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Genes and Their Role in Intellectual Disabilities and Brain Development

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Abstract

Intellectual disability (ID) is a highly heterogeneous neurodevelopmental condition characterized by deficits in intellectual and adaptive functioning. Comprehensive cognitive and adaptive behavior assessments are essential for investigating its underlying causes. While environmental factors contribute, particularly in mild cases, genetic etiologies predominate in moderate to severe forms, accounting for over 50% of these cases. This review explores the complex genomic architecture of ID, including chromosomal abnormalities, monogenic disorders, de novo mutations, polygenic inheritance, and epigenetic dysregulation. We highlight emblematic genetic syndromes such as trisomy 21 (Down syndrome) and Fragile X syndrome, illustrating how diverse genetic mechanisms from gene dosage effects to dynamic mutations—translate into specific neurocognitive and behavioral phenotypes. Further, we examine developmental channelopathies and chromatinopathies, emphasizing the critical role of neuronal excitability and epigenetic regulation in brain development.

The advent of next-generation sequencing (NGS) has revolutionized diagnostic capabilities, facilitating the identification of causal variants and significantly reducing the diagnostic odyssey for families. These advances have also paved the way for precision medicine, with emerging therapeutic approaches including gene therapy, RNA-based strategies, targeted pharmacology, and drug repurposing showing promise in clinical trials. However, the complexity of the brain, developmental timing, and challenges in clinical trial design especially for rare disorders remain significant hurdles. This review underscores the transformative impact of genomic technologies not only on the understanding and diagnosis of ID but also on the development of personalized treatments aimed at improving outcomes for individuals with ID.

Keywords: Intellectual disability, Neurodevelopmental disorders, Genetic etiologies**,** Chromosomal aberrations, Monogenic disorders, Polygenic inheritance, Epigenetic regulation, Precision medicine, Next generation sequencing

Introduction

At the heart of cognitive neuroscience and clinical genetics lies a fundamental quest: to decipher the etiology of variations in human development. Intellectual disability (ID), once confined to purely behavioral descriptions and classifications based on intelligence quotient, is now at the center of a conceptual revolution [1]. Intellectual disability, formerly in DSM-IV TR called Mental Retardation nowadays due to the name stigmatization the new DSM-5 named it Intellectual Disability or ICD-11th Intellectual developmental disorder. We no longer view it simply as an endpoint on a continuum of abilities, but as the observable outcome the phenotype of complex and profoundly altered neurodevelopmental trajectories. The advent of genomic technologies has opened an unprecedented window onto the molecular mechanisms underlying these trajectories. This article sets out to navigate this complex genetic landscape. It is not a mere catalog of syndromes, but an exploration of fundamental biological principles that, when disrupted, impede the establishment of the neural networks essential for higher cognition. Moving from large-scale chromosomal abnormalities to subtle single-nucleotide mutations, we will seek to understand how a change in the code of life can translate into profound challenges in learning, adapting, and interacting with the world. This journey to the heart of the genome is not just

an academic exercise; it redefines diagnosis, sheds light on pathophysiological mechanisms, and, most importantly, paves the way for targeted therapeutic interventions, transforming hope into a tangible scientific strategy.

Conceptual and Epidemiological Framework of Intellectual Disability

Before exploring the genetic underpinnings, it is imperative to establish a rigorous diagnostic and conceptual framework for intellectual disability. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), ID is a neurodevelopmental disorder characterized by deficits in intellectual and adaptive functioning, with onset during the developmental period. This diagnosis is based on three essential criteria [2]:

Intellectual functioning deficits

These deficits involve reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and experiential learning. They are confirmed by both clinical assessment and standardized and individualized intelligence tests. An intelligence quotient (IQ) score of approximately 70 ± 5 (two standard deviations below the mean) is generally considered an indicative threshold, although it is no longer sufficient on its own to make the diagnosis [3].

Deficits in adaptive functioning

This criterion is equally crucial. It refers to an individual's inability to meet the demands of their age and sociocultural context in terms of personal independence and social responsibility [4]. Adaptive functioning is assessed in three areas:

1. **Conceptual:** memory skills, language, reading, writing, mathematical reasoning, practical knowledge.
2. **Social:** awareness of others' thoughts and feelings, empathy, interpersonal communication skills, social judgment.
3. **Practical:** personal management (caregiving, transportation, safety), professional or academic responsibilities, money management, task organization.

Intellectual and adaptive deficits must be present before the age of 18. The prevalence of ID in the general population is estimated at between 1 and 3%. This heterogeneity in estimates reflects methodological differences, but more importantly highlights the immense clinical and etiological diversity of the disorder. ID can be classified into levels of severity (mild, moderate, severe, profound) based not only on IQ score but also on the level of support required for adaptive functioning [5].

From an etiological perspective, ID is a converging symptom of hundreds of distinct conditions. While environmental causes (prenatal infections, exposure to teratogens, perinatal complications, severe malnutrition) play a role, it is now established that genetic factors are predominant, particularly in moderate to profound forms. It is estimated that genetic causes can be identified in over 50% of cases of severe ID. The genetic landscape of ID is extraordinarily vast, involving a wide range of mutational mechanisms that we will now explore [6].

The Genomic Landscape of Intellectual Disability: A Complex Architecture

The genetic basis of ID is not monolithic. It can be conceptualized as a pyramid of causes, ranging from massive and easily identifiable chromosomal alterations to subtle variations in a single gene, the identification of which has required major technological advances [7].

Numerical and structural chromosomal aberrations

These large-scale abnormalities affect the number or structure of chromosomes. They represent the oldest known cause of ID [8].

Aneuploidies

These are variations in the number of chromosomes. The best known is trisomy 21 (Down syndrome), where an extra chromosome 21 is present. Other trisomies 13, 18 or sex chromosome abnormalities (Klinefelter syndrome XXY, Turner syndrome X0) are also associated with specific cognitive profiles, often within the spectrum of ID [9].

Structural abnormalities

These include deletions (loss of a chromosome segment), duplications (gain of a segment), inversions, and translocations. Microdeletion/microduplication syndromes, too small to be seen on a standard karyotype, are a significant cause of ID. Examples include Williams-Beuren syndrome (microdeletion at 7q11.23) or 22q11.2 deletion syndrome (DiGeorge/velocardiofacial syndrome). The pathogenic effect is often related to a "gene dosage effect": the loss or gain of dosage-sensitive gene copies disrupts crucial biological processes [10].

Monogenic disorders

In this case, ID is caused by a mutation in a single gene. More than 1,000 monogenic genes are currently implicated in ID. The mode of inheritance varies: X-linked inheritance: Genes located on the X chromosome partially explain the male overrepresentation in ID (approximately 25% more than in females). Since males (XY) have only one X chromosome, a

recessive mutation on this chromosome will systematically be expressed. Fragile X syndrome is the paradigmatic example. Autosomal recessive inheritance: Both copies of the gene (one from each parent) must be mutated. These disorders are more common in populations with high inbreeding and are often associated with inborn errors of metabolism that secondarily affect brain development (e.g., phenylketonuria). Autosomal dominant inheritance: A single mutated copy of the gene is sufficient to cause the disorder. Often, these mutations are *de novo*, that is, they appear spontaneously in the individual and are not inherited from their parents [11].

The preponderant role of *de novo* mutations

One of the most important discoveries of the last decade is the major role of *de novo* mutations in sporadic and severe forms of ID. These new mutations, occurring in parental gametes or early in embryonic development, are particularly deleterious because they have not been subjected to the pressure of negative selection. Large-scale sequencing studies on trios (unaffected parents and affected child) have shown that *de novo* mutations in genes crucial for brain development are a major cause of unexplained ID [12].

Complex and polygenic heritability

For milder forms of ID, the pattern is less clear. It is likely that some of the variance is explained by a polygenic model, in which the accumulation of many small genetic variations common in the population (polymorphisms), each with a tiny effect, exceeds a certain threshold and predisposes to cognitive difficulties, often in interaction with environmental factors. This complex genetic architecture explains the immense clinical heterogeneity of ID. Each gene, each affected chromosomal region, defines a distinct molecular pathway that, when disrupted, leads to a unique neurodevelopmental phenotype [13].

Focus on Emblematic Chromosomal Syndrome: Trisomy 21

Trisomy 21, or Down syndrome, is the most common genetic cause of intellectual disability. Its prevalence is approximately 1 in 700 to 1,000 births. It results from the presence of a third copy, complete or partial, of chromosome 21. In 95% of cases, it is a free and homogeneous trisomy 21, resulting from a meiotic nondisjunction error, most often of maternal origin [14]. The presence of this additional chromosomal material leads to the overexpression of several hundred genes located on chromosome 21. Rather than a single "trisomy gene," it is the collective deregulation of these genes that disrupts cellular homeostasis and development [15]. Several candidate genes have been intensively studied for their potential role in the cognitive phenotype:

DYRK1A (Dual-specificity tyrosine-phosphorylation-regulated kinase 1A)

This gene is a key regulator of brain development, involved in neurogenesis, synaptic plasticity, and cell proliferation. Its overexpression is strongly suspected of contributing to cognitive deficits, particularly by altering dendritic morphology and synaptic function in the hippocampus and cortex [16].

APP (Amyloid Precursor Protein)

The *APP* gene, whose overexpression is directly linked to the early development of Alzheimer's disease in people with Down syndrome, also plays a role in neuronal development, synaptogenesis, and axonal transport. Its early deregulation could contribute to intellectual deficits well before the appearance of amyloid plaques [17].

SOD1 (Superoxide Dismutase 1)

Overexpression of this antioxidant enzyme could, paradoxically, lead to a redox imbalance and increased oxidative stress, contributing to the observed neurodegeneration [18].

These molecular deregulations result in neuroanatomical and functional abnormalities, such as a reduction in total brain volume, a hypoplastic cerebellum and hippocampus, and alterations in functional connectivity between brain regions.

Intellectual disability in Down syndrome is generally mild to moderate. The cognitive profile is characterized by dissociation: visuospatial skills and implicit memory are relatively preserved, while verbal functions and explicit memory (especially working memory and verbal long-term memory) are significantly more affected. Executive functions, such as planning, inhibition, and cognitive flexibility, are also a major area of weakness. Behaviorally, marked sociability and affection are often observed, but also an increased risk of comorbid disorders such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and anxiety or depressive disorders, particularly in adolescence and adulthood [19].

Monogenic Disorders: The Example of Fragile X Syndrome

Fragile X syndrome (FXS) is the leading cause of hereditary ID and the second most common genetic cause of ID after Down syndrome. It perfectly illustrates how dynamic mutation in a single gene can have profound neurodevelopmental consequences [20]. A Trinucleotide Repeat Expansion FXS is caused by a mutation in the FMR1 (Fragile X Mental Retardation 1) gene, located on the X chromosome. The mutation consists of an abnormal expansion of a CGG trinucleotide sequence in the 5' untranslated region of the gene [21]. Premutation

carriers are generally free of ID but are at risk of developing other disorders (fragile X-associated tremor/ataxia syndrome - FXTAS, premature ovarian failure - FXPOI) and have a high risk of passing on a full mutation to their offspring [22].

When full mutation there are 200 repeats. This massive expansion results in hypermethylation of the *FMR1* gene promoter region and associated histones, leading to transcriptional silencing. The production of the Fragile X Mental Retardation Protein (FMRP) is then drastically reduced or absent [23].

FMRP is an RNA-binding protein that plays a crucial role at synapses. It acts as a brake on the local translation of many synaptic mRNAs. By binding on these mRNAs, it represses their translation into proteins. When the synapse is activated (particularly via metabotropic glutamate receptors, mGluRs), FMRP is phosphorylated and releases the mRNAs, enabling a wave of local protein synthesis necessary for long-term synaptic plasticity (such as long-term depression, or LTD) [24].

In the absence of FMRP, this barrier is removed. The "mGluR" theory of FXS posits that this results in excessive and dysregulated protein synthesis in response to synaptic stimulation. This leads to exaggerated LTD, immaturity of dendritic spines (which appear long, thin, and dense), and alterations in synaptic plasticity, which are considered the cellular substrate of cognitive deficits [25].

In boys, ID is nearly constant, ranging from moderate to severe. The cognitive profile is marked by significant deficits in executive functions, working memory, and abstract reasoning. Language often exhibits rapid tempo and verbal perseveration. The behavioral phenotype is also characteristic, with severe social anxiety, hyperactivity, stereotyped behaviors, and evasive eye contact. There is significant clinical and biological overlap with ASD, and approximately 30–50% of boys with FXS meet criteria for ASD. Girls, protected by the presence of a second healthy X chromosome (X inactivation phenomenon), present a much more variable phenotype, ranging from the absence of symptoms to mild ID, including specific learning disabilities or psycho-affective difficulties (anxiety, shyness) [26].

Developmental Channelopathies: When Neuronal Excitability is Disrupted

An increasingly recognized class of genes involved in ID is that encoding ion channels. Ion channels are transmembrane proteins that control the flow of ions (Na+, K+, Ca2+, Cl-) across the neuronal membrane, thereby regulating cellular excitability, resting potential, action potential generation, and neurotransmitter release. Mutations in these genes, or "channelopathies," can profoundly disrupt the development and function of neural circuits [27]. These disorders are often grouped together under the term "developmental and epileptic encephalopathies," because ID is frequently accompanied by early-onset, drug-resistant epilepsy. The hypothesis is that abnormal and persistent epileptic activity during critical periods of brain development itself contributes to cognitive deterioration, in addition to the direct effect of the mutation on neuronal function [28].

Examples of channelopathies associated with ID

Dravet syndrome: Caused by *de novo* mutations in the *SCN1A* gene, which encodes the alpha 1 subunit of the voltage-gated sodium channel Nav1.1. This channel is primarily expressed in GABAergic inhibitory interneurons. Loss of Nav1.1 function results in hypoexcitability of these interneurons, disrupting the excitation/inhibition balance in the cortex in favor of overall hyperexcitability. This results in severe seizures and stagnation, then regression, of psychomotor development, leading to severe ID [29].

Timothy syndrome: It is caused by gain-of-function mutations in the *CACNA1C* gene, encoding the alpha 1C subunit of the L-type calcium channel, Cav1.2. These mutations prevent normal inactivation of the channel, causing excessive and prolonged calcium inflow into neurons. This abnormal calcium influx disrupts a multitude of cellular processes, including activity-dependent gene transcription, neuronal differentiation, and cytoskeletal structure. Clinically, Timothy syndrome combines physical malformations (syndactyly), severe cardiac arrhythmias, and a profound neurodevelopmental disorder with marked autistic features [30].

These examples illustrate a fundamental principle: normal brain function relies on a delicate balance of neuronal excitability. Channelopathies demonstrate how a disruption of this single physiological parameter, dictated by a genetic defect, can be enough to devastate the entire neurodevelopmental trajectory [31].

Chromatin Remodeling Disorders: "Chromatinopathies"

Beyond genes encoding synaptic proteins or ion channels, another major category of genes involved in ID is epigenetic regulators. These genes do not encode the "building blocks" of the cell, but rather the "architects" that control the expression of a multitude of other genes. They modulate the structure of chromatin the complex of DNA and proteins (histones) in the cell nucleus to make genes accessible or inaccessible to the transcription machinery. Mutations in these genes cause "chromatinopathies," disorders in which overall epigenetic regulation is impaired [32]. Brain development is a process orchestrated with exquisite precision, requiring the activation and repression of thousands of genes at specific times

and locations. Chromatin regulators are at the heart of this orchestration. A mutation in one of them can therefore have cascading consequences, deregulating the expression of vast networks of target genes essential for neuronal proliferation, migration, differentiation and synaptogenesis [33].

Examples of chromatinopathies

Rett syndrome: Linked in 95% of cases to *de novo* mutations in the *MECP2* gene on the X chromosome, this disorder affects almost exclusively girls. The gene encodes the protein MeCP2 (Methyl-CpG-binding protein 2), a major reader of the DNA methylation landscape. MeCP2 binds to methylated DNA sites and recruit's corepressor complexes to compact chromatin and silence gene transcription. In the absence of functional MeCP2, this repression is lost, leading to inappropriate expression of many genes. Clinically, Rett syndrome is characterized by initially normal development followed, between 6 and 18 months of age, by a phase of rapid regression with loss of language and voluntary hand use, the appearance of characteristic manual stereotypies, and the development of severe to profound ID [34].

Rubinstein-Taybi syndrome: Caused by mutations in the *CREBBP* or *EP300* genes, which encode two histone acetyltransferases (HATs). These enzymes add acetyl groups to histones, which "relax" the chromatin and promote gene expression. Loss of function of one copy of these genes results in global hypoacetylation and defective transcriptional regulation. The syndrome combines moderate to severe ID, facial anomalies, and broad thumbs and big toes [35].

Cornelia de Lange syndrome: Most caused by mutations in the *NIPBL* gene, which encodes a regulatory protein of the cohesin complex. Cohesin is a protein ring that holds sister chromatids together but also plays a fundamental role in regulating gene expression by forming chromatin loops that bring enhancers closer to their target promoters. Defective cohesin disrupts this 3D architecture of the genome, altering the transcription of genes crucial for development [36].

Chromatinopathies highlight that ID can result not only from defects in the structural components of the brain, but also from defects in the regulatory program that governs its construction [37].

The Impact of High-throughput Sequencing Technologies on Diagnosis

The genetic landscape of ID is so vast and heterogeneous that the traditional diagnostic approach, based on targeted tests (karyotype, analysis of a suspected gene), left most cases without an etiological explanation. This "diagnostic odyssey," often long and trying for families, has been radically transformed by the advent of next-generation sequencing (NGS) technologies [38].

These technologies allow for the rapid and cost-effective sequencing of large portions of the genome. The two main clinical approaches are:

Whole Exome Sequencing (WES)

This method focuses on sequencing the exome, i.e., the entire coding regions of genes (approximately 1-2% of the genome), where the majority (≈85%) of known pathogenic mutations are located [39].

Whole Genome Sequencing (WGS)

This more comprehensive approach sequences the entire genome, including non-coding regions (introns, intergenic regions) that contain regulatory elements whose importance is increasingly recognized [40].

The application of WES, particularly in a "trio" approach (sequencing the child and both biological parents), has proven extraordinarily powerful. It allows for the high reliability of identifying de novo mutations, which are a major cause of severe ID. The diagnostic yield of WES/WGS for unexplained ID is currently between 25% and 50%, depending on the severity of the phenotype and the rigor of case selection [41].

Challenges and Implications

The NGS era is not without challenges. The main one is data interpretation. Sequencing reveals thousands of genetic variants for everyone, and the vast majority are benign. The difficulty is distinguishing the pathogenic causal variant from the genomic "noise." This has led to the classification of variants into five categories (pathogenic, probably pathogenic, of uncertain significance (VUS), probably benign, benign). Management of VUS is a major clinical and ethical challenge [42].

Despite these challenges, the impact of accurate genetic diagnosis is profound:

End of the diagnostic odyssey: Providing families with an answer to the cause of their child's condition.

Accurate genetic counseling: Assessing the risk of recurrence in future pregnancies.

Anticipatory medical management: For many syndromes, knowledge of the causative gene allows for the monitoring and prevention of specific comorbidities (cardiac, renal, epileptic).

Access to support groups and research: Connecting families with others affected by the same rare disorder.

Foundation for precision medicine: Genetic diagnosis is the essential prerequisite for the development and application of targeted therapies [43].

From Genes to Therapy: Prospects and Challenges of Precision Medicine

A detailed understanding of molecular mechanisms opens the door to therapeutic strategies that no longer aim solely at managing symptoms, but to correct or compensate for the fundamental biological defect. Although we are still in the early stages, several promising avenues are actively being explored.

Gene therapy

The idea is to replace or correct the defective gene. For loss-of-function disorders, viral vectors (such as AAVs) can be used to deliver a healthy copy of the gene to target brain cells. Clinical trials are underway for monogenic diseases such as Rett syndrome (with MECP2). The challenges remain immense: crossing the blood-brain barrier, ensuring broad and controlled expression in the brain, and intervening during a critical developmental time window [44].

Modulation of gene expression

For disorders such as Down syndrome or certain microduplications, where the problem is overexpression (gene dosage), the strategy is to reduce the expression of the critical gene(s). Antisense oligonucleotides (ASOs) or RNA interference (RNAi) approaches can be designed to specifically degrade the mRNA of the overexpressed gene. ASOs are already used successfully for other neurological diseases such as spinal muscular atrophy [45].

Targeted pharmacology

When the pathophysiological mechanism is known, it can be targeted with small molecules.

Fragile X: The mGluR theory has led to numerous clinical trials testing mGluR5 receptor antagonists to normalize synaptic protein synthesis. Although results in humans have been disappointing so far, they have helped refine our understanding of the disorder and allow us to explore other targets.

Tuberous sclerosis complex (TSC): This disorder, caused by mutations in the *TSC1* or *TSC2* genes, leads to hyperactivation of the mTOR signaling pathway. mTOR inhibitors (such as everolimus) have been shown to be effective in reducing the size of associated tumors and show benefits for epilepsy and certain cognitive-behavioral aspects [46].

Drug repositioning and high-throughput screening

Identifying a molecular pathway allows thousands of compounds already approved or in development to be tested to see if they can modulate it. This approach can significantly accelerate the drug discovery process [47].

The challenges are considerable. The brain is incredibly complex, and developmental processes are often irreversible. The window for therapeutic intervention is likely early and narrow. Furthermore, each genetic syndrome is a rare disorder, which complicates the implementation of large-scale clinical trials. Nevertheless, the momentum is building. The convergence of genomics, cell biology and pharmacology is creating an ecosystem of innovation that was unthinkable twenty years ago [48].

Conclusion

The genetic underpinnings of intellectual disability (ID) are as diverse and complex as the disorder itself. Advances in genomic technologies have significantly deepened our understanding of the myriad causes of ID, from large chromosomal abnormalities like trisomy 21, to monogenic mutations in genes such as *FMR1* in Fragile X syndrome, to the growing recognition of developmental channelopathies and chromatinopathies. These discoveries have not only reshaped our diagnostic capabilities, moving us beyond traditional approaches to next-generation sequencing (NGS), but have also paved the way for a more personalized approach to treatment.

While the field has made remarkable strides in identifying genetic causes and understanding their mechanisms, much remains to be done. The clinical heterogeneity of ID, coupled with the challenge of distinguishing pathogenic mutations from benign genetic variants, highlights the need for further refinement in diagnostic techniques and the development of clearer genetic counseling frameworks. Moreover, while precision medicine offers exciting prospects from gene therapy to targeted pharmacology, the path toward effective therapeutic interventions is fraught with challenges, including overcoming the complexities of brain development, understanding critical developmental windows, and designing trials for rare genetic conditions.

Nevertheless, the convergence of genomics, cell biology, and pharmacology holds immense promise. As we continue to unravel the genetic mechanisms behind ID, the future of precision medicine focusing on early intervention, symptom alleviation, and even disease modification appears increasingly within reach. The goal is not only to improve the lives of individuals with ID but also to provide hope for families through more accurate diagnoses, personalized therapies, and better outcomes in the years to come.

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