, TACR1, DBH, ADRA1A, DRD2, TPH1, TPH2, HTR2A, SLC6A2, SLC6A4, CHRNA4,* and *MAOA*) were prominently linked with ADHD, while the remaining nine genes (*DNAAF4, DCDC2, KIAA0319, MRPL19, C2ORF3, ROBO1, KIAA0319L, LRRC56* and *PHRF1*) exhibited specific connections with DD in diverse populations (Supplementary Reference). This selection was based on their extensively studied roles, which have been substantiated through valid sources such as OMIM, PubMed, NCBI, and Google Scholar databases [25].

There was a total of 147850 genomic variations and 23584 variations were found in Exons or Splicing sites. Our analysis was based on 25 variations which were found in genes reported for ADHD. Synonymous variations were removed from the list as they don't change the amino acid sequence. Four de novo pathogenic variations in gene *COMT*, *ADRA1A* and *HTR2A* respectively were the non-synonymous type. The sequencing analysis revealed a mutant de novo variant in exon 2 of the COMT gene (NM_007310: exon2: c. G322A: p.V108M), causing a Valine to Methionine substitution at position 108. Additionally, we found two de novo variations in exon 2 of the *ADRA1A* gene; one (NM_033 302: exon2: c. T1039C: p.C347R) led to a Cysteine to Arginine mutation at the position 347, and the other (NM_001322504: exon2: c. A925T: p.S309C) resulted in a Serine to Cysteine change at the position 309. Furthermore, a de novo variation was observed in exon 1 of the *HTR2A* gene (NM_00116 5947: exon1: c. G145A: p.D49N), converting Aspartic Acid to Asparagine at position 49 (Table 2).

We identified nine de novo pathogenic variations in relevant genes related to DD after excluding synonymous variations, we found seven de novo non-synonymous variations in the genes *DCDC2*, *LRRC56*, and *PHRF1* including two separate variations in the *DNAAF4* and *KIAA0319*, respectively. Sequencing analysis recognize two de novo variations in *DNAAF4*, one in exon 5 (NM_001033559:exon5:c. A572G:p. E191G) resulting in the change of Glutamic Acid to Glycine at the position 191, and the other in exon 3 (NM_001033559:exon3:c.G271A:p.V91I) leading to the substitution of Valine with Isoleucine at position 91. Moving on to the *DCDC2* gene, a de novo variation in exon 5 (NM_016356: exon5: c.A661 G: p.S221G) caused the transformation of Serine into Glycine at position 221. We additionally identified two important de novo variations in the *KIAA0319*gene; one in exon 3 (NM_001168376: exon 3: c. G796A: p.A266T) that resulted in the change of Alanine to Threonine at position 266, and another in exon 2 (NM_001168376: exon2: c. A289C: p.T97P) which led to the conversion of Threonine to Proline at position 97. In the LRRC56 gene, a de novo variation in exon 14 (NM_198075: exon14: c. G1567C: p.D523H) caused the substitution of Aspartic Acid with Histidine at position 523. Finally, in the *PHRF1* gene at exon 15 (NM_001286581: exon15: c. T4346C: p.V1449A), we observed a de novo variation that changed Valine into Alanine at position 1449 (Table 2).

2.3 Identification of Cellular Processes and Pathways by Ingenuity Pathways Analysis (IPA)

Ingenuity Pathway Analysis (IPA, Qiagen) was performed to identify canonical pathways, diseases and functions, and gene networks that are most significant to understand the gene links with disorder conditions like ADHD and DD. The IPA was conducted according to manufacturer protocol (without having the differential gene expression datasets) [26]. Briefly, the targeted genes were imported into *IPA* using the gene-search tab, and networks were generated algorithmically based on their connectivity. Using IPA, we identified the canonical pathways and associated functions with the goal of discovering the relationships among the selected genes based on the Ingenuity Knowledge Base [26]. Gene network and Singling pathways which describes the potential mechanism of action to understand gene expression changes and was done by mechanistic network analysis feature. Canonical pathways (CP) were investigated to understand the most significant affected pathway associated with disorder that is predicted to be activated or inhibited.

The network analysis revealed some intriguing observations on the interactions of genes associated with ADHD and DD phenotypes. Specifically, three (3) genes were linked to ADHD (*ADRA1A*, *HTR2A*, and *COMT*) and two (2) genes were associated with DD (*DCDC2* and *DNAAF4*) were interconnected within the network (Figure2). Based on the selected genes in the proband, we identified the top canonical pathways within the gene network viz., S*100 Signaling Pathway*, *G-Protein Coupled Receptor Signaling*, *CREB Signaling in Neurons*, *FAK Signaling*, and *Dopamine Receptor Signaling pathway*. These predicted pathways may play significant roles in the manifestation of the phenotypes (observed) in the studied participant. We also evaluated the top physiological system developments and functions associated with the gene network. These included *Cognitive impairments*, *Learning disability*, *attention deficit hyperactivity disorder*, and *Major depression*. Furthermore, the key genes *OPRM1*, *ESR1*, *CTNNB1*, and *WNT3A* were identified as central molecules (key genes) within the network, suggesting their significant role in shaping overall dynamics and adding to the complexity of disorder in the patient.

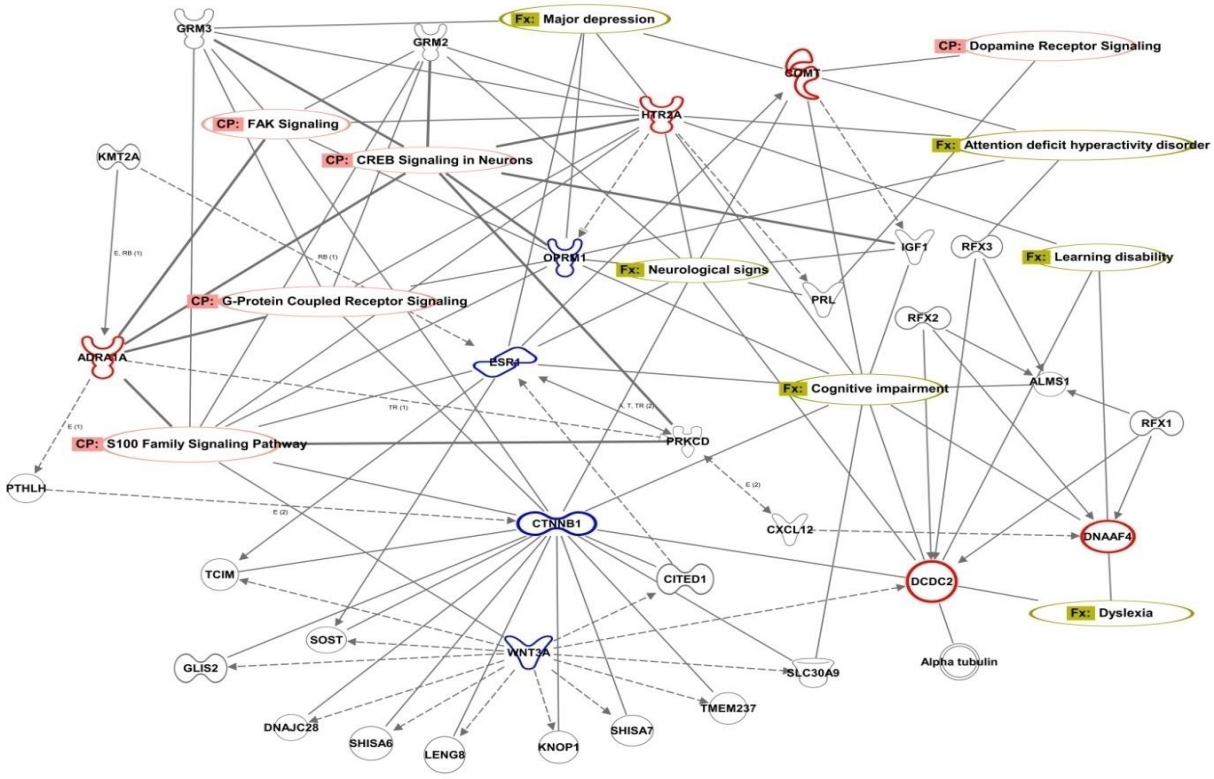

Figure 2. Network of targeted ADHD and DD-related genes of the proband generated using *IPA* (Ingenuity Pathway Analysis from QIAGEN, USA, March 2023 Release) according to the method described by the manufacturer protocol when without having the differential gene expression datasets

[26]. The construction of the network relied on information stored in the Ingenuity Pathways Knowledge Base (IPKB). The network includes canonical pathways (CP) associated with the targeted genes, which are represented in **red** color. Genes that are central molecules are represented in **blue** color.

4. Discussion

ADHD and DD are common neurodevelopmental disorders often coexisting with complex symptoms [2]. As per the recent reported data, the worldwide prevalence of ADHD in children, 7.6% of 96,907 children aged 3 to 12 years had ADHD, and 5.6% of teenagers aged 12 to 18 years have ADHD [27]. In the US, 9.4% of children aged 2 to 17 (6.1 million) were diagnosed with ADHD, while Dyslexia affects 20% of the population and most learning disabilities [3]. The prevalence of ADHD in Pakistan also has been found to be around 11.2% [9]. ADHD and Dyslexia sometimes overlapped and around 30% of Dyslexia cases involve ADHD [28].

The present study was conducted to understand the relationship/association between these two disorders (DD and ADHD) by investigating any genetic factors contributing to their co-occurrence. We used whole exome sequencing, blood analysis, and in-depth psychological assessments to study the complex genetic factors contributing to their simultaneous occurrence. Focusing on a single proband, this study endeavors to shed light on the genetic underpinnings and potential pathways of physiological conditions like ADHD when coexisting with DD. Our psychological assessments of batteries provide a precise understanding of the individual's strengths and vulnerabilities. Notably the proband demonstrated above average performance in nonverbal reasoning and problem-solving skills, indicating a normal range of intellectual ability with strong cognitive capabilities. Despite these strengths, the proband exhibited dyslexic features and ADHD characteristics, as highlighted by the results of the *Bangor Dyslexia Test* and *CPRS-R: L* test (Table 1). The presence of these dyslexic features raises concerns about potential impacts on reading and language processing for the proband. Furthermore, the proband showed clear ADHD symptoms, marked by significant hyperactivity and impulsivity (Table 1). These symptoms strongly suggest the possibility of an ADHD diagnosis for the proband. It's important to note that these test scores provide valuable information. They should be interpreted with the conjunctions of other clinical assessments and observations to form a comprehensive understanding of the individual's cognitive and psychological profile [29]. Many research studies have indicated that children with ADHD tend to exhibit notably lower serum levels of certain vitamins (specifically Vitamin D3, B12, and B6) and higher levels of saturated fatty acids when compared to normal children [5,30]. However, it's worth noting that when we examined the medical records of the affected individuals, we did not detect any significant alterations in their blood biochemical factors.

To explore further the genetic basis of Dyslexia and ADHD co-occurrence in children, our study employs exome sequencing. This high-throughput technique scrutinizes the protein-coding regions of genes, allowing for the identification of genetic variants linked to these conditions. Our study observed the *COMT* gene, which is well-known for its soluble and membrane-bound forms. This gene plays a crucial role in the degradation of catecholamines and is strongly associated with neurodevelopment [31]. Many researchers reported the association of *COMT* val158met polymorphism with brain development and ADHD [32,33]. In our study, we have identified a heterozygous de novo non-synonymous SNV in the proband. This SNV leads to a Valine to Methionine substitution at position 108 (supplementary Figure 1). This finding is corroborated with reported studies and provides a probable indication of the mutation's effects on neurodevelopment. This mutation impacts the signal channels of Ca2+-dependent catecholaminergic neurotransmitters and influences the physiological activity of the COMT enzyme [32, 33]. Consequently, this enzymatic activity alteration promotes the depletion of catecholaminergic neurotransmitters from synapses in the prefrontal cortex [33].

Another gene of importance is*ADRA2A* which encodes the alpha-2A adrenergic receptor, which plays a role in regulating neurotransmitter release, including norepinephrine [34]. Variations in this gene could impact norepinephrine signaling which engages in attention, arousal, and stress response [35]. Alterations in norepinephrine levels and receptor functions could influence the hyperactivity, attention regulation, and emotional processing observed in ADHD [35]. The child (our proband) presented a unique scenario where we see (first to report) the presence of two distinct non-synonymous de novo single nucleotide variants (SNVs) within the same gene located on chromosome 8. These variations might be the keys behind the significant role in changing the physiological characteristics observed in the affected proband. The findings corroborating other studies, who explored the potential role of the *ADRA2A* gene in ADHD assessing three different SNPs and their functional implications (on memory and arousal on executive function tasks in the ADHD individuals) in other population [36,37].

The *HTR2A* gene encodes the serotonin receptor 2A, which is part of the serotonin signaling pathway. Serotonin is known to influence mood, emotion, and behavior [38]. Variations in the *HTR2A* gene could lead to changes in serotonin receptor function, potentially affecting emotional regulation, anxiety responses, and cognitive control [39]. Dysregulation of serotonin signaling has been implicated in both ADHD and mood disorders, which could contribute to the observed ADHD-related symptoms [39]. A recent study suggests an association between gene polymorphisms in the serotonin receptor family (5-HTR) and ADHD which highlighted that the 861G allele of the 5-HTR1B SNP rs6296 could significantly elevate the risk of ADHD [40]. We also observed a homozygous non-synonymous SNV on chromosome 13, which could be a potential contributors of mutation factor to the ADHD phenotype in the proband.

Interestingly, the Dyslexia-associated genes also exhibit non-synonymous de novo variations in our proband. The *DNAAF4* gene participates in neuronal migration and interacts with estrogen receptors and heat shock proteins [41]. Variations in this gene could influence neuronal connectivity and plasticity which are essential for cognitive functions such as reading and spelling [42]. Earlier, many SNP based studies reported the polymorphic nature of *DNAAF4*thatcontributes to neuronal migration in the developing rodent brain [42]. Interestingly, we also identified two distinct non-synonymous SNVs within the same gene on chromosome 15. These variations led to the substitution of Glutamic acid with glycine at position 191, and Valine with Isoleucine at position 91 (supplementary Figure 2). Additionally, we observed the presence of non-synonymous SNVs in the *DCDC2* and *KIAA0319* genes. These genes are recognized for their involvement in neuronal migration and cell adhesion, both of which are crucial processes for brain development and connectivity [43,44]. Variations in these genes could impact the formation of neural circuits and communication between brain regions. Disrupted neural connectivity has been suggested as a potential mechanism underlying Dyslexia, affecting language processing, and reading skills [45]. We observed a homozygous non- synonymous SNV by altering Serin into a Glycine at position 221 at *DCDC2* gene and two distinct non-synonymous, homozygous, SNVs within the same gene on chromosome six with possible mutation for the specific phenotype (ADHD with DD). We noted two homozygous non-synonymous SNVs on chromosome 11, specifically in the *LRRC56* and *PHRF1* genes. A prior study on the US population highlighted variants of these genes associated with inversion-type mutations in the dyslexic phenotype [46]. Our findings support the hypothesis that genetic risk variants within eight specific genes exert a significant impact on both ADHD and DD phenotypes. These variants could potentially contribute as mutation factors to the ADHD phenotype observed in the current proband whom we investigated.

The pathway (gene-network) analysis by IPA reveals significant connections between our ADHD-related genes *ADRA1A, HTR2A,* and *COMT* identified along with Dyslexia-related genes *DCDC2* and *DNAAF4* that converge with pathways viz., *S100 Family Signaling, G-Protein Coupled Receptor Signaling, CREB Signaling in Neurons, FAK Signaling, and Dopamine Receptor Signaling*. These

pathways may have crucial roles in influencing the neurological development that we observed in the child (proband) with ADHD and DD comorbid condition. Earlier studies that focused on patients have indicated that variations in G-Protein Coupled Receptors (GPCRs) are linked to an increased risk of ADHD in specific individuals [47]. Additionally, research also highlighted that the ADHD phenotype is influenced by a dysregulation of CREB signaling, which is influenced by a kinase-independent PI3Kγ-PDE4D interaction within noradrenergic neurons [48]. Notably, the interplay of dopaminergic or norepinephrine neurotransmitters and pro-inflammatory actions of S100 family proteins could mediate neuroinflammatory mechanisms preceding ADHD symptoms [49]. G protein-coupled receptors and their association with neurodegenerative and psychiatric disorders also lend insight [50]. Moreover, the study identifies additional genes like *OPRM1*, *ESR1*, *CTNNB1*, and *WNT3A*, which could further contribute to the intricate network interactions [51-53]. These findings suggest that the interactions between the identified genes are relevant to these physiological processes which corroborated with current patient's case. Overall, our network analysis yielded a significant insight into the potential gene interactions and pathways that underlie the neurodevelopmental phenotypes of ADHD and DD. This enhances our understanding of the pathobiology of the co-existence of the disorders in the child. Nevertheless, there remains a considerable amount to comprehend about the precise molecular pathways which are altered in individuals with ADHD. Our study suggests that the mutation in the eighth gene played a key role in the coexisting conditions of ADHD and DD thereby contributing to both phenotypes and needs further detailed sequencing and evident by functional validation of these findings.

5. Conclusions

The co-occurrence of ADHD and Dyslexia still poses a puzzle in neurophysiology and the neurodevelopmental disorders in biomedical filed. This study utilized an integrated approach that combined psychological assessments, exome sequencing, and genetic pathway analysis focused on a single proband. The results provided valuable insights into the genetic basis of the complex interplay of these disorder conditions to a phenotypic outcome. The results attained so far emphasize the need for largescale multidisciplinary research approach in studying such complex conditions as ADHD and DD. A personalized interventional approach is essential for the individuals facing the challenges of ADHD and DD which are currently being undergoing in our laboratory.

Supplementary Materials: Table S1: Gene List for whole exome analysis; Table S2: Clinical Evaluation Cognitive and Learning Disabilities; Table S3: Biochemistry profile of Proband with DD comorbid ADHD phenotype; S4: Description of blood DNA isolation and Sequencing QC.

Author Contributions: S.H., M.A, S.G., T.M., and I.N. together conceptualized the work and the manuscript. M.A supervised the study, S.H. Collected Blood sampling, Clinical information and performed experimental work, I.N. - psychological evaluation and assessment. S.G, T.M performed Ingenuity Pathway Analysis, result, and interpretation. S.H., M.A, S.G., T.M, and I.N all participated in writing, reviewing, and editing the manuscript. All the author(s) read and approved the final manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of COMSATS University (CUI), Islamabad, Pakistan (CUI/BIO/ERB/2022/11) and the Howard University Institutional Review Board (IRB-2023-0810)

Informed Consent Statement: Written informed consent was obtained from the patient's legal guardian for publication of this case report.

Data Availability Statement: Data available as per the reasonable request.

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Reference

1. Salari, N.; Ghasemi, H.; Abdoli, N.; Rahmani, A.; Shiri, M. H.; Hashemian, A. H.; Akbari, H.; Mohammadi, M. The global prevalence of ADHD in children and adolescents: a systematic review and meta-analysis. *Ital. J. Pediatr.*2023, 49(1), 48.
2. Slaby, R. J.; Arrington, C. N.; Malins, J.; Sevcik, R. A.; Pugh, K. R.; Morris, R. Properties of white matter tract diffusivity in children with developmental dyslexia and comorbid attention deficit/hyperactivity disorder. *J Neurodev Disord*. 2023, 15(1), 25.
3. Serrallach, B.; Groß, C.; Bernhofs, V.; Engelmann, D.; Benner, J.; Gündert, N.; Blatow, M.; Wengenroth, M.; Seitz, A.; Brunner, M.; Seither, S.; Parncutt, R.; Schneider, P.; Seither-Preisler, A. Neural Biomarkers for Dyslexia, ADHD, and ADD in the Auditory Cortex of Children. *Front Neurosci.*2016, 10, 324.
4. Karalunas, S. L.; Hawkey, E.; Gustafsson, H.; Miller, M.; Langhorst, M.; Cordova, M.; Fair, D.; Nigg, J. T. Overlapping and Distinct Cognitive Impairments in Attention-Deficit/Hyperactivity and Autism Spectrum Disorder without Intellectual Disability. *J Abnorm Child Psychol*. 2018, 46(8), 1705-1716.
5. Wang, L.J.; Yu, Y.H.; Fu, M.L.; Yeh, W.T.; Hsu JL, Yang, Y.H.; Yang, H.T.; Huang, S.Y.; Wei, I.L.; Chen, W.J.; Chiang, B.L.; Pan, W.H. Dietary Profiles, Nutritional Biochemistry Status, and Attention-Deficit/Hyperactivity Disorder Path Analysis for a Case-Control Study. J Clin Med. 2019, 8(5), 709.
6. Wagner, R.K.; Zirps, F.A.; Edwards, A.A.; et al. The Prevalence of Dyslexia: A New Approach to Its Estimation. J Learn Disabil. 2020, 53(5), 354-365.
7. Chung, W.; Jiang, S.F.; Paksarian. D.; et al. Trends in the Prevalence and Incidence of Attention-Deficit/Hyperactivity Disorder Among Adults and Children of Different Racial and Ethnic Groups. JAMA Netw Open. 2019, 2(11), e1914344.
8. Ashraf, A.; Tohid, H. The Lack of Trained Child Psychiatrists Leading to Underreported Cases of ADHD in Pakistan. J Cell Sci Ther. 2016, 7, e125
9. Ibrahim, M.; Saeed Ullah, Jan. Bibliometric analysis of the Journal of Pakistan Medical Association form 2009 to 2013. J Pak Med Assoc. 2015, 65(9), 978-983.
10. Jalkh, N.; Corbani, S.; Haidar, Z.; et al. The added value of WES reanalysis in the field of genetic diagnosis: lessons learned from 200 exomes in the Lebanese population. BMC Med Genomics. 2019, 12(1), 11.
11. Chong, J.X.; Buckingham, K.J.; Jhangiani, S.N.; et al. The Genetic Basis of Mendelian Phenotypes: Discoveries, Challenges, and Opportunities. Am J Hum Genet. 2015, 97(2):199-215.
12. Rabbani, B.; Tekin, M.; Mahdieh, N. The promise of whole-exome sequencing in medical genetics. J Hum Genet. 2014, 59(1), 5-15.
13. Retterer, K.; Juusola, J.; Cho, M.T.; et al. Clinical application of whole-exome sequencing across clinical indications. Genet Med. 2016, 18(7), 696-704.

14. Wright, C.F; Fitzpatrick, D.R.; Firth, H.V. Paediatric genomics: diagnosing rare disease in children [published correction appears in Nat Rev Genet. 2018 Feb 19;]. Nat Rev Genet. 2018, 19(5), 253-268.
15. American Psychiatric Association, D. S. M. T. F.; American Psychiatric Association; Diagnostic and statistical manual of mental disorders. 2013, DSM-5 (Vol. 5, No. 5). Washington, D; American psychiatric association.
16. Ashraf, M.; Majeed, S. Prevalence of Dyslexia in Secondary School Students in Lahore. Pakistan Journal of Psychological Research. 2011, 26, 73-85.
17. Jaffar, R.; Ali, A. Z. USING URDU-ENGLISH CODE-SWITCHING IN THE TRANSLATION OF SLOSSON INTELLIGENCE TEST. Pakistan Journal of Educational Research. 2021, 4(4).
18. Reynolds, M. R.; Niileksela, C. R. Test Review: Schrank, F.A.; McGrew, K.S.; Mather, N. 2015. Woodcock-Johnson IV Tests of Cognitive Abilities.
19. Schrank, F. A.; Wendling, B. J. The Woodcock–Johnson IV: Tests of cognitive abilities, tests of oral language; tests of achievement. In D. P. Flanagan & E. M. McDonough (Eds.), Contemporary intellectual assessment: Theories, tests, and issues. 2018 , pp. 383–451. The Guilford Press.
20. Conners, C.K. Rating scales in attention-deficit/hyperactivity disorder: use in assessment and treatment monitoring. J Clin Psychiatry. 1998, 59 Suppl 7, 24-30.
21. Conners, C.K.; Sitarenios, G.; Parker, J.D.; Epstein, J.N. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol. 1998, 26(4), 257-268.
22. Cerminara, M.; Spirito, G.; Pisciotta, L.; et al. Case Report: Whole Exome Sequencing Revealed Disease-Causing Variants in Two Genes in a Patient with Autism Spectrum Disorder, Intellectual Disability, Hyperactivity, Sleep and Gastrointestinal Disturbances. Front Genet. 2021, 12:625564.
23. Chen, S.; Huang. T.; Zhou, Y.; Han, Y.; Xu, M.; Gu, J. After QC: automatic filtering, trimming, error removing and quality control for fastq data. BMC Bioinformatics. 2017, 18(Suppl 3):80.
24. Richards, S.; Aziz, N.; Bale, S.; et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015, 17(5), 405-424.
25. Venselaar, H.; Te Beek, T.A.; Kuipers, R.K.; Hekkelman, M.L.; Vriend, G. Protein structure analysis of mutations causing inheritable diseases. An e-Science approach with life scientist friendly interfaces. BMC Bioinformatics. 2010, 11:548.
26. Ingenuity Pathway Analysis | QIAGEN Digital Insights. Bioinformatics Software and Services | QIAGEN Digital Insights. https://digitalinsights.qiagen.com/products-overview/discovery-insights portfolio/analysis-and visualization/qiagenipa/?gclid=CjwKCAjwl6OiBhA2EiwAuUwWZcAVHivk4hOg0XkKn64B NfqEV5 x-Yc2LyGthp3AbtdztMxXDuxcYOhoCXU0QAvD_BwE (accessed on 26/04/ 2023).
27. Polanczyk, G.; De Lima, M.S.; Horta, B.L.; Biederman, J.; Rohde, L.A. The worldwide prevalence of ADHD: a systematic review and meta regression analysis. Am J Psychiatry. 2007, 164(6):942-948.
28. Attention-Deficit/Hyperactivity Disorder (AD/HD) and Dyslexia. https://dyslexiaida.org /attention-deficithyperactivity-disorder-adhd-and-dyslexia/. (accessed on 08/14/2023).
29. Committee on Psychological Testing, Including Validity Testing, for Social Security Administration Disability Determinations; Board on the Health of Select Populations; Institute of Medicine. Psychological Testing in the Service of Disability Determination. Washington (DC): National Academies Press (US). 2015, Available from: https://www.ncbi.nlm.nih.gov/ books/NBK305236.
30. Sharif, M.R; Madani, M.; Tabatabaei, F.; Tabatabaee, Z. The Relationship between Serum Vitamin D Level and Attention Deficit Hyperactivity Disorder. Iran J Child Neurol. 2015, 9(4), 48-53.

31. Qayyum, A.; Zai, C.C.; Hirata, Y.; et al. The Role of the Catechol-o-Methyltransferase (COMT) GeneVal158Met in Aggressive Behavior, a Review of Genetic Studies. Curr Neuropharmacol. 2015, 13(6), 802-814.
32. Kereszturi, E.; Tarnok, Z.; Bognar, E.; et al. Catechol-O-methyltransferase Val158Met polymorphism is associated with methylphenidate response in ADHD children. Am J Med Genet B Neuropsychiatr Genet. 2008, 147B(8), 1431-1435.
33. Kabukcu, B.B.; Buber, A.; Basay, O.; et al. White matter alterations related to attention-deficit hyperactivity disorder and COMT val158met polymorphism: children with valine homozygote attention-deficit hyperactivity disorder have altered white matter connectivity in the right cingulum (cingulate gyrus), Neuropsychiatric disease and treatment. 2016, 969-981.
34. Gallaway, K.A.; Skaar, T.C.; Biju, A.; Slaven, J.; Tillman, E.M. A pilot study of ADRA2A genotype association with doses of dexmedetomidine for sedation in pediatric patients. Pharmacotherapy. 2022, 42(6),453-459.
35. Yang, L.; Qian, Q.; Liu, L.; Li, H.; Faraone, S.V.; Wang, Y. Adrenergic neurotransmitter system transporter and receptor genes associated with atomoxetine response in attention-deficit hyperactivity disorder children. J Neural Transm (Vienna). 2013, 120(7), 1127-1133.
36. Roman, T.; Polanczyk, G.V.; Zeni, C.; Genro, J.P.; Rohde, L.A.; Hutz, M.H. Further evidence of the involvement of alpha-2A-adrenergic receptor gene (ADRA2A) in inattentive dimensional scores of attention-deficit/hyperactivity disorder. Mol Psychiatry. 2006, 11(1), 8-10.
37. Cheon, K.A.; Cho, D.Y.; Koo, M.S.; Song, D.H.; Namkoong, K. Association between homozygosity of a G allele of the alpha-2a-adrenergic receptor gene and methylphenidate response in Korean children and adolescents with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2009, 65(7), 564-570.
38. Hervas, A.; Serra-LLovich, A.; Rueda, I.; Targa, I.; Guijarro S, Bigorra A, Cancino, M.; Bote, V.; Cárcel, M.; Amasi-Hartoonian, N.; Hernandez, M.; Arranz, M.J. Pharmacogenetic influences on the response to pharmacological treatment in autism spectrum disorders. Journal of Translational Genetics and Genomics. 2021, 5(3), 278-87.
39. Liu, Y.; Zhao, J.; Fan, X.; Guo, W. Dysfunction in Serotonergic and Noradrenergic Systems and Somatic Symptoms in Psychiatric Disorders. Front Psychiatry. 2019,10:286.
40. Hou, Y.W.; Xiong, P.; Gu, X.; Huang, X.; Wang, M.; Wu, J. Association of Serotonin Receptors with Attention Deficit Hyperactivity Disorder: A Systematic Review and Meta-analysis. Curr Med Sci. 2018, 38(3), 538-551.
41. Venkatesh, S.K.; Siddaiah, A.; Padakannaya, P.; Ramachandra, N.B. Association of SNPs of DYX1C1 with developmental dyslexia in an Indian population. Psychiatr Genet. 2014, 24 (1):10-20.
42. Wang, Y.; Paramasivam, M.; Thomas, A.; et al. DYX1C1 functions in neuronal migration in developing neocortex. Neuroscience. 2006, 143(2):515-522.
43. Diaz, R.; Kronenberg, N.M.; Martinelli, A.; Liehm, P.; Riches, A.C.; Gather, M.C. ; Paracchini, S. KIAA0319 influences cilia length, cell migration and mechanical cell–substrate interaction." Scientific Reports 12.1 ,2022, 722.
44. Price, K.M.; Wigg, K.G.; Eising, E.; Feng, Y.; Blokland, K.; Wilkinson, M.; Kerr, E.N.; Guger, S.L. Quantitative Trait Working Group of the GenLang Consortium; S.E. Fisher, M.W. Lovett, L.J. Strug, C.L. Barr. Hypothesis-driven genome-wide association studies provide novel insights into genetics of reading disabilities, Translational psychiatry 12.1, 2022, 495.
45. Cui, Z.; Xia, Z.; Su, M.; Shu, H.; Gong, G. Disrupted white matter connectivity underlying developmental dyslexia: A machine learning approach. Hum Brain Mapp. 2016, 37(4):1443-1458.
46. Liu, Y.; Chang, X.; Qu, H.; et al. Non-coding structural variation differentially impacts attention-deficit hyperactivity disorder (ADHD) gene networks in African American vs Caucasian children. Sci Rep. 2020, 10(1):15252.
47. Regan, S.L.; Williams , M.T.; Vorhees, C.V. Latrophilin-3 disruption: Effects on brain and behavior. Neurosci Biobehav Rev. 2021, 127:619-629.

48. D'Andrea, I.; Fardella, V.; Fardella, S.; et al. Lack of kinase-independent activity of PI3Kγ in locus coeruleus induces ADHD symptoms through increased CREB signaling. EMBO Mol Med. 2015, 7(7), 904-917.
49. Ouadih-Moran, M.; Muñoz-Hoyos, A.; DMarco, L.; Molina-Carballo, A.; Seiquer, I.; Checa-Ros, A. Is S100B Involved in Attention-Deficit/Hyperactivity Disorder (ADHD)? Comparisons with Controls and Changes Following a Triple Therapy Containing Methylphenidate, Melatonin and ω-3 PUFAs. Nutrients. 2023, 15(3):712.
50. Wong, T.S.; Li, G.; Li, S.; et al. G protein-coupled receptors in neurodegenerative diseases and psychiatric disorders. Signal Transduct Target Ther. 2023, 8(1), 177.
51. Sánchez-Morán, M.; Hernández, J.A.; Duñabeitia, J.A.; et al. Genetic association study of dyslexia and ADHD candidate genes in a Spanish cohort: Implications of comorbid samples [published correction appears in PLoS One. 2018 Dec 19, 13(12), e0209718]. PLoS One. 2018, 13 (10):e0206431.
52. Ho, S.K.L.; Tsang, M.H.Y.; Lee, M.; et al. CTNNB1 Neurodevelopmental Disorder. 2022 May 19. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. Gene Reviews® [Internet]. Seattle (WA): University of Washington, Seattle, 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK580527/
53. Kim, K.M.; Choi, S.W.; Kim, D.; Lee, J.; Kim, J.W. Associations among the opioid receptor gene (OPRM1) A118G polymorphism, psychiatric symptoms, and quantitative EEG in Korean males with gambling disorder: A pilot study. J Behav Addict. 2019, 8(3):463-470.