Genetic Associations with Dyslexia and Attention Deficit Hyperactivity Disorder

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Abstract

Dyslexia and attention deficit hyperactivity disorder (ADHD) are each highly heritable neurodevelopmental disorders. Dyslexia is a learning disability that generally causes difficulty in reading and associated language tasks while ADHD is associated with difficulty focusing and excess energy, among other symptoms. Dyslexia and ADHD affect approximately 20% and 5% of the population, respectively, and it is fairly common for patients with one of these disorders to also have the other (roughly 24% of people with dyslexia also have ADHD). The high heritability of both conditions suggest that genetics play a large role in their development. Various studies have discovered candidate risk genes and associated chromosome regions for these two disorders, and overlap between the associated genes and regions for both. This literature review overviews strong candidate genes and describes their functions, as well as some specifics of their associations. With this information, we hope to estimate how mutation in the genes would increase the risk of a patient having one or both of these disorders. The genes reviewed that were associated with ADHD or dyslexia individually encoded proteins with similar functions to one another—likely due to consistencies in how each disorder impacts neural functions—while the genes associated with both had more varied roles. Based on this finding, more studies should be conducted to strengthen the association between ADHD and dyslexia and these genes so that we can come closer to proving causation of the disorders.

1. Introduction

Dyslexia and attention-deficit hyperactivity disorder (ADHD) are neurodevelopmental disorders, found in approximately 20% of the overall population for dyslexia and 8.7% of adolescents for ADHD.[1,2] The high prevalence of the disorders results in a large impact in much of the population socially, educationally, and economically. There is also a significant number of people who experience both disorders simultaneously; approximately 24% of dyslexic individuals also have ADHD.[3]

ADHD and dyslexia are both commonly diagnosed in children and generally impact learning. Common symptoms of ADHD include impulsivity, difficulty focusing, and hyperactivity. Dyslexia is generally characterized by difficulties with reading, writing, spelling, short-term memory, and recognition of units of sound in language (phonemes).[4]

Both disorders are also highly heritable—meaning there is a high rate of family members of individuals with the disorders also being diagnosed with them. To investigate this high heritability, many studies have been conducted evaluating genetic and environmental factors that could influence the development of dyslexia or ADHD. As a result, regions in the human genome as well as specific gene variants have been strongly associated with the disorders, though direct genetic causations have not been found.[5,6]

The study of genetic associations with dyslexia and ADHD led to the discovery that the two disorders share some overlapping risk factors, meaning that one risk allele could increase the likelihood of having both disorders.[7] This could lead to interesting explanations for the common

co-occurrence of the two disorders, as the likelihood of co-occurrence would strengthen when individuals have these overlapping risk alleles.

Given that ADHD and dyslexia are prominent disorders that commonly co-occur, it is crucial to study genetic factors involved in their development in order to assess what distinguishes them and what causes them to often appear simultaneously. This review evaluates a select number of genes that have been associated with incidence of dyslexia, ADHD, or both of these disorders. To explore how mutations in these genes increase risk of having dyslexia and ADHD, we discuss their functions as well as individual traits they have been associated with.

1.1 Dyslexia and ADHD

Dyslexia and attention-deficit hyperactivity disorder are very complex, and the specific symptoms people experience with the disorders can differ and occur at varying degrees (Figure 1). Dyslexia generally impacts reading and language abilities, like word reading, phoneme awareness, and spelling.[8] It decreases performances in verbal and numerical Stroop tasks—which test the delay in reaction time caused by contrast between written words or numbers and the visual stimuli attached to them. People with dyslexia are typically worse at rapid automatized naming (RAN) tests, in which the participant must quickly name images and colors.[8,9] Dyslexia can also cause symptoms beyond language processing, such as issues with short-term memory and distinguishing between left and right.[4] Many studies on the correlation between genes and dyslexia have participants do tests like the Stroop and RAN tasks to determine if genes are related to specific phenotypes seen in dyslexia.

ADHD is primarily associated with inattention, hyperactivity, and impulsivity, and, in studies on ADHD, attentiveness in particular is focused on. This inattentiveness can relate to difficulty focusing, maintaining concentration on a task, and struggling with long-term tasks.[10] Tests such as the Attentional Network Task are used to evaluate attentiveness of participants in studies.[8] Though not related to typical symptoms of ADHD, the numerical and verbal Stroop tasks are also used on participants with ADHD in some studies.[8]

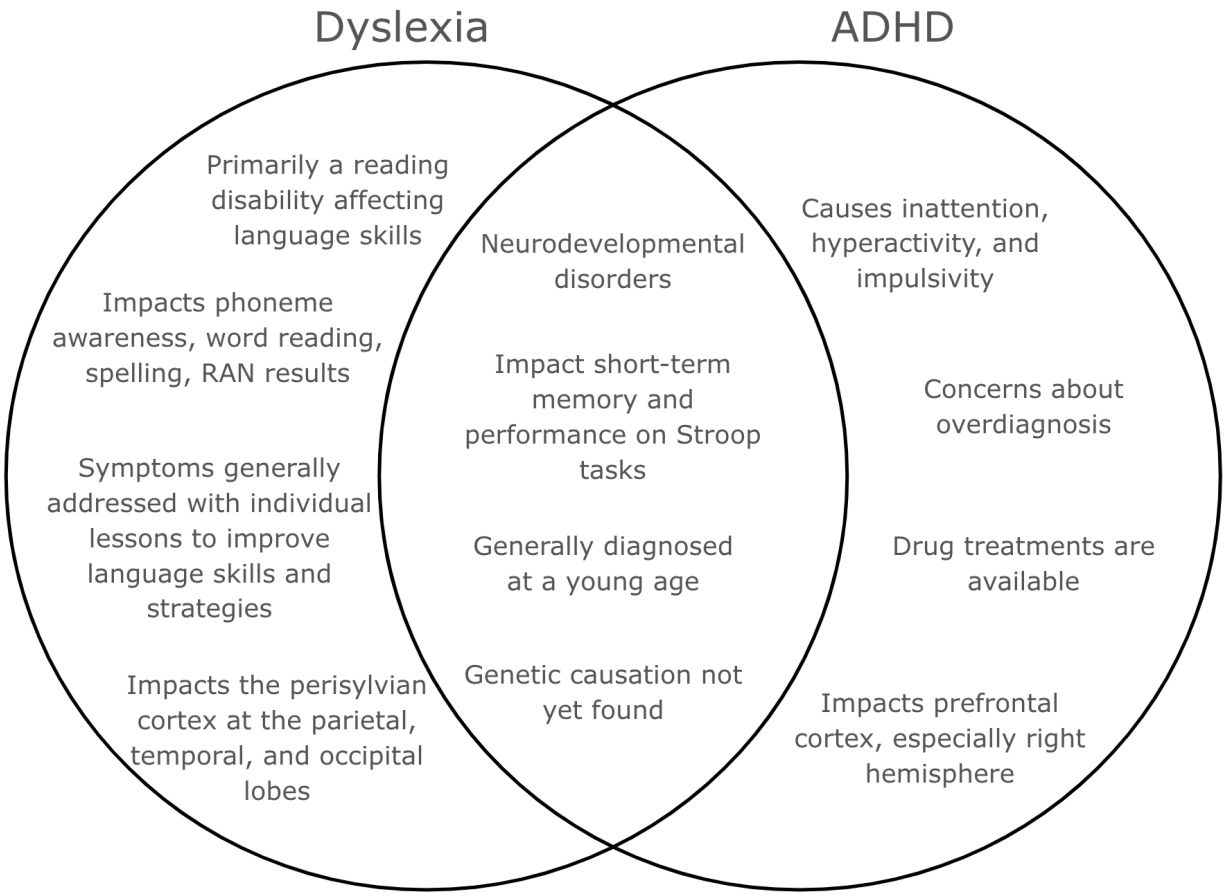

Figure 1. Dyslexia and ADHD Comparison. A summary of traits specific to either ADHD or dyslexia individually, and traits that are shared in common between the two neurodevelopmental disorders. Recognizing the similarities and differences between the two disorders is important to understand the significant overlap of the disorders in individuals.[11,12]

1.2 Difficulties in Studying Dyslexia and ADHD

Dyslexia and ADHD can be very difficult to study because their symptoms can be experienced to different degrees, creating inconsistencies in the experience and presentation of the disorders in individuals.[8,13] As genes are often correlated with specific phenotypes, having participants that experience phenotypes differently could negatively impact the results of the study.[8]

Another difficulty with studies on these disorders relates to diagnoses; the complexity of dyslexia and ADHD make it difficult to always be accurate with diagnoses. With ADHD in particular, the steady rise in diagnoses over time has caused concern that it is being overdiagnosed, which would cause issues with studies because some people diagnosed with ADHD may not actually have it.[14] Conversely, there is concern that certain communities are underdiagnosed with these learning disorders, partially due to the cost of getting tested for them.[14] In addition, there are errors due to sex, where males are three times more likely to get diagnosed, likely because they typically display more hyperactive symptoms, while females generally display inattention symptoms, which may be missed by doctors.[13] The overall misrepresentation of these disorders

could cause errors in studies on them. Still, it is this difficulty that makes it especially important to study genetic factors involved with ADHD and dyslexia, as knowing more about genetic risk factors may aid in diagnosis.

1.3 Understanding Genetics

To understand genetic risk factors of ADHD and dyslexia, it is first important to understand the mechanics of genes. Genes contain information that cells use to build proteins in a particular structure that enables them to function properly and support various systems in the body. Genes are located on different loci, or regions, of chromosomes. Loci are named first by identifying which chromosome they are on with a number from 1 to 22 or an X or a Y, then whether they are on the short arm (p) or long arm (q), and finally by a number denoting its position on that arm (Figure 2).[15] For example, the locus 6p22 is on the sixth chromosome, on the short arm, at position 22.[15] Humans have two copies of each chromosome, one from each biological parent, and the differences between these chromosomes comes from the different alleles on each of them.[16] Alleles are different versions of each gene created by mutations in that gene.[16] An incredibly common type of mutation is a SNP, or single nucleotide polymorphism, which happens when one nucleotide, a building block of genes, is put in place of another.[17] Some SNPs and other mutations can cause minimal to no changes to protein structure, while others can stop the full protein from being made at all; generally, different alleles cause proteins to function slightly differently, creating the differences observed between each person.[17] So, studies on the genetics of disorders look for specific alleles of genes that change the encoded protein structure in such a way that it causes or encourages a symptom seen in the disorder.[17]

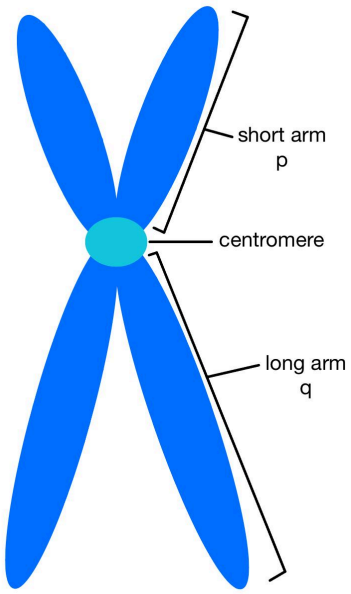

Figure 2. Chromosome Regions. A visual representation of short (p) and long (q) arms of a chromosome, where the numerical position of a locus on each arm increases the farther it is from the centromere. Adapted from a figure by the U.S. National Library of Medicine.[15]

1.4 Studies on Genetics of Neurodevelopmental Disorders

In studies on genetics of disorders, there is a crucial distinction between association and causation. Association is found when there is a trend of people with a disorder commonly having a specific allele of a gene; association implies that people with this allele are more likely to have the disorder. The strength of associations between genes and disorders can vary, and many studies find contradictory results on whether or not an allele is associated with a disorder.[8] Gene associations can be useful in estimating the likelihood of someone having a disorder. Polygenic risk scores use the amount of risk alleles—alleles associated with a disorder—a person has to approximate the chances they have a disorder, with people with more risk alleles having a higher approximated likelihood.[7] In short, though having associated alleles does not guarantee that one has a disorder, they can be useful indicators that could aid in the process of diagnosis.[7]

Findings of genetic causation, however, does produce definitive results. Causal genes must be directly related to symptoms of the disorder, and having a certain allele of these genes leads to the development of these symptoms. Causation is more useful in diagnosis, but it is much more difficult to find and prove—particularly because we cannot control all variables in studies on humans, which is necessary for proving causation.

Finding causal genes of neurodevelopmental disorders is very difficult and, consequently, rare—one of the few genes found to cause a neurodevelopmental disorder is FOXP2 with speech language disorder 1.[18] Still, many associations have been found, and it is very likely that these disorders are caused by combinations of different alleles, along with environmental factors.[19] Neurodevelopmental disorders are caused by disturbance of different neurodevelopmental pathways and processes, so most genes associated with or causing them have functions in these pathways, and it is common for them to overlap between disorders.

1.5 Overview of Studies on Genetic Association with Dyslexia and ADHD

Dyslexia and ADHD are two disorders that commonly have overlapping associated genes, and there is particularly strong overlap in polygenic risk scores calculated for the two disorders. Genetic causation has not been found for either disorder, so the associations are the strongest genetic factors known so far and are the focus of this paper.

Many different types of studies have been conducted to find these associations. One of the most common types is a genome-wide association study (GWAS). GWAS collects information on genotypes of participants and use statistically-significant trends in which alleles frequently appear in people with the disorder or the phenotype in order to determine whether an allele can be associated with the disorder, and how strong the association is.[3]

Family studies are also commonly conducted on ADHD and dyslexia, though generally for finding evidence of heritability and influence of genetic factors. Twin and adoption studies are two common subsets in family studies. Adoption studies are generally conducted to distinguish between the influence of genetic and environmental factors in the development of a disorder. Twin studies focus on twins with identical genetic information and have found that they are much more likely to have the same diagnosis than with other siblings.[20] Family studies in general can track the inheritance of certain alleles of genes and of dyslexia or ADHD in order to find

association between the two. Large families are generally used to decrease error, though it is generally difficult to replicate results in other studies.

2. Genes Associated with Dyslexia and ADHD

Gene Symbol	Disorder Associated With	General Function
TTRAP/TDP2	Dyslexia	Repairing errors in gene transcription, preventing mutation
DCDC2	Dyslexia	Involved in neuron migration and signal pathways
KIAA0319	Dyslexia	Influences neuron migration
ROBO1	Dyslexia	Neuron migration and axon guidance
DRD4	ADHD	Dopamine receptor
DAT1/SLC6A3	ADHD	Dopamine transporter
HTR1B	ADHD	Signals release of serotonin and dopamine
5HTT/SLC6A4	ADHD	Serotonin transporter
DYX1C1	Dyslexia & ADHD	Interacts with estrogen receptor, maintains cell function
FOXP2	Dyslexia & ADHD	Transcription factor
SORCS3	Dyslexia & ADHD	Cell signaling and protein sorting
AMT	Dyslexia & ADHD	Glycine breakdown into methyl groups

Table 1. Symbol, Association, and Function of Reviewed Genes.

2.1 Genes Associated with Dyslexia

Dyslexia is a neurodevelopmental disorder related to language and reading ability. It primarily impacts spelling, writing, and reading fluency, but has also been found to lower performance on RAN tasks, phoneme recognition, short term memory, and word recognition.[4] Dyslexia is highly heritable and has been associated with various genetic risk factors, though no genetic causation

has been found.[3] Four genes in particular, TTRAP, DCDC2, KIAA0319, and ROBO1, are strongly associated with dyslexia.

2.1.1 TTRAP (TDP2)

The gene TTRAP has been found to have strong association with dyslexia. The official name of TTRAP is tyrosyl-DNA phosphodiesterase 2 and the official symbol is TDP2. It is located at 6p22.3 in the human genome and is expressed mostly in the colon, small intestine, and duodenum.[21] The TDP2 protein plays an important role in gene transcription, repairing double strand breaks in DNA caused by topoisomerase II, an enzyme that makes breaks in the backbone of one strand of DNA to lessen supercoiling during gene transcription.[22] This function makes TDP2 an essential for gene replication without increased risk of mutation. In mice, TDP2 deficiency resulted in abnormal levels of expression of certain genes in the developing brain because there was less protection against topoisomerase-induced double strand breaks.[22] This included genes associated with neurological functions and the density in between neurons in the cerebellum.[22] Decreased expression in the TTRAP gene due to mutation could inhibit normal neuron development in the brain, and abnormal neuron development could cause some of the learning differences seen in people with dyslexia.[22]

The SNP rs2143340 in the TTRAP gene is part of a 3-SNP haplotype in the TTRAP, KIAA0319, and THEM2 region that has been strongly associated with dyslexia in multiple studies.[23] These three SNPs cause reduced expression in the genes, which matches the connection found in mice between TTRAP expression and normal neural development.[23] In a study analyzing reading and spelling ability in twins and siblings, the rs2143340 mutation was also specifically associated to these skills.[24] Therefore, strong association has been found between the rs2143340 mutation and traits for dyslexia, and possible explanations for this association can be found in the gene's function during gene replication.

2.1.2 DYX2

TTRAP is located on dyslexia-susceptibility 2 (DYX2), one of nine primary loci that have been strongly associated with risk of having dyslexia.[6] Also on DYX2 are KIAA0319 (6p22.3) and DCDC2 (6p22.1), are strongly associated with dyslexia.[8] KIAA0319 is most expressed in the brain, while expression of DCDC2 is highest in the kidney and thyroid.[25,26]

DCDC2 is a member of the doublecortin domain-containing family, which aids in forming microtubules in the body by binding tubulin proteins together.[25] The general function of the family does not explain the association found between the gene and dyslexia, but DCDC2 is specifically involved in neuron migration and signal pathways.[25] Because the DCDC2 protein impacts the location of neurons and signaling in the brain, it is plausible that mutations in the gene would impact learning and increase risk of dyslexia.

The KIAA0319 gene encodes a transmembrane protein that also is likely to influence neuronal migration, and consequently impacts the development of the cerebral cortex.[26] As the cerebral cortex handles many tasks impacted by dyslexia, such as memory and writing, the role of KIAA0319 in cerebral cortex development would support its identification as a risk region for dyslexia.[27]

Multiple SNPs of both genes have been associated with dyslexia, including rs4504469, rs3212236, and rs6935076 in KIAA0319 and rs807724, rs2274305, and rs4599626 in DCDC2.[28,29] The rs4504469 variation of KIAA0319 has been associated with the phenotypes for word reading, syllable discrimination, and the RAN and numerical Stroop tasks. The rs2274305 allele in DCDC2 is also associated with RAN performance as well as the recognition of different sounds in a language, or phoneme awareness.[8] Interestingly, having risk alleles in both KIAA0319 and DCDC2 greatly increases the likelihood of having dyslexia compared to when only a risk allele in one is present.[8] As they both function in neuronal migration, it is likely that having the risk alleles in combination impacts neuron pathways by such an extent that the risk for dyslexia is greatly increased. The association with dyslexia and dyslexia-related phenotypes in the DYX2 locus and in the KIAA0319 and DCDC2 genes make these two genes strong candidates for risk genes.

2.1.3 ROBO1

Roundabout guidance receptor 1 (ROBO1) is another strong candidate risk gene for dyslexia. It is located at 3p12.3.[30] It is expressed throughout the body, but most in the brain and skin.[30] The high expression in the brain increases the likelihood mutation in the gene could heighten risk of dyslexia by disrupting normal brain function. The ROBO1 protein is part of the immunoglobulin gene superfamily, and it aids in neuron migration, specifically in guiding axons across the midline of the brain.[30,31] Because of this important role in the structure of the brain, like with KIAA0319 and DCDC2, mutation in ROBO1 that decreases its expression or prevents its functions would likely disrupt normal brain function and could possibly lead to a neurodevelopmental disorder like dyslexia.

One study on dyslexic individuals with an allele for ROBO1 that impacted the expression of the gene found that inhibition of the ROBO1 protein's functions is a likely risk factor for dyslexia.[31] This result aligns with the theory that underexpression of ROBO1 could encourage the development of dyslexia by disturbing normal brain structure. Seven primary mutations in the ROBO1 gene were found in a sample of dyslexic individuals: two SNPs at the 12th and 18th exons, the deletion and insertion of 3 base pairs, four SNPs in introns of the gene, and four SNPs in the noncoding region of the gene.[31] The SNP rs12495133 is one of few in ROBO1 that has been associated with dyslexia in multiple studies with little evidence to the contrary, making it the strongest candidate allele in ROBO1 for dyslexia.[4]

2.2 Genes Associated with ADHD

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized primarily by inattention and impulsivity. Neurotransmitters, signaling molecules that travel between neurons, often function abnormally in ADHD brains; neurotransmitter dysfunction is a large contributor to ADHD symptoms.[10] Like dyslexia, ADHD is highly heritable, and many risk genes have been associated with increased risk of developing ADHD.

2.2.1 Dopamine Receptor and Transporter

The neurotransmitter dopamine is key in the reward and pleasure systems in the brain.[10] Individuals with ADHD are likely to have lower levels of dopamine in the brain, causing them to focus on immediate rewards and struggle to complete long-term tasks.[10] Two genes whose proteins interact with dopamine, and thus could influence some ADHD symptoms, are dopamine receptor 4 (DRD4) and solute carrier family 6 member 3 (SLC6A3), also known as DAT1. DRD4 is located on chromosome 11 at 11p15.5.[32] DAT1 is found at 5p15.33.[33] The DRD4 protein is a G-protein coupled receptor and a receptor for dopamine.[32] DAT1 is a member of the sodium- and chloride-dependent neurotransmitter transporter family and aids in transport of dopamine.[33] Because both proteins interact with dopamine, they could impact levels and function of dopamine in the brain, causing abnormalities in the rewards system and possibly certain symptoms associated with ADHD.

Strong association has been found for DAT1 and DRD4 in studies with selected candidates, though GWAS have not been as successful in replicating these results.[34] So, the association with DAT1 and DRD4 currently does not have the strongest or most consistent support, though some evidence of association has been produced. Associations between these genes and phenotypes for ADHD have also been weaker, though DRD4 is expressed in regions of the brain dealing with planning and the rewards system, both of which are often impacted by ADHD.[34,35] In spite of the weaker associations found in various studies, the regions DRD4 is expressed and the interaction between the genes and a neurotransmitter that is impacted by ADHD suggest that mutations in DRD4 and DAT1 are likely to increase likelihood of someone having ADHD.

2.2.2 Serotonin Receptor and Transporter

Serotonin, like dopamine, is a neurotransmitter working in the rewards and pleasure system, so it is probable that it, too, acts or appears differently in the ADHD brain. Two genes, HTR1B and 5HTT, are known to interact with serotonin. 5-hydroxytryptamine receptor 1B (HTR1B) is located at 6q14.1.[36] The 5HTT gene, or solute carrier family 6 member 4 (SLC6A4), is located at 17q11.2 and is most expressed in the lungs and small intestine.[37]

5HTT encodes a membrane protein that facilitates the reuptake of serotonin into the presynaptic neuron after signaling.[37] Mutation in 5HTT would limit uptake of serotonin, leaving less serotonin in the presynaptic neuron the next time the signal must be sent and decreasing the amount of active serotonin in the brain. HTR1B is a G-protein coupled receptor for serotonin that, after binding to serotonin, acts as a messenger regulating the release of neurotransmitters like serotonin and dopamine. Because serotonin is involved in the brain's rewards system, change in its activity and concentration in the brain can also be correlated with ADHD phenotypes. As 5HTT and HTR1B proteins impact the levels that are or can be released, there is a high likelihood that mutations in these genes are involved in ADHD symptoms like preference of short-term rewards over long-term.

Association of ADHD between dopamine-related genes has been more extensively studied than that with genes that interact with serotonin, but animal studies have found that disruption in serotonin role can lead to the inattentive and hyperactive traits seen in ADHD, so HTR1B and 5HTT can be linked to ADHD symptoms through their impact on serotonin.[38] Linkage between

the HTR1B gene and ADHD has not been particularly strong, but multiple studies have identified the G861 allele as a potential risk factor, possibly just for the inattentive aspect of ADHD.[39,40] Some studies have found association between ADHD and an allele of 5HTT with 44 deleted base pairs in the untranslated region—a mutation that would hinder expression of the gene—though there has not always been success in replicating this association.[38] In spite of its weakness, there is evidence of association between 5HTT and HTR1B and ADHD, and the interactions of these proteins with serotonin supports their association.

2.3 Genes Associated with Both Dyslexia and ADHD

An estimate of about 24% of people with dyslexia also have ADHD, and strong genetic correlation between the two disorders has been found.[3] DYX1C1, FOXP2, SORCS3, and AMT are strong examples of overlapping risk genes for the two disorders.

2.3.1 DYX1C1

The DYX1C1 gene, also known as dynein axonemal assembly factor 4 of DNAAF4, is located on chromosome 15 at 15q21.3.[41] It has broad expression across many tissues, primarily the thyroid and testis.[41] In the brain, the protein encoded by the gene is accumulated in neurons and white matter glial cells—cells that surround neurons and support their function.[42] The DYX1C1 protein interacts with estrogen receptors as well as the heat shock proteins Hsp70 and Hsp90.[41] The protein is likely responsible for maintaining cell function when it is challenged or exposed to different environments.[42] The known functions of the DYX1C1 protein, which are broadly needed in the whole body or part to processes unrelated to neurodevelopmental disorders, make it unlikely that the gene is directly related to neurodevelopmental disorders such as ADHD and dyslexia. Still, association between them has nonetheless been found.[20]

Studies have associated the DYX1C1 gene with both ADHD and dyslexia, though the association with dyslexia is much stronger than that with ADHD. Two different mutations in the DYX1C1 gene have been associated with dyslexia, the first being an adenine in place of a guanine in the -3 location in the binding site for the Elk-1 transcription factor, and the second being a premature stop caused by a thymine replacing the 1249 guanine, shortening the coding region by 4 amino acids.[42] The first mutation would influence gene expression by making transcription factors, which encourage transcription, less likely to bind to binding sites; the latter mutation would inhibit functions of the protein due to the change in structure from the premature stop. Mutations in the gene have been shown to specifically influence word-reading, spelling, performance on RAN tasks, and short-term memory, all of which are impacted by dyslexia.[8] Specific risk alleles for ADHD, meanwhile, have not been found, though one allele containing six SNPs was correlated with attention-related symptoms.[43]

DYX1C1 has been linked to both disorders, or at least their symptoms. The specific mutations involved in the association differ, so it is improbable that the gene influences the likelihood of individuals having both disorders.

2.3.2 FOXP2

Another gene associated with dyslexia and ADHD is forkhead box P2 (FOXP2), located at 7q31.1.[18] The highest expression of the FOXP2 gene has been found in the ovary, esophagus, endometrium, and thyroid.[18] FOXP2 is a member of the forkhead/winged-helix family and a transcription factor, which regulates expression of other genes by binding to gene promoter regions.[18] This transcription factor regulates the expression of approximately 300 to 400 genes, causing it to have a broad influence.[18] It may be involved in various processes indirectly influencing language development, and it is necessary for development of speech and language—it has even been found to cause speech-language disorder 1.[18] The FOXP2 protein's crucial role influencing speech language, likely through its impact on the expression of hundreds of other genes, make it a strong candidate risk gene for dyslexia—but the correlation is less strong with ADHD.

The rs12533005 SNP in FOXP2 has been associated with dyslexia as well as specific phenotypes related to dyslexia, such as performance in verbal and numerical Stroop tasks, short-term memory, and phoneme awareness.[8] Though association certainly seems stronger with dyslexia, rs12533005 has also been correlated with attentional tasks related to ADHD.[8] FOXP2, like DYX1C1 has a stronger association with dyslexia, though it has been correlated with phenotypes from both disorders, and its general role as a transcription factor make it plausible that FOXP2 indirectly impacts attention or hyperactivity along with speech and language issues.[8]

2.3.3 SORCS3

Sortilin-related receptor 3 (SORCS3), another and ADHD- and dyslexia-associated gene, is located at 10q25.1.[44] The gene is expressed most in the brain, and the encoded protein is found in high abundance in the central nervous system.[44] The SORCS3 protein is a member of the vacuolar protein sorting 10 receptor family and acts as a receptor membrane protein.[44] It plays a role in cell signaling and, in the intracellular space, it aids in sorting proteins between organelles and the cell membrane.[45] Because of the protein's role in cell signaling and its abundance in the brain, SORCS3 is likely critical for signaling in the brain. Therefore, mutation in the SORCS3 gene could disrupt signaling in the brain, leading to symptoms of ADHD and dyslexia.[44]

The SORCS3 gene has been associated with both of these disorders, and it has also been connected to intellectual delay, which further suggests that mutation in the gene can impact learning and brain functions.[45] In mice, SORCS3 protein deficiency often caused reduction in spatial learning and memory, which, if also true for humans, would support the association between the gene and the two disorders, as decreased spatial learning is often associated with both ADHD and dyslexia.[45] The SORCS3 association with both disorders is strong due to its role in cell signaling and prevalence in the brain, as well as its correlation with the disorders and some of their phenotypes.

2.3.4 AMT

Another prominent gene associated with dyslexia and ADHD is AMT. Its official name is aminomethyltransferase, and it is located at 3p21.31.[46] The gene is expressed in many tissues throughout the body.[46] The AMT protein is a member of the glycine cleavage system, which is

responsible for breaking down the neurotransmitter glycine.[47] The breakdown of excess glycine, aided by the AMT protein, is critical for normal neuron development. Glycine decomposition also produces methyl groups that can be used by folate, a key substance for normal brain development.[47] The AMT protein is key for developing normal neuronal and brain structures because it breaks down glycine and indirectly causes folate to be methylated. It is thus probable that mutation in the AMT gene would disrupt normal brain development and increase the risk of having neurodevelopmental disorders like ADHD and dyslexia.

A strong association was found, through GWAS, between AMT and level of education reached by an individual, and it is likely also associated with learning ability.[45] ADHD and dyslexia are linked to an impact on both of these traits, strengthening the association between the AMT gene and both of these disorders, though many other phenotypes related to them were found to have weaker associations.[45] Still, AMT's essential role in developing brains through glycine breakdown and consequent methylation of folates along with its correlation with some traits associated with dyslexia and ADHD make it a strong candidate risk gene.

3. Conclusion

There is a wide range of genes associated with dyslexia and ADHD—and a rather significant amount associated with both—though some trends stand out. For example, many genes strongly associated with dyslexia played critical roles in neuronal migration, and many associated with ADHD had functions related to neurotransmitters. The genes associated with both disorders had more variance in functions, though it is likely that the broader nature of their roles explains why they were associated with both of these complex disorders.

Though these genes have not been found to cause ADHD or dyslexia, studying their function and influence is still critical to better understand the disorders and, possibly, why they so commonly co-occur. It is likewise important that studies continue to be conducted to further strengthen or discover genetic associations; in fact, strong, statistically significant association between a disorder and a gene is one of the strongest and most common bases for causal inference, so researching and reinforcing associations can be a large step towards finding causation.[48] In addition, making more discoveries on this topic can ameliorate understanding of differences in ADHD and dyslexic brains, and possibly improve support given to these individuals. It could also aid in diagnosing these disorders by identifying who should be tested based on genotype, hopefully decreasing some disparities seen in diagnoses. Overall, associations should continue to be studied, with functions of genes simultaneously researched in order to find not only which alleles increase likelihood of having a disorder, but also how they influence this outcome.

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