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Review Article

Unraveling the Genetic and Phenotypic Complexity of Down Syndrome from Trisomy 21 to Comorbid Conditions

Raja Sekhar Moka*, Meenakshi Puliyath Sudheer, Prabodh Kumar

Department of Cell and Molecular Biology, Manipal School of Life Sciences, Manipal Academy of Higher Education, Manipal, India

Abstract

Down syndrome (DS), caused by trisomy of chromosome 21, exhibits significant phenotypic variability, including intellectual disability, early-onset Alzheimer disease (AD), congenital heart defects (CHDs), haematological malignancies, and immune dysregulation. While gene dosage effects have long been recognized, emerging evidence suggests that additional genetic variants contribute to individual differences in disease susceptibility and clinical outcomes. In this context, we reviewed genetic variants associated with DS phenotypes, aiming to elucidate genotype–phenotype correlations and explore their potential clinical applications in precision medicine. To achieve this, we analyzed literature published between 2000 and 2024 from databases such as PubMed, Scopus, and Web of Science, focusing on studies utilizing next-generation sequencing (NGS), whole exome sequencing (WES), genome-wide association studies (GWAS), and transcriptomic profiling to identify critical genetic alterations and gene networks associated with DS-related conditions. Our review highlights that variants in APP and BACE2 influence Aβ metabolism and contribute to AD risk in DS, while APOE and PICALM variants are implicated in neurodegeneration. CHDs are associated with variants in CRELD1, COL6A1/2, and other genes involved in extracellular matrix (ECM) organization. Additionally, blood disorders such as myeloid leukaemia in Down syndrome (ML-DS) are linked to mutations in GATA1 and aberrant signalling involving JAK2 and CRLF2. Immune dysregulation in DS appears to be influenced by alterations in IFNAR1/2 and polymorphisms in TRPM2 and OAS1. Collectively, these findings underscore the potential for targeted therapies, including BACE inhibitors, JAK-STAT pathway modulators, and immunomodulatory agents. Ultimately, understanding DS's complex genetic architecture through integrated multi-omics and clinical profiling holds promise for the development of personalized interventions and the advancement of genotype-informed precision medicine.

Keywords

Down Syndrome (DS), Trisomy 21, Phenotypic Variability, Intellectual Disability, Early-onset Alzheimer's Disease (AD), Congenital Heart Defects (CHDs), Hematological Malignancies

1. Introduction

Down syndrome (DS), also known as trisomy 21, is the most common chromosomal disorder in liveborn infants, occurring in approximately 1 in 700 births worldwide, though rates vary by maternal age, population, and access to prenatal diagnostics [1]. It is the leading genetic cause of intellectual disability and is associated with a spectrum of multi-systemic

*Corresponding author: rsmoka@gmail.com (Raja Sekhar Moka)

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anomalies, including congenital heart defects, hypotonia, craniofacial dysmorphisms, gastrointestinal malformations, visual and auditory impairments, hematological abnormalities, and early-onset neurodegeneration resembling Alzheimer's disease [2, 3].

DS results from an extra copy of all or part of human chromosome 21 (Hsa21), leading to a global gene dosage imbalance and subsequent dysregulation of genetic networks [4]. This increased dosage of trisomic genes leads to their overexpression, disrupting cellular homeostasis and developmental pathways across organ systems [5, 6]. In most individuals, DS is caused by free trisomy 21 due to meiotic nondisjunction, while a minority have mosaicism or Robertsonian translocations [7].

Mouse models that harbor duplications of orthologous regions of Hsa21 have provided invaluable insights into genotype-phenotype correlations in DS. These models mimic various DS features and help delineate the contribution of specific genes or gene clusters [8]. However, given that Hsa21 harbors over 200 protein-coding genes, determining the contribution of each gene or gene set to specific phenotypes remains a complex challenge [9].

Notably, analyses of individuals with partial trisomy 21 have led to the identification of a highly conserved region termed the Down syndrome critical region (DSCR), spanning approximately 3.8–6.5 Mb at 21q21.22 [10]. The DSCR contains several genes—including DYRK1A, DSCAM, APP, and RCAN1—implicated in neurodevelopmental delay, cardiac defects, and other hallmark DS traits [11]. Advances in sequencing and transcriptomic profiling have improved our understanding of how trisomic gene interactions and epigenetic dysregulation contribute to phenotypic heterogeneity in DS [12, 13]. Table 1 summarizes key protein-coding genes located on chromosome 21 and their established or proposed contributions to major phenotypes observed in individuals with Down syndrome.

Table 1. *Key Genes on Human Chromosome 21 and Their Roles in Down Syndrome Phenotypes.*

Gene	Full Name	Location (21q)	Function	Phenotypic Contribution in DS
APP	Amyloid Precursor Protein	21q21.3	Precursor to amyloid-beta; involved in synapse formation	Alzheimer-like neurodegeneration, early-onset dementia
DYRK1A	Dual-specificity Tyrosine-(Y)-Phosphorylation Regulated Kinase 1A	21q22.13	Regulates neuronal development, synaptic plasticity, and cell proliferation	Cognitive deficits, brain size reduction, learning impairments
BACE2	Beta-site APP Cleaving Enzyme 2	21q22.3	Involved in amyloid-beta processing	Modulates amyloid-beta metabolism; possible neurodegeneration role
RCAN1	Regulator of Calcineurin 1 (DSCR1)	21q22.12	Inhibits calcineurin; involved in signal transduction	Alters neurodevelopment, cardiac and immune functions
SOD1	Superoxide Dismutase 1	21q22.11	Detoxifies superoxide radicals	Oxidative stress; neurodegeneration
RUNX1	Runt-related Transcription Factor 1	21q22.12	Hematopoiesis and megakaryocyte differentiation	Linked to transient myeloproliferative disorder and leukemia risk
ETS2	ETS Proto-Oncogene 2	21q22.3	Transcriptional regulation, cell proliferation, and apoptosis	Craniofacial anomalies; apoptosis dysregulation
COL6A1	Collagen Type VI Alpha 1 Chain	21q22.3	Extracellular matrix structural protein	Muscle hypotonia, connective tissue abnormalities
COL6A2	Collagen Type VI Alpha 2 Chain	21q22.3	Extracellular matrix protein	Similar to COL6A1, muscle weakness
PICALM	Phosphatidylinositol Binding Clathrin Assembly Protein	21q22.2	Endocytosis and synaptic vesicle trafficking	Alzheimer’s disease susceptibility
CRELD1	Cysteine Rich with EGF Like Domains 1	21q22.3	Cardiac development signaling pathways	Associated with atrioventricular septal defects (AVSD)
IFNAR1/2	Interferon Alpha and Beta Receptor Subunits 1 & 2	21q22.11	Mediates interferon signaling, immune response	Increased interferon activity, autoimmunity
CBS	Cystathionine Beta-Synthase	21q22.3	Metabolism of homocysteine	Altered methylation, neurological abnormalities
TMPRSS2	Transmembrane Serine Protease 2	21q22.3	Protease in epithelial cells	Potential immune and respiratory dysfunction
PRMT2	Protein Arginine Methyltransferase 2	21q22.3	Epigenetic regulation, histone modification	May contribute to epigenetic dysregulation in DS

In addition to developmental abnormalities, individuals with DS are predisposed to certain diseases (e.g., acute megakaryoblastic leukemia, autoimmune disorders, and Alzheimer's disease) and relatively protected against others, such as solid tumors [14]. These divergent susceptibilities highlight the need to further dissect the molecular architecture of Hsa21 and its systemic consequences. A deeper understanding of the dosage-sensitive genes and pathways underlying DS will not only clarify its pathogenesis but may also inform targeted therapeutic approaches. Table 2 summarizes key phenotypic features commonly observed in individuals with Down syndrome, their estimated frequencies, and major genes implicated in their pathogenesis.

Table 2. *Phenotypic Features and Associated Genetic Factors in Down Syndrome.*

Phenotype	Frequency in DS (%)	Major Associated Genes	Mechanism
Intellectual disability	>95%	DYRK1A, DSCAM	Neurodevelopmental delay
Alzheimer's (early-onset)	50–70% by age 60	APP, BACE2	Amyloid plaque accumulation
Congenital heart defects	~40–50%	CRELD1, COL6A1/2	Abnormal septal development
Leukemia (especially AMKL)	↑ risk	RUNX1, GATA1 mutations	Impaired hematopoiesis

2. Genetic Blueprint of Down Syndrome

Down syndrome (DS), or trisomy 21, is the most common chromosomal disorder associated with intellectual disability and multisystem involvement. It arises from the presence of an extra copy of chromosome 21, which disrupts normal gene dosage and developmental regulation, leading to a broad spectrum of phenotypic features and medical complications. This genomic imbalance results in widespread transcriptional dysregulation, not only of genes located on chromosome 21 but also of genes throughout the genome due to downstream epigenetic and regulatory network effects [13].

Approximately 95% of DS cases result from full free trisomy 21, caused by nondisjunction during maternal meiosis, wherein all somatic cells carry three copies of chromosome 21 [7]. Mosaic DS, accounting for 1–2% of cases, involves a post-zygotic mitotic error, producing a mixture of normal and trisomic cells [15]. In contrast, translocation DS (3–4%) occurs when all or part of chromosome 21 is attached to another acrocentric chromosome (commonly chromosomes 14 or 21), often via Robertsonian translocations [16]. Unlike free trisomy 21, approximately one-third of translocation DS cases are inherited, emphasizing the role of parental karyotyping in genetic counselling [4].

The clinical features of DS are well documented and include craniofacial dysmorphism (flat facial profile, epicanthal folds, upslanting palpebral fissures), short stature, hypotonia, brachydactyly, single transverse palmar crease, and cognitive impairment, often in the mild to moderate range [17]. Behavioural and psychiatric phenotypes, such as attention deficits and autistic traits, are also common [18]. Beyond these hallmark features, DS is associated with an increased risk of congenital heart disease (CHD), particularly atrioventricular septal defects, occurring in 40–60% of individuals [19]. Other systemic manifestations include gastrointestinal anomalies (e.g., duodenal atresia, Hirschsprung disease), immune dysregulation, endocrine disorders (e.g., hypothyroidism, diabetes), sensory impairments, and hematologic abnormalities, including an increased risk of leukemia in infancy [12].

The molecular basis for this wide phenotypic range stems from the gene-dosage imbalance caused by trisomy of chromosome 21, which harbors approximately 225 protein-coding genes along with numerous noncoding RNAs and regulatory elements [20]. Key genes implicated in DS pathogenesis and comorbid conditions include APP (Amyloid precursor protein): Triplication of APP leads to overproduction of amyloid-β, contributing to early-onset Alzheimer disease in DS [21]. BACE2: Another gene involved in amyloid metabolism, potentially modulating the onset of neurodegeneration [22]. PICALM and APOE: Lipid transport and amyloid clearance genes that modulate Alzheimer risk and severity [23]. CRELD1: Associated with atrioventricular septal defects, a common CHD in DS. [24]. DSCAM: Plays a role in neuronal connectivity and heart development. [25]. GATA1: Mutations in this X-linked transcription factor, in combination with trisomy 21, underlie transient abnormal myelopoiesis and megakaryoblastic leukemia in DS infants. [26]. JAK2 and AGTR1: Involved in hematopoiesis and cardiovascular regulation, respectively [27]. Importantly, the Down Syndrome Critical Region (DSCR) on chromosome 21q21–q22, spanning approximately 3.8–6.5 Mb, is considered central to the core DS phenotype, although newer studies suggest a polygenic contribution extending beyond DSCR. [10].

3. Alzheimer Disease in Down Syndrome

Individuals with DS are at exceptionally high risk for

developing early-onset Alzheimer disease (AD) due to the triplication of the APP gene on chromosome 21, which leads to overproduction and accumulation of amyloid-β plaques [25]. By age 40, virtually all individuals with DS show neuropathologic features of AD, including amyloid deposition, tau neurofibrillary tangles, and neurodegeneration, though the clinical onset of dementia varies [28].

Epidemiological studies estimate that 6.8% of individuals with DS are diagnosed with AD dementia, with a dramatic increase in incidence beyond age 50 [29]. Preclinical symptoms such as mood changes, sleep disturbances, and seizures may precede overt cognitive decline [30]. The overlap between DS and AD has made DS a valuable model for studying the early mechanisms of Alzheimer pathology, including inflammation, synaptic dysfunction, and impaired clearance pathways [31].

4. Genetic Factors Influencing Alzheimer Disease (AD) Down Syndrome (DS)

Individuals with Down syndrome (DS) have a significantly increased risk of developing Alzheimer disease (AD), with all individuals exhibiting AD-like neuropathology by age 40, and a substantial proportion progressing to clinical dementia by their 60s. This heightened susceptibility arises due to both gene dosage effects and secondary neurobiological mechanisms, including oxidative stress and mitochondrial dysfunction [32, 33]. "Multiple genes are involved in influencing the pathogenesis and age of onset of Alzheimer's disease (AD) in individuals with Down syndrome (DS), with APP, BACE2, PICALM, and APOE being among the most critical contributors."

4.1. Amyloid Precursor Protein (APP)

The *APP* gene, located on chromosome 21q21, encodes amyloid precursor protein, which undergoes proteolytic processing to generate amyloid-β (Aβ) peptides. Trisomy 21 leads to its overexpression, thereby amplifying the production of Aβ and promoting early-onset amyloid deposition in the DS brain [34]. Soluble APP-alpha (sAPPα) exhibits neurotrophic and gliogenic properties, while the APP intracellular domain (AICD) interferes with neural progenitor differentiation, thus contributing to impaired neurogenesis [35, 36]. An intronic polymorphism (ATTT insertion in intron 7) of *APP* has been associated with earlier onset of AD in DS patients [37]. These findings support the amyloid cascade hypothesis as a central mechanism in DS-associated AD.

4.2. β-Site APP Cleaving Enzyme 2 (BACE2)

BACE2, a paralog of *BACE1*, resides on chromosome 21q22.3 within the Down Syndrome Critical Region (DSCR). Initially considered neuroprotective due to its role in non-amyloidogenic APP cleavage, recent studies show that BACE2 may also contribute to Aβ production under oxidative or inflammatory stress conditions [38, 39]. Genetic variants in *BACE2* have been linked to interindividual variability in the age of dementia onset among DS individuals [40, 41], suggesting a dual and context-dependent role in AD pathogenesis.

4.3. Phosphatidylinositol Binding Clathrin Assembly Protein (PICALM)

PICALM, located on chromosome 11q14, is integral to clathrin-mediated endocytosis, influencing synaptic vesicle cycling and endosomal trafficking. Genome-wide association studies (GWAS) have consistently identified *PICALM* polymorphisms as susceptibility loci for late-onset AD in the general population [42]. In DS, modified GWAS and expression analyses suggest *PICALM* variants may modulate disease severity and rate of progression by affecting APP endocytosis and clearance [43-45].

4.4. Apolipoprotein E (APOE)

APOE on chromosome 19q13 encodes apolipoprotein E, a key protein in lipid metabolism, neuroinflammation, and synaptic plasticity. The ε4 allele (*APOE4*) is the most potent genetic risk factor for sporadic AD, increasing amyloid plaque burden and accelerating neurodegeneration in DS as well [46, 47]. Conversely, the *APOE2* allele is neuroprotective and associated with reduced plaque load and delayed cognitive decline in DS individuals [48-50]. APOE polymorphisms therefore critically modulate the penetrance and progression of AD in the trisomic context.

5. Genetic Basis of Congenital Heart Disease in Down Syndrome

Congenital heart defects (CHDs) affect approximately 40% of individuals with DS, with atrioventricular septal defects (AVSDs) being most common. These defects arise from abnormal development of the endocardial cushions, essential for septation of the atria and ventricles.

Cysteine-Rich with EGF-Like Domains 1 (CRELD1)

Though *CRELD1* is located on chromosome 3p25.3 and not on chromosome 21, it encodes a transmembrane protein expressed during early cardiac development. Mutations and rare variants in *CRELD1* have been identified in individuals with DS and AVSDs, implicating it as a modifier gene that contributes to the DS cardiac phenotype [51, 52]. The gene's expression in the atrioventricular canal and its role in epithelial-to-mesenchymal transformation underscore its relevance in cardiac septation. The intersection of trisomy 21 and genetic modifiers contributes to the variable phenotypic manifestations of AD and CHDs in DS. Genes such as *APP* and *BACE2*, residing on chromosome 21, directly participate

in AD pathogenesis due to dosage imbalance. Meanwhile, susceptibility alleles in *PICALM*, *APOE*, and *CRELD1*, though located outside chromosome 21—play significant roles as modifiers, altering disease onset, progression, and severity. Understanding these gene-disease associations provides insights into therapeutic targets and risk stratification in DS.

6. Genetic Variants in Down Syndrome: Insights from Targeted, Exome, and Genome Sequencing

Advancements in high-throughput sequencing technologies—including targeted gene panels, whole exome sequencing (WES), and whole genome sequencing (WGS)—have significantly expanded our understanding of phenotypic variability in individuals with Down syndrome (DS). Although the presence of trisomy 21 remains the defining genetic hallmark, emerging data indicate that additional rare or common variants—either on chromosome 21 or elsewhere in the genome—may contribute to the severity, onset, and diversity of DS-associated phenotypes. These include neurodegenerative disorders such as Alzheimer disease (AD), congenital heart defects (CHDs), hematological malignancies, immune dysregulation, and cognitive impairment.

6.1. Alzheimer Disease and Neurodegeneration

Down syndrome is characterized by a markedly increased risk of early-onset Alzheimer disease due to the triplication of the APP gene located on chromosome 21. Beyond gene dosage, specific APP variants, such as an intronic ATTT insertion in intron 7 identified through targeted sequencing, have been implicated in altered splicing and accelerated amyloid-β (Aβ) accumulation, thereby contributing to early AD pathology in DS patients [53].

Another significant player is BACE2, which encodes β-secretase 2, involved in Aβ peptide metabolism. Certain polymorphisms such as rs2252576, identified via WES/WGS, have been associated with the age of AD onset in DS. Interestingly, BACE2 demonstrates dual roles—both promoting and inhibiting Aβ production depending on cellular context [54].

The APOE genotype is another key modulator. The ε4 allele is linked to an earlier onset and more rapid cognitive decline in DS-AD, while ε2 appears to confer a degree of neuroprotection and is associated with longer lifespan and cognitive resilience in some DS individuals [55].

Additional genome-wide association studies (GWAS) have pinpointed variants in PICALM, particularly rs3851179, which modulate risk and onset of AD in both the general population and individuals with DS, potentially via altered endocytosis of APP and Aβ clearance mechanisms [12].

6.2. Congenital Heart Defects (CHDs)

Congenital heart defects are among the most common structural anomalies in DS. Mutations in CRELD1, especially p.R329C and p.E414K, have been detected via targeted sequencing in DS patients presenting with atrioventricular septal defects (AVSDs). These mutations impair cardiac cushion development and epithelial-mesenchymal transition, both critical for proper septation [56].

Variants in extracellular matrix genes such as COL6A1 and COL6A2 have also been identified via WES. These genes influence tissue structural integrity and their mutations are associated with both cardiac septal defects and muscular hypotonia in DS [57].

6.3. Hematologic Malignancies

Individuals with DS are predisposed to transient abnormal myelopoiesis (TAM) and myeloid leukemia of Down syndrome (ML-DS), a unique leukemic entity. Acquired mutations in GATA1, especially exon 2 truncating mutations, produce a short isoform (GATA1s) that disrupts megakaryocyte and erythroid differentiation. These mutations are detectable by targeted sequencing in nearly all cases of TAM and ML-DS [58].

In DS-associated acute lymphoblastic leukemia (DS-ALL), activating JAK2 mutations—such as R683G and R683S—are observed in about 20% of cases. These variants activate the JAK-STAT pathway, particularly in conjunction with CRLF2 overexpression, offering avenues for targeted therapy [59].

6.4. Immune Dysregulation and Infection Susceptibility

Individuals with DS exhibit chronic inflammation and heightened autoimmunity, attributed in part to genetic alterations in interferon signaling components. IFNAR1/IFNAR2 gene duplications and polymorphisms, detected via WGS-based copy number variation (CNV) analysis, correlate with increased interferon-stimulated gene expression and sustained inflammatory responses [60]. Variants in immune-related genes such as TRPM2 and OAS1, identified in immune-focused sequencing studies, have also been implicated in exaggerated antiviral responses and increased susceptibility to infections [61].

7. Therapeutic and Translational Implications

The identification of Down syndrome (DS)-specific genetic variants, along with those associated with comorbid conditions such as Alzheimer's disease (AD), autoimmune disorders, and congenital heart defects, has established a foundation for genotype-based risk stratification, early diagnostic efforts, and the implementation of precision

medicine in individuals with DS. For instance, overexpression of genes on chromosome 21, such as APP, DYRK1A, and IFNAR1, contributes to the neuropathological and immunological manifestations of DS, including early-onset AD and chronic inflammation [25, 12, 62]. Current therapeutic research emphasizes targeting these molecular pathways, with anti-amyloid therapies like lecanemab showing promise in mitigating AD pathology in DS models [63]. Furthermore, Janus kinase (JAK) inhibitors, such as baricitinib, are being investigated to counteract interferon hyperactivity and immune dysregulation—a hallmark of DS [64]. Interferon receptor overexpression resulting in heightened IFN signaling also presents an opportunity for interferon-targeted modulation [65]. Collectively, these precision-targeted strategies reflect a paradigm shift from symptomatic management toward disease-modifying interventions in DS. Several molecular targets implicated in DS-related AD pathophysiology are under active investigation for therapeutic modulation. Table 3 summarizes key candidate targets and the status of their associated interventions.

Table 3. *Candidate Therapeutic Targets in DS-related Alzheimer's Disease.*

Target	Pathway	Potential Intervention	Current Status
BACE2	Amyloid cleavage	BACE inhibitors	Clinical trials
DYRK1A	Kinase signaling	Inhibitors (e.g., harmine)	Preclinical/early trials
GSK3β	Tau phosphorylation	GSK3β inhibitors	Experimental

8. Conclusion

Down syndrome (DS), the most prevalent chromosomal disorder, exemplifies the intricate consequences of gene dosage imbalance arising from trisomy 21. This genomic alteration leads to widespread disruption of developmental, metabolic, and regulatory pathways, manifesting in a broad spectrum of phenotypes ranging from intellectual disability and congenital heart disease to early-onset Alzheimer disease and altered immune function. Key dosage-sensitive genes—such as APP, BACE2, DSCAM, CRELD1, and GATA1 have emerged as central players in the pathogenesis of hallmark DS traits, including neurodevelopmental delay, atrioventricular septal defects, and hematologic malignancies [21, 22, 24, 26, 38].

The contribution of these genes is further modulated by genetic background, epigenetic dysregulation, and environmental factors, all of which shape the phenotypic variability seen among individuals with DS. Recent genomic and transcriptomic advances, including GWAS, expression profiling, and model organism studies, have deepened our understanding of critical gene networks such as the Down Syndrome Critical Region (DSCR), while highlighting complex polygenic influences beyond this locus [11, 10, 45].

Furthermore, the universal development of Alzheimer-like neuropathology in DS underscores its value as a unique human model for studying early mechanisms of neurodegeneration. Modifier genes such as APOE and PICALM significantly influence the onset and progression of dementia, offering translational relevance for both DS and sporadic AD populations [42, 46, 49]. Similarly, the role of non-Hsa21 genes like CRELD1 in congenital heart disease emphasizes the importance of exploring interactions beyond the trisomic chromosome [51, 52].

Table 4. *Therapeutically Relevant Genetic Variants in Down Syndrome.*

Gene/Variant	Therapeutic Relevance	Implication
APP (triplication/intronic insertion)	Anti-amyloid therapies (e.g., monoclonal antibodies, BACE inhibitors)	Targeting Aβ accumulation in preclinical AD
BACE2 (rs2252576)	BACE2-specific inhibitors or modulators	Modulation of Aβ production pathways
APOE (ε4/ε2)	Lifestyle/dietary interventions; stratification in trials	Prognostic role in AD onset and progression
GATA1 (exon 2 mutations)	Early detection and surveillance in neonates with DS	Monitoring for TAM/ML-DS transition
JAK2 (R683G/S)	JAK inhibitors (e.g., ruxolitinib)	Potential therapeutic option in DS-ALL with

Gene/Variant	Therapeutic Relevance	Implication
		JAK2/CRLF2 activation
IFNAR1/IFNAR2 duplications	Anti-interferon therapies (e.g., JAK inhibitors, anti-IFN-α antibodies)	May alleviate chronic inflammation/autoimmune symptoms

Moving forward, integrative multi-omic analyses, coupled with patient-derived iPSC models and refined mouse models, will be essential to unravel the full landscape of DS pathophysiology. Such efforts will not only enhance risk stratification and early diagnostics but may also pave the way for targeted interventions to alleviate or prevent some of the most debilitating features of DS. Ultimately, a systems-level understanding of trisomy 21 will bridge basic science with clinical care, offering hope for improved outcomes and quality of life in individuals living with DS. Table 4 summarizes the most therapeutically relevant variants identified in Down syndrome [20], their biological implications, and emerging intervention strategies.

Abbreviations

AD	Alzheimer Disease
AICD	APP Intracellular Domain
APP	Amyloid Precursor Protein
APOE	Apolipoprotein E
AVSD	Atrioventricular Septal Defect
BACE1	β-Site APP Cleaving Enzyme 1
CHD	Congenital Heart Disease
CRELD1	Cysteine-Rich with EGF-Like Domains 1
DS	Down syndrome
DSCR	Down Syndrome Critical Region
DYRK1A	Dual-Specificity Tyrosine-(Y)-Phosphorylation Regulated Kinase 1A
GWAS	Genome-Wide Association Studies
Hsa21	Homo Sapiens Chromosome 21
PICALM	Phosphatidylinositol Binding Clathrin Assembly Protein
RCAN1	Regulator of Calcineurin 1
sAPPα	Soluble Amyloid Precursor Protein Alpha

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Conflicts of Interest

The authors declare no conflicts of interest.

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