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Genetic variants and influence in cognitive diseases

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Abstract

The relationship between genetic variation and cognitive ability has become a central focus in modern genetics and neuroscience. Cognitive functions are complex traits influenced by both genetic and environmental factors. Over the past decades, advances in genomic technologies, such as genome-wide association studies (GWAS), have revealed a multitude of genetic variants associated with cognitive performance. One of the most studied types of genetic variation are single nucleotide polymorphisms (SNPs), which represent the most common form of variation in the human genome. Evidence indicates that copy number variations (CNVs) play an important role along with the SNPs.

Keywords: Hippocampal; SNP; CNV; APOE; TAQ1A; BDNF; COMT; HOMER1A

1. Introduction

Cognitive capacity is the brain's ability to process information and carry out daily actions; within this set of mental skills we can find attention, perception, memory, comprehension, language, orientation and problem solving. It is also known that the degree of cognitive ability can be measured with different tests such as the Montreal Cognitive Assessment (MoCA), Mini Mental State Examination (MMSE) and more others, that, along with molecular techniques, were used to describe· Variant as the presence of two or more variable forms of a specific DNA sequence that can occur among different individuals or populations, affecting the development of normal cognitive capacities. There are two different types of genetic variants or polymorphisms described which are: Single nucleotide polymorphisms due to base substitution and sequence size polymorphisms due to insertions or deletions of DNA sequences or continuous base repeats in a DNA segment [1, 2, 3].

The subtle changes in the DNA sequence can have profound impacts on gene function, affecting brain development and neural pathways that underpin cognitive processes [4].

Additionally, larger-scale genomic alterations, such as copy number variations (CNVs), have been linked to cognitive disorders and intellectual disabilities, underscoring the complex relationship between genomic architecture and cognitive ability. Rare CNV are more likely to affect genes that play functional roles in neurodevelopmental pathways. Many CVN loci can cause cognitive impairment, ranging from mild to severe [5].

The following study aims to collect existing data based on certain specific genes that are associated with disorders that may affect neurodevelopmental functions, such as neuroplasticity, and its fundamental contribution to cognitive basic functions, going from specific genes affecting central areas involved in cognition, to disorders affected by the minimum change in the genome.

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This narrower approach still encompasses a diverse and overlapping set of cognitive constructs, the main focus is to highlight from a very general perspective the effects of common variants in a single nucleotide polymorphism (SNP), or copy number variations (CNV) of the following genes that are going to be approached: *APOE, TAQ1A, BDNF, COMT, HOMER1A*, which have been identified as key players in influencing some cognitive traits.

2. *APOE* gene and product ApoE isoform E4, and *ABCA1* cholesterol transporter in brain homeostasis

Knowledge of the effects of *APOE* (OMIM: 107741) genotype prior to Alzheimer's Disease (AD) could provide insight into normal cognitive strengths and weaknesses of individuals based on their *APOE* genotypes as well as their later risks of cognitive dysfunctions. These approaches demonstrate effects of *APOE* genotype primarily related to the hippocampal areas [6].

APOE encodes different ApoE proteins, which are produced predominantly in the brain by specialized cells; astrocytes. Is has a role in the transfer of cholesterol and phospholipids between brain cells, which maintains a long-term homeostasis by regulating vascular function, neuroinflammation, and metabolism. There are three mayor isoforms (ApoE2, ApoE3 and ApoE4) whereas apoE4 contains arginine and cysteine in positions 112 and 158, respectively. The difference in these positions dramatically changes the structure and function in this isoform, which mainly affects its affinity to LDL receptor (LDLR), leading to malfunctions in the transfer of lipids and amyloid β clearance. For instance, the *APOE* ε4 allele is associated with a higher risk of developing AD and cognitive decline overall, yet these molecular mechanisms are still unclear, there are studies that collate these developments and suggest possible explanations to this ApoE4 phenotypes [7]. In addition, Transporter ABCA1 mediates cholesterol efflux to the nascent ApoE particle in the brain. After sufficient amount of cholesterol and phospholipids bind to ABCA1, ABCA1 undergoes conformational changes, leading to dimerization and transfer of lipids to ApoE. This also indirectly facilitates amyloid β clearance through ApoE lipidation in brain [8].

Deletion of *ABCA1* (OMIM: 600046) has shown to increase amyloid β accumulation, which indirectly leads to long term cognitive disfunction [9].

3. Brain-derived neurotrophic factor (BDNF), kinase TrkB, receptor P75NTR and neuroplasticity

Neurotrophins are growth factors expressed in the central nervous system. Being *BDNF* gene (OMIM: 113505) an element that has shown to be important in neuronal growth and differentiation, along with synaptic plasticity. The human gene for *BDNF* was identified in 1991 (chromosome 11 band p13). It encodes a protein that compromises 247 amino acids, after being synthetized, binds 2 fundamental receptors: p75 NTR-sortilin complex and the TrkB receptor, both implicated in biological neuroplasticity effects, synaptic function and susceptible to malfunction due to the common *BDNF* Val66Met point substitution. These variants in *BDNF* have been linked to memory and learning capabilities. It highlights the intricate network of genetic factors that contribute to individual differences in cognitive function [10].

Memory deficits and reduction of some cognitive abilities were found to be associated with low functional BDNF protein concentrations caused by variants that compromises both the gene expression and receptor expression.

NTRK3 gene (OMIM: 191316), member of the TRK family of tyrosine protein kinase genes, and its product, a trkB receptor, also shows affinity for BDNF protein, with a high expression in the hippocampus and cerebral cortex, which helps regulating neurite development, promotes pathways that regulates synaptic plasticity (example: phospholipase Cγ pathway), showing an important capability to interact and influence neurotrophins and its role in cognitive development [11]. In humans, it has been discovered several variants in *NTRK3,* carriers exhibited learning difficulties, impaired memory, hyperactivity, stereotyped and sometimes, maladaptive behaviors, all impacting on hippocampal synaptogenesis [12].

4. Dopamine; *TAQ1A* variants for D2/D3 receptors, COMT as a regulator of synaptic dopamine and its influence on cognition

Dopamine is a key neurotransmitter known to influence cognitive function by having a strong activity on the prefrontal cortex (PFC), the dopaminergic system in modulating cognitive functions is well established. Dopamine dysfunction is well-documented in disorders in which cognitive traits plays a key role. A meta-analysis suggested that variants in *TAQ1A* gene (OMIM:166540) affecting Dopamine Receptor DRD2, limited cognitive performance on young adults [13, 14]. In addition, the evidence found a stronger influence in cognitive function, along with the BDNF protein, the enzyme

Catechol-O-methyltransferase (COMT) in dopamine catabolism in the PFC, which is found in the mitochondrial membranes of catecholaminergic neurons, being also concentrated in the extrasynaptic spaces maintaining normal dopamine levels in the PFC, influenciating inter-individual cognition [15].

COMT gene (OMIM:116790) appears to play a central role in modulation of subcortical and cortical dopamine transmission, the most common and well-studied variation has been described as a SNP val158met located on chromosome 22q11, resulting in the substitution of valine with methionine, producing an enzyme that results unstable at a normal body temperature [16].

This variation has been used to characterize atypical genotypes that shows lack of cognitive performance, this *COMT* variant was associated with poor episodic memory performance, midbrain activation, with gradual development of the long-term plasticity negative outcomes [17].

5. Hippocampal specific *HOMER1A* gene for Homer1A protein expression; variation susceptibility and overexpression

HOMER1A gene (OMIM: 604798) encodes for Homer1a, a type of postsynaptic juxtaposed protein, that has shown to play a role in activity-dependent changes of postsynaptic regions in the hippocampus, helping with neuroplasticity, specifically on neurons that are stimulated with glutamate, Homer1a appears to be a constitutive postsynaptic element, having its effect only when synapse occurs. This has been demonstrated by using fluorescent images of dendrites taken at various points right after glutamate stimulation on living neurons. The analysis of relative immunofluorescence intensity of endogenous Homer1a has been studied by using this technique along with anti-Homer1a antibodies, when it comes to quantify Homer1a protein expression. Other synaptic proteins (F-actin, synaptotagmin, synaptothypsin and synapsin) shows a similar pattern when glutamate stimulation induces a global alteration, being Homer1a the long term activity-induced biphasic changes regulator in the synaptic spaces [18].

When it comes to support cognition, hippocampus plays a role in the homeostatic build-up of sleep, which is known to have restorative benefits that support neural changes. Homer1a and its principal receptor metabotropic glutamate receptor 1/5 (mGluR1/5), both are implicated in sleep function [19]. Abnormal sleep phenotypes are likely to have poor promotion of cognitive development due to either a low *HOMER1A* or MGluR5 expression on the hippocampus, when other factors of circadian cycle regulation are not affected [20]. The contribution of mGluR1/5 to this molecular process was proven by using temporal RNAi-mediated knockdown of mGluR1/5 via *HOMER1A*, changing the threshold for glutamate activation [21].

6. Examples of common genetic variants in cognitive disorders

Any impairment of the intellectual functions has the potential to result in a range of adverse consequences for the individual, including diminished independence and an impaired capacity to adapt and learn from diverse environments, caused by different variants located in the same loci, or multiple impairments that can affect indirectly.

Schizophrenia; a multicausal disorder influenced by environmental and genetic factors

Schizophrenia is a chronic psychotic disorder in which the person experiences psychotic episodes characterized by positive, negative, and cognitive symptoms, each of which varies greatly from case to case [22, 23]. Negative symptoms include asociality, anhedonia, alogia, and avolition, which can lead to secondary clinical manifestations. Positive symptoms include delusions, hallucinations, and abnormal motor behavior [24]. Cognitive symptoms are nonspecific, meaning they may go unnoticed by the individual and are not associated with either positive or negative symptoms. They include deficits in working memory, executive function, and processing speed [25].

The etiology of schizophrenia remains unclear; however, it is widely accepted that it is a multicausal disorder influenced by both environmental and genetic factors [26]. Recent studies have identified various risk factors associated with the development of schizophrenia. Research indicates that the risk increases by about 50% if both parents have schizophrenia compared to individuals with no family history of the disorder [27].

In 2009, a genome-wide search identified three significant deletions associated with schizophrenia and psychosis, located at 1q21.1, 15q11.2, and 15q13.3 [28]. Among these, the deletion at 1q21.1 was found to be particularly relevant when distinguishing between cases of psychosis and schizoaffective disorder. This deletion spans approximately 1.38 Mb and includes the *GJA8* gene (OMIM:600897), also known as connexin-50; which encodes a gap junction subunit that

participates in intercellular communication [29, 30]. Has previously been linked to the manifestation of schizophrenia. However, the deletion is rare occurring in approx. 0.1% to 0.3% of cases [31].

Translocation in two genes, disrupted in schizophrenia 1, *DISC1* gene (OMIM: 605210), and disrupted in schizophrenia 2 or *DISC2* gene (OMIM: 606271), have been identified as potential risk factors for psychiatric illnesses such as major depression, bipolar disorder, and schizophrenia. *DISC1* encodes a protein involved in the regulation of neural development, while *DISC2* is a noncoding RNA gene [32, 33].

7. Progressive neurological diseases; how numerous variants contribute to Alzheimer's predisposition

7.1. Alzheimer's Disease

Alzheimer's disease is defined as a progressive neurodegenerative disorder and is the leading cause of dementia. The most common presentation is late-onset Alzheimer's disease (after the age of 65), which typically begins with mild memory loss; confusion, aggressive or amnesic episodes, agitation, hallucinations, and even seizures may occur as the disease slowly progresses [34]. The exact pathophysiologic mechanism remains unclear as multiple hypotheses have been formulated with discoveries; however, it is widely believed to be related to the formation of amyloid beta peptide (Aβ) plaques or the development of neurofibrillary tangles, causing cell death by triggering an inflammatory immune response. The proteolytic scission of amyloid precursor protein (APP) by β-secretase gene *BACE1* (OMIM: 604252) and γ-secretase gene *GSAP* (OMIM:612552) can generate a misfolded Aβ42 peptide that starts to deposit in the extracellular membrane. These plaques create a toxic environment, interrupting cellular communication; the consequent neuritic injury is created by microglial activation, cytokine release and inflammatory response [35].

Multiple factors can contribute to the increased accumulation of Aβ plaques in Alzheimer's disease, including genetic variations over *BDNF* expression (explained early on), variants in *APP* gene (OMIM:104760) and the presenilins *PSEN1* (OMIM: 104111) and *PSEN2* (OMIM: 600759), which are components of γ-secretase responsible for cleaving *APP.* To date, approximately 452 mutations have been identified in *APP*, 323 in *PSEN1*, and 63 in *PSEN2*. A re-evaluation study conducted in 2021 revealed that 89.16% of *PSEN1* variants, 46.97% of *APP* variants and 20.63% of *PSEN2* variants were classified as pathogenic or likely pathogenic; based on the guidelines set forth by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) in 2015 [36, 37].

8. Epigenetics and neurodevelopment; new genes on research

Epigenetics changes are still hereditable conditions, which alter the gene expression leading to disorders well known, this comes along with DNA methylation, histone modifications and chromatin remodeling. Epigenetic regulation plays a crucial role in all aspects of neurodevelopmental patterns [38, 39].

Most DNA methylations reported are associated with regression of gene expression, exclusively in promoters, this has been shown to be crucial for neurogenesis and maturation. Imprinting is also a mechanism that can be triggered by DNA methylations. Prader-Willi syndrome and Angelman syndrome both highlight this vital role on the biological events that occur in response of external factors, changing the gene expression patterns without changing the DNA sequence [40].

When it comes to DNA Histone modification, it has been shown that the presence of disruptions on acetylation/deacetylation regulation can lead to abnormalities on specific proteins associated with neurodevelopment, such as Dpy30, a protein subunit among many methyltransferases that leads to neurogenic deficits when affected [41].

Chromatin remodeling enzymes have been in the sight for several studies to show its implication on synaptic plasticity, even though the molecular mechanism of how genes *CHD1* (OMIM: 602118)*, BAF53B* (OMIM: 612458)*, ATRX* (OMIM: 300032) and *NEAT1* (OMIM: 612769) are related to remodeling hippocampus neural plasticity still unclear, collective studies reveal a potential for beginning to understand their functions and correlate sequencing analysis with diagnose [42, 43, 44].

9. A perspective on how twin studies reveal gene-environment interaction in cognitive development.

Twin studies are foundational in exploring gene-environment interactions (GxE) in cognitive development, distinguishing between genetic predispositions and environmental influences on traits like intelligence and language

skills. By comparing monozygotic (identical) twins, who share nearly all their genetic makeup, to dizygotic (fraternal) twins, researchers can better understand the role of both genetics and environment in these traits [45].

Findings typically show that cognitive traits are heritable, with genetics explaining up to 80% of the variance in traits like IQ by adulthood, though this influence is often lower in early childhood. This increase with age may reflect the individual's growing ability to control and shape their own environment. Notably, the "Twins Early Development Study" (TEDS) has shown that environmental factors can enhance or moderate genetic predispositions for cognitive development. For instance, children in enriched environments often display stronger genetic influences on intelligence, aligning with the Scarr-Rowe hypothesis, which posits that favorable settings can enhance the expression of genetic potentials in cognitive abilities [46].

Some studies, however, report challenges in identifying robust GxE effects in early childhood due to the large sample sizes needed. Early life environments have substantial impacts, particularly in adverse conditions such as socioeconomic deprivation, where genetic potential may not fully manifest. Conversely, children with higher genetic propensities for cognitive abilities tend to excel more in resource-rich environments. Overall, these studies indicate that in early childhood, environmental influences often outweigh genetic effects as measured by current methodologies [47].

Electronic-database information

[1] Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

10. Conclusion

This study highlights the intricate relationship between genetic variants, such as SNPs and CNVs, and cognitive functions, emphasizing the roles of key genes like APOE, BDNF, COMT, and HOMER1A in neurodevelopment and cognitive disorders. By elucidating these genetic mechanisms, the research provides valuable insights into the molecular basis of cognitive impairments and potential pathways for therapeutic intervention. This knowledge not only looks to arise the field of neurogenetics but also sets the stage for developing personalized medicine approaches to improve cognitive health and address related disorders in society.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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