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REVIEW ARTICLE

From understanding to action: Exploring molecular connections of Down syndrome to Alzheimer's disease for targeted therapeutic approach

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Abstract

Down syndrome (DS) is caused by a third copy of chromosome 21. Alzheimer's disease (AD) is a neurodegenerative condition characterized by the deposition of amyloid-beta (Aβ) plaques and neurofibrillary tangles in the brain. Both disorders have elevated Aβ, tau, dysregulated immune response, and inflammation. In people with DS, Hsa21 genes like APP and DYRK1A are overexpressed, causing an accumulation of amyloid and neurofibrillary tangles, and potentially contributing to an increased risk of AD. As a result, people with DS are a key demographic for research into AD therapeutics and prevention. The molecular links between DS and AD shed insights into the underlying causes of both diseases and highlight potential therapeutic targets. Also, using biomarkers for early diagnosis and treatment monitoring is an active area of research, and genetic screening for high-risk individuals may enable earlier intervention. Finally, the fundamental mechanistic parallels between DS and AD emphasize the necessity for continued research into effective treatments and prevention measures for DS patients at risk for AD. Genetic screening with customized therapy approaches may help the DS population in current clinical studies and future biomarkers.

KEYWORDS
Alzheimer's disease, blood based biomarkers, Down syndrome, endosomal dysfunction, extracellular vesicles, Hsa21 genes and proteins, precision therapy

1 | OVERVIEW

Down syndrome (DS) is a genetic disorder characterized by trisomy of chromosome 21 (T21), and its human karyotype is represented as 47, XX,+21; 47, XY,+21; and trisomy G.[1,2] DS can either be complete or mosaic/partial Hsa21, depending on the presence of a full or partial Hsa21, and about seven million people are affected with DS globally.[1,3] A complete T21 accounts for 95% of individuals with DS and results from either maternal (~87%) or paternal meiosis error (~8%).[4] Approximately 4% of cases with T21 are due to either translocation {t(14;21) or t(21;21)} while ~1% are due to mosaicism.[4] Partial T21 is rare and depending on the length and arm of the partial triplication of Hsa21, DS mosaics exhibit a wide range of symptoms. Fewer than 50 cases of partial T21 have been documented.[5,6] Phenotypes such as intellectual disability (ID), congenital heart disease, hypotonia, respiratory issues, and early-onset dementia due to Alzheimer's disease (DSAD) are noted in people with DS.

The brain and related neurobiology, gene expression, and predictive blood-based biomarkers are the focus of this review, partly because ID is crucial to the DS phenotype and because of the increased risk

of developing AD in this population.[7,8] Individuals with DS have a reduced brain size and total gray/white matter involving the cortical lobar, hippocampus, underdeveloped frontal lobe, and early cortical degenerative process before the onset of AD.[9–11] These factors may provide a neuroanatomical basis for the attention and working memory changes in people with DS. Now, with better access to healthcare, the life expectancy of individuals with DS has doubled in the past couple of decades, with a substantially higher risk of developing AD in this population.[12–14] By the age of 40 years, all adults with DS develop AD neuropathology with an increased risk of dementia.[15–17] However, the presence of developmental abnormalities, the lack of established diagnostic measures, and a general lack of knowledge among family members and caretakers make it difficult to diagnose dementia in the DS community.[18] AD neuropathology in individuals with DS can be recognized at an early age or even at the prenatal stage, hence making the DS population a prospective demographic for early intervention or prevention of AD. However, researchers must be mindful of the preexisting distinctions between those with DS and AD in the general population. To address these gaps in knowledge, researchers around the world are working together with various DS research cohorts to investigate the pathogenic and mechanistic links between AD and DS, to create a robust set of diagnostic and prognostic biomarkers for DSAD and determine at what age people with DS should be recruited for AD clinical trials.[18–20] For the same, several national and international funding agencies have developed collaborative research programs, like National Institutes of Health's (NIH) funded projects-INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE); Alzheimer's Biomarkers Consortium—Down Syndrome (ABC-DS); Alzheimer's Clinical Trial Consortium—Down Syndrome (ACTC-DS) and Horizon 21 DS, a European Consortium to work toward the similar goals of developing effective treatment against DSAD and expediting AD drug development for DS population.[18]

In this review, we explore the genetic landscape of DS, highlighting not only the T21 but also the gene expression profiles of multiple genes involved in neurodevelopment and neurodegeneration. Through this lens, we aim to elucidate how alterations in gene expression patterns contribute to the neurobiological changes observed in DS individuals predisposed to early dementia. Furthermore, we show the intricate involvement of key molecular pathways such as the endo-lyso-cycle, exosomes, and their cargoes in the pathogenesis of dementia in DS. We dissect the roles of these pathways in protein aggregation, synaptic dysfunction, and neuronal degeneration, shedding light on their potential as diagnostic, prognostic, and therapeutic targets against cognitive decline in DS individuals. This review offers a comprehensive framework for understanding the complex etiology of early-onset dementia in DS to encourage further research endeavors aimed at unraveling the intricate mechanisms underlying cognitive decline in DS individuals and pave the way for the development of targeted interventions to delay or prevent the onset of dementia in this vulnerable population.

RESEARCH IN CONTEXT

1. **Systemic review**: The present in-depth review explores the association between Down syndrome (DS) and Alzheimer's disease (AD). Both disorders have underlying biological features such as high amyloid-beta (Aβ) and tau protein levels, as well as dysregulated immune response, inflammation, and endocytosis. People with DS have an additional copy of chromosome 21, which causes them to overexpress genes, including APP and DYRK1A, which contribute to Aβ, neurofibrillary tangles, oxidative stress, and dysregulated endocytosis. As a result, individuals with DS are critical in researching AD therapies and prevention.
2. **Interpretation**: People with DS are genetically predisposed to dementia and AD. The molecular linkages between DS and AD provide valuable insights into the underlying causes of both disorders and offer prospective therapeutic targets. Early diagnosis and treatment monitoring using fluid biomarkers are active areas of research. Genetic screening for high-risk individuals may enable earlier intervention, while gene editing research with customized therapy approaches holds promise. Continued investigation into effective treatments and prevention measures for DS patients at risk for AD is crucial.
3. **Future directions**: Future research should focus on developing reliable biomarkers for early diagnosis and monitoring of AD in individuals with DS. Genetic screening programs can help identify those at higher risk, allowing for targeted interventions. Additionally, exploring gene editing techniques may offer customized therapies tailored to the specific genetic abnormalities present in DS and AD. Continued clinical studies are necessary to evaluate the efficacy and safety of potential treatments and prevention strategies for DS and AD (DSAD). Overall, these research directions promise to improve outcomes and quality of life for individuals with DS who are at risk of developing AD.

2 | PREVALENCE

DS is reported in about 1 in 700 newborns in the United States (http://www.ndss.org). Approximately 5300 babies with DS are born in the United States annually, and nearly 200,000 individuals have this developmental disability.[21] Up to the 1960s, the mortality rate of DS cases was high as a result of failure to treat intercurrent diseases during early ages. Over the past 30 years, improvements in access to medical care, research advances, and support for people with DS have led to a

significant extension in their life expectancy (almost double from 25–30 to >60 years of age).[12,13] Up to 80% of people with DS reach their sixties, and certain nations are seeing a growing number of DS septuagenarians, too.[22–26] With an increased life expectancy of individuals with DS, there is an increased accumulation of their multiple health risks, including AD dementia.[15,27–29] All individuals with DS acquire AD neuropathology by age 40, almost two to three decades earlier than the normal population.[15–17,30–33] Dementia prevalence in individuals with DS is about 10% in the age range of 35–50 years, 55% in the 50–60 years, while 85% reach 60 years.[17,34–38] Interestingly, there is still a subset of aged individuals with DS who never develop clinical signs of dementia at any age despite having pathological features of AD.[39,40]

3 | GENETIC CAUSES AND TYPES OF T21

T21 can be either complete or partial Hsa21 depending on the presence of a part of Hsa21 short (p) versus long (q) arms or a complete Hsa21. The root of a complete or partial chromosome is still unknown. To date, late maternal age is the only factor linked to an increased risk of carrying a baby with DS due to nondisjunction, translocation, or mosaicism.[4,41] However, high birth rates of approximately 52% of newborns with DS are noted in women <35 years of age.[42] Unfortunately, to date, no definitive research is available to pinpoint the exact cause of DS, as it can originate from either the mother or the father or possibly from environmental factors. So far, approximately 5% of the DS cases have been traced to the father.[43]

3.1 | Complete or non-disjunction T21

About 95% of individuals with DS have complete T21.[43] Approximately 86% of the extra 21st chromosomes in complete T21 cases are maternally derived as an outcome of non-disjunction in meiosis II (75%) than meiosis I (25%). While ~9% of complete T21 cases are due to paternal meiotic error, non-disjunction occurs equally in meiosis I and II. Altogether, <5% of complete T21 is attributable to mitotic errors.[44] Complete T21 is strongly associated with rising maternal age, presumably due to reduced genetic recombination.[41] The advanced maternal age-related errors in meiosis I are the typical situation that leads to reduced recombination of 21q between the non-disjoined chromosomes and could partially explain the increased T21 fetus development.[45]

3.2 | Translocation and partial trisomy

Unlike complete T21, translocation DS is independent of the parent's age, and ~4% of DS have a part of Hsa21 attached to another chromosome {t(14;21) or t(21;21)}.[46,47] The process of chromosomes breaking and joining other chromosomes is known as translocation, as the chromosome material transfers from its original location to the new one. In cases of translocation DS, q arms of Hsa21 and another chromosome break, followed by the fusion of the long arms of two acrocentric chromosomes. This process is widely known as "Robertsonian translocation" or "centric fusion."[48,49] It is an isolated event mainly occurring during the formation of an individual ovum or sperm involved in their conception. Hsa21q is primarily translocated to chromosome 14 or 21; rarely, Hsa13, 15, and 22 could be involved too.[48,50]

The usual set of 23 chromosomes, including the translocated one, are present in either ovum or sperm during conception. Hence, this results in one intact Hsa21 and a second affected Hsa21 attached to another chromosome. When the ovum or sperm containing 23 chromosomes (+ translocated part) merges with a normal sperm or egg with 23 chromosomes, the future fetus has 46 single chromosomes along with a translocated chromosome with an extra copy of Hsa21 attached to it. During cell division, the translocated chromosome acts like a single chromosome; hence, all cells produced from this first cell consist of an extra Hsa21 portion, leading to a DS fetus.[4] These have been the basis of studies aimed at understanding and associating the variance of a specific DS trait with a particular region of Hsa21.[8,51,52]

Whereas Hsa21p comprises tandemly repeated redundant ribosomal RNA genes, no clinical consequences are noted in the case of an unbalanced p arm.[53–55]

3.3 | Mosaicism

An individual with mosaicism has two or more genetically distinct cell lines from a single zygote.[56] A mosaic DS could happen due to a mitotic error following fertilization of an ovum or could alternatively arise from an early mitotic error in an embryo of T21. Post-fusion of an ovum, as the zygote divides and multiplies by conventional cell division, an imbalance during the chromosome process leads to the formation of a single cell with an extra Hsa21. As the cells with extra Hsa21 and the non-trisomic cells continue to divide and multiply by conventional cell division, a mixture of cells is produced.[56] Mosaic DS is rare.[48]

Unlike other types of DS, individuals with mosaicism consist of an extra Hsa21 in some cell lineages while not in other cells. As a result, mosaicist DS have a mixture of trisomic and normal cells, varying from few to 100% trisomic cells. Rather than their quantity, the anatomical distribution of trisomic cells determines the DS phenotype in mosaic individuals, making the genotype-phenotype relationship relatively complex.[57,58]

4 | GENE EXPRESSIONS IN T21

Even with increased knowledge of coding and non-coding genes and regulatory motifs on genetic material, as yet, only half of Hsa21 has been annotated; 233 protein-coding genes, 423 non-protein-coding genes (69 small, 330 long, and 24 miscellaneous non-coding genes), and 188 pseudogenes on 21q5.[59] The rest of Hsa21 (~48%) mainly represents repetitive elements that need to be annotated. Considering these facts, it is an immense challenge to understand and explain the genetic etiology and multiple manifestations related to DS individuals.[60,61]

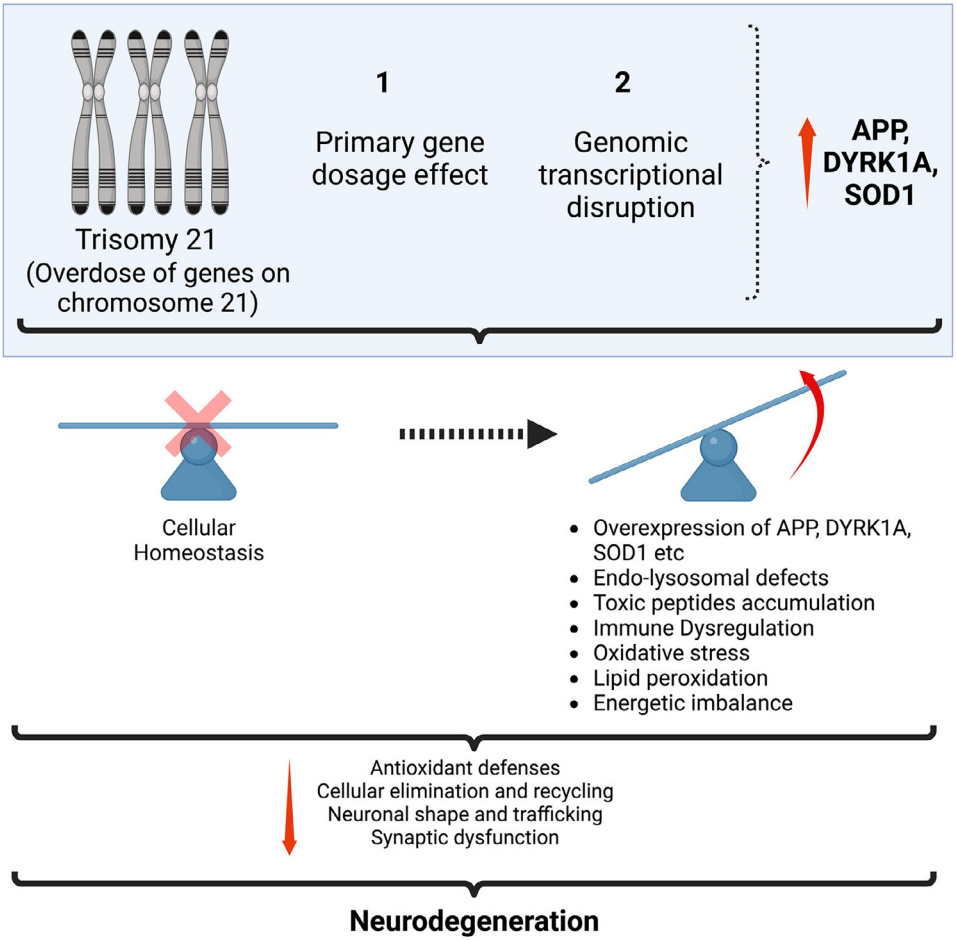

FIGURE 1 Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease (AD) in Down syndrome (DS). (A) Primary 1.5 times overdose of genes on chromosome 21 (Hsa21) causes overexpression of genes on Hsa21. (B) The overexpression of amyloid precursor protein (*APP*) and superoxide dismutase 1 (*SOD1*) are associated with an increased production of amyloid beta-peptide (Aβ) and superoxide anion (O2−), respectively. These events boost ROS and RNS, which peroxidize proteins and lipids and damage protein structures. Damaged proteins in the DS brain are associated with reduced autophagy, unfolded protein response, glucose metabolism, antioxidant defense, neuronal trafficking, and synaptic dysfunction. (C) Subsequently causing progressive neuronal dysfunction and degeneration.

Researchers have proposed two hypotheses for explaining the underlying genetic and phenotypic manifestations in T21 cases. The first hypothesis is commonly known as a "Hsa21 overdosage effect"; there is the gain of function of genes residing on Hsa21.[62] The DS manifestations directly relate to overexpression of Hsa21 genes, and the downstream consequences associated with it (Figure 1). The most common gene dose effect of Hsa21 trisomy is a 1.5-fold higher expression of trisomic genes in the various tissues of T21 individuals. The essential genes located on Hsa21 that directly or indirectly lead to AD-like dementia are: amyloid precursor protein gene (*APP*), tyrosine phosphorylation regulated kinase 1A (*DYRK1A*), superoxide dismutase (*SOD1*), endosome-to-Golgi-trafficking gene *DOPEY2*, the transcription factor BTB and CNC homology 1 (*BACH1*), Down syndrome cell adhesion molecule (*DSCAM*), oligodendrocyte transcription factor (*OLIG2*), single-minded 2 (*SIM2*), Purkinje cell protein 4 (*PCP4*), and erythroblast transformation-specific related gene (*ETS*-related gene) (Figure 2A; Table 1).[63–77] The extra genomic Hsa21 is directly responsible for the upregulation of trio genes *APP, DYRK1A, and SOD1*, and their association induces a potent cascade of central and peripheral imbalance in oxidative homeostasis leading to ID in T21 cases. The upregulated trio genes directly escalate oxidative stress (OS) and increase neurotoxic peptides (Aβ42) and amyloid plaques in the brain, leading to early-onset AD (EOAD).[33,78–86] The cyclic relationship between *APP* dosage and OS is an essential determinant of AD risk in T21 individuals (Figure 3). Interestingly, individuals with partial or mosaic trisomy with disomic APP having normal APP expression levels do not develop EOAD.[78]

Meanwhile, the second hypothesis suggests the disruption of global transcription homeostasis either due to the direct involvement of Hsa21 gene functions in transcription regulation or indirectly as a by-product of the additional genetic material.[87] A noted global imbalance in gene expression is due to the direct or indirect participation of Hsa21 genes in transcription regulation and the gene expression of those on chromosomes other than 21.[74,88–90] A plethora of recent studies support the mentioned concept. However, the main question is whether the entire transcriptome is disrupted or a more limited increase in gene

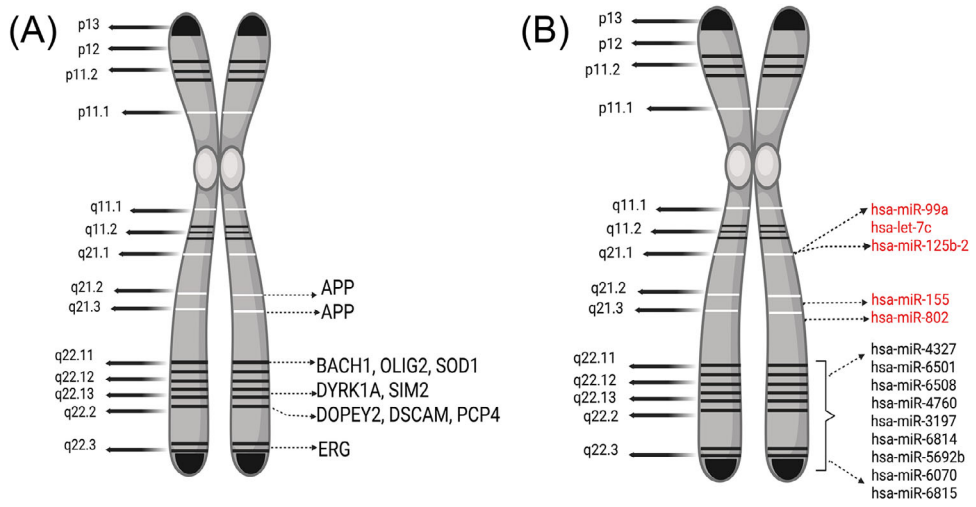

FIGURE 2 Location of essential genes on chromosome 21. (A) Genes on chromosome 21 influence the structure and function of the brain. (B) miRNA loci on chromosome 21; hsa-miR-99a, hsa-miR-802, hsa-miR-125b, and hsa-let-7c play a role in neuropathology.

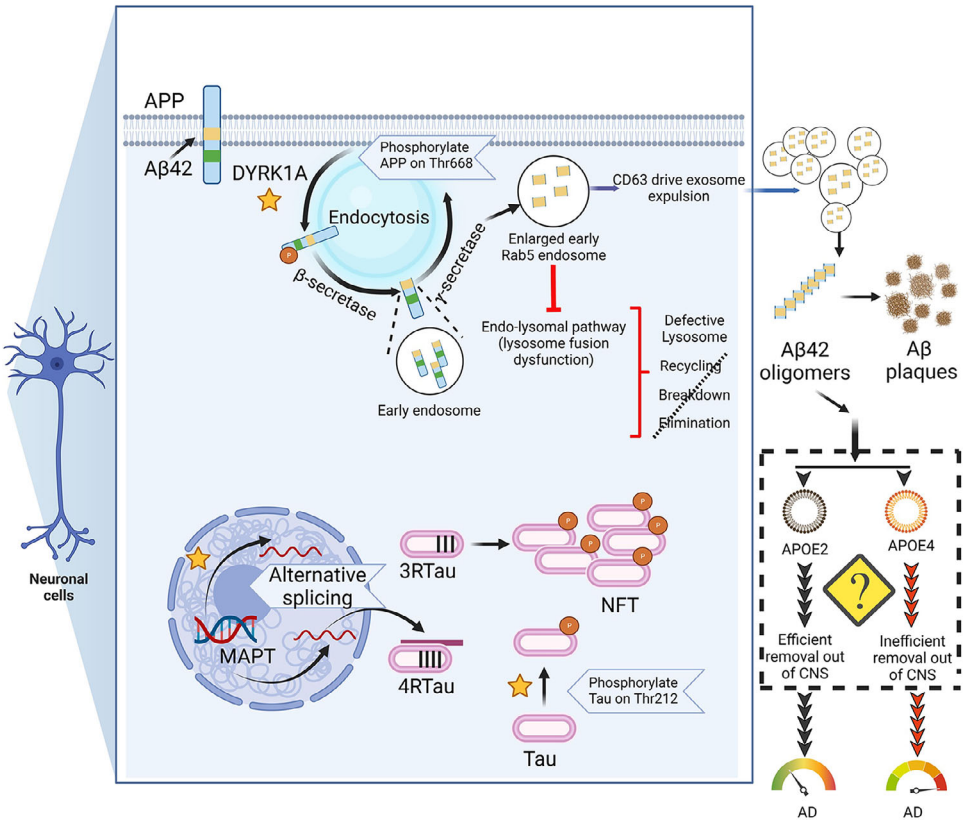

FIGURE 3 Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease (AD) in Down syndrome (DS). In individuals with DS, overdose of amyloid precursor protein (*APP*) and dual-specificity tyrosine-phosphorylation-regulated kinase 1A (*DYRK1A*) increases AD risk. DYRK1A phosphorylates APP at Thr668, resulting in amyloidogenic processing of APP and the high neurotoxic Aβ42 peptide. DYRK1A also targets splicing factors and the microtubule-binding protein tau (*MAPT*), which alters the splicing of the *MAPT* mRNA (encoding tau) and increases three-repeat (3R) tau and decreases 4R tau. Due to 3R tau's decreased affinity for microtubules, the imbalance causes neurofibrillary tangles (NFTs). DYRK1A phosphorylation also changes tau's framework, reducing its affinity for microtubules and increasing NFT formation. The apolipoprotein E (APOE) ε4 allele modifies the processing, deposition, and clearance of Aβ, making it a risk allele for AD. Despite the higher risk, the ε 4 alleles are not required to develop AD in the DS population, though it causes early onset of dementia in this population.

TABLE 1 Functional annotation of genes on chromosome 21. The genes located on chromosome 21 and their encoded proteins are overexpressed in DS and play a role in neurodegeneration and dementia

Gene symbol	Gene location	Candidate gene for
APP	21q21.3	Neurodegeneration
BACH1	21q22.11	Alzheimer's disease-like neuropathological changes
OLIG2	21q22.11	Developmental brain defects
SOD1	21q22.11	Oxidative stress and neurodegeneration
DYRK1A	21q22.13	Leukemogenesis; Impaired brain development; early onset of neurofibrillary degeneration
SIM2	21q22.13	Impairment of learning and memory; pathogenesis of intellectual disability
DOPEY2	21q22.2	Functional brain alterations and intellectual disability
DSCAM	21q22.2	Intellectual disability and the precocious dementia
PCP4	21q22.2	Abnormal neuronal development
ERG	21q22.3	Alzheimer's disease-like neuropathological changes

TABLE 2 Summary of microRNAs on chromosome 21

MicroRNA	Functional annotation
hsa-miR-155	Repress methyl CpG binding protein 2 and irregular dendritic development
	Impaired hippocampal synaptic plasticity and neurogenesis
hsa-miR-802	Repress the methyl CpG binding protein 2 and irregular dendritic development
	Impaired hippocampal synaptic plasticity and neurogenesis
hsa-miR-125b	Glial proliferative effect via suppression of CDKN2A
	Impaired synaptogenesis and long-term potentiation
hsa-miR-99a	Regulates transforming growth factor-β pathway and retrograde synaptic signaling
hsa-let-7c	Neuronal loss in a dose- and time-dependent manner by acting on toll-like receptor 7

Note: Several T21-encoded microRNAs are associated with intellectual disability and regulate neuronal functions. Overexpression of these microRNAs leads to defective neurodevelopment in individuals with DS.

expression is connected directly/indirectly to those genes associated with Hsa21. Also, Hsa21 accommodates several miRNAs, which are small non-coding RNAs regulating post-transcriptionally (Figure 2B; Table 2). An extra copy of the miRNAs may contribute to cognitive dysfunction and EOAD in individuals with DS. There are five most studied clustered miRNAs (let-7c, miRNA-99a, miRNA-125b, miRNA-155, and miRNA-802) around on the long arm of Hsa21 - chr21q21.1-chr21q21.3.[91] The clustered miRNAs downregulate the expression of innate immunoregulatory and anti-inflammatory genes in AD and/or DS while being upregulated in AD and DS brains compared to control brains.[92–98] Let-7c and miR-155 are shown to be contributors to neuroinflammation and hippocampal parenchyma in the general AD population.[99–101] Overexpression of these miRNAs also causes dysfunctional neuronal development, impaired synapse strength, and synapse formation with reduced neuronal excitability.[99,100,102] Further study and analysis of Hsa21-encoded miRNAs are warranted to investigate their regulatory mechanism and potential role in a transcriptional imbalance in individuals with DS. Aberration in the expression of these genes on Hsa21 could disrupt global genetic homeostasis disruption. However, the nature and extent of such effects in T21 individuals remain to be explored.

5 | ALZHEIMERS DISEASE IN T21

The compelling evidence associates higher APP dosage in T21 with a greater risk of AD in people with DS, hence classifying APP as an "effector" gene. However, it is unclear whether the signs of AD dementia in T21 are exclusively the result of APP overexpression and its downstream effects or whether other genetic characteristics of T21 also play a role. Multiple molecular processes are being investigated to account for the higher DSAD risk. Here we present a single mechanism connecting all proposed explanations for AD in people with DS: the "vicious cycle of neuropeptide buildup, endosomal dysfunction, and OS due to overexpression of trio genes (SOD1, APP, and DYRK1A) as a driver of AD-like cognitive impairment in DS population."

As discussed previously, redox equilibrium in neuronal cells and other tissues is disrupted in DS because several genes on Hsa21 either directly or indirectly enhance free radical generation or cease the defense systems. When the potential genes are considered, a vicious cycle is formed between the OS, neurotoxic peptide accumulations, and endosomal and proteasomal dysfunction. Though cognitive impairment in DSAD is not often immediately apparent, neuroinflammation and neuropathology often appear as early as puberty.[15,103–106] Increased OS is observed in DS as early as in the embryonic brain compared to non-DS controls.[107–109] While neuroinflammation is caused in early adolescence by activated microglia and astrocytes, the release of cytokines and chemokines, and more reactive species linked with amyloid plaques in the later stages of individuals with DS.[15] Two OS markers, lipid peroxidation and hydroxy-2-trans-noneal have been demonstrated to be elevated in young people with DS (1–15 years) compared to their age-matched controls.[110,111] DS mitochondrial dysfunction eventually induces APP processing abnormalities, increasing Aβ generation.[112–114] As the first line of defense against OS, Aβ, and neurofibrillary tangles (NFTs), microglial cells act to clear out the damaged neurons and toxic species by triggering inflammation via cytokine production.[115] Further, mitochondrial-derived extracellular vesicles (mDEVs) evolve as rescuers during mitochondrial damage and

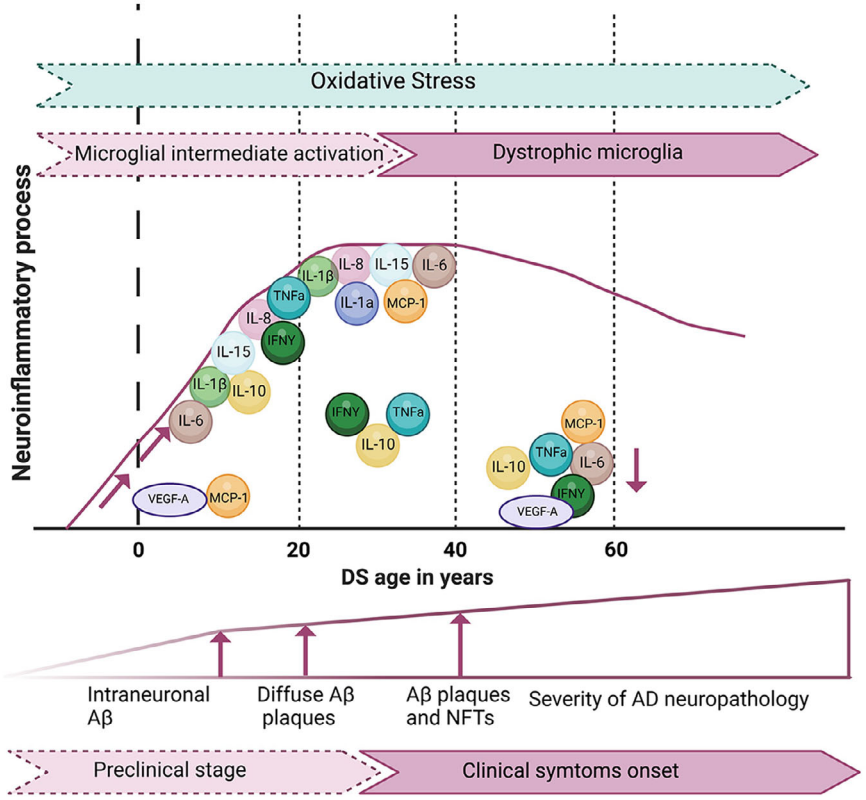

FIGURE 4 Neuroinflammation underlying the pathogenesis of Alzheimer's disease (AD) in Down syndrome (DS). DS fetuses show early oxidative stress. DS neuroinflammation precedes AD pathogenesis. The neuroinflammatory profile is amplified in children and young DS individuals at preclinical AD stages. In midlife, dystrophic microglia and chronic neuroinflammation rise, but inflammatory markers decrease.

OS, performing as an additional step in mitochondrial quality control coordinated with mitochondrial-lysosomal crosstalk to clear dysfunctional proteins and organelles.[116,117] The release of mDEVs with toxic mitochondrial disposal can potentially instigate inflammation in the neurons and other tissues.[115,116] Neuroinflammation, involving both pro- and anti-inflammatory pathways, contributes significantly to many neurodegenerative diseases. However, its exclusive role in the pathogenesis of DSAD has not been explored well. Is neuroinflammation a life-long phenomenon in DS, or does it intensify with age and AD? Unique neuroinflammatory manifestations are displayed in the brains of people with DS, consistent with immune activation due to the invasion of serum proteins in the brain compared to that of the AD population (Figure 4; adapted from[106]).[103–106] The neuroinflammation markers such as interleukins (IL) including IL-1, IL-6, and IL-10 are upregulated in young DS brains and aggravated before overt AD pathology.103–106 The neuroinflammation markers such as interleukins (IL), including IL-1, IL-6, and IL-10, are upregulated in young DS brains and aggravated before overt AD pathology. Whereas epidermal growth factor-A (EGF-A), interferon γ (IFNγ), tumor necrosis factor α (TNFα), and IL-12p40 wane at an advanced age in DS population. Besides, DS brains undergo a different intermediate activation phenotype of microglia before reaching a completely activated state.[106] The complement (C1q) activation is more consistently reported in post-30 years of age in DS population than in younger individuals with DS.[118,119] The Hsa21 associated pro-neuroinflammatory genes like ATP binding cassette subfamily G member 1 (*ABCG1*), ADAM metallopeptidase with thrombospondin type 1 motif 1/5 (*ADAMTS1/S5*), β-Secretase 2 (*BACE2*), Cystathionine β-Synthase (*CBS*), Calcium Binding Protein B (*S100B*), and T Cell Lymphoma Invasion And Metastasis1 (*TIAM1*) are increased 1.5-fold in DS; future studies on DSAD should focus on neuroinflammation and its mechanistic role and span in DS population (Table 3).[120–123]

TABLE 3 Functional annotation of neuroinflammatory genes on chromosome 21

Gene symbol	Gene location	Candidate gene for
ABCG1	21q22.3	Efflux of phospholipid and cholesterol and maintains macrophages in an anti-inflammatory state
ADAMTS1/S5	21q21.3	S1/induced by IL-1β. S2/ induced by IL-1β and TGFβ
APP	21q21.3	Inducer of IL-1β
BACE2	21q22.2/3	Increases IL-1R2, a decoy protein for excess IL-1 captures
CBS	21q22.3	Catalyzes production of hydrogen sulfide bimodal regulation of inflammation
S100B	21q22.3	Upregulates IL-1β and APP expression, released in response to TNFα
TIAM1	21q22.11	Generation of oxidative species through NADPH oxidase

Note: The genes located on chromosome 21 and their encoded proteins are overexpressed in DS and play a role in neuroinflammation in T21.

6 | ENDOSOMAL DYSFUNCTION, EXTRACELLULAR VESICLES, AND THEIR CARGOES IN T21

Early endosomes are essential for sorting the cargoes to late endosomes for degradation, recycling selective loads by delivering to the plasma membrane or the Golgi for utilization, or releasing exosomes in the extracellular matrix.[124] In the brain, early endosomes support neuronal growth, development, synaptic functions, and homeostasis by sorting the cargoes into late endosomes, a small subset of extracellular vesicles, that is, exosomes (sEVs), and lysosomes as needed.[125] sEVs secretion is constitutive and controlled by the state of cells (e.g., inflammation, cellular stress), and these natural nanoparticles are representative of their mother cells and can be isolated from all biological fluids.[126–128] Recent work has demonstrated that enhanced sEVs secretion is a compensatory mechanism in response to cellular homeostasis imbalance.[129] However, not all pathological conditions induce sEVs secretion.

In both AD and DS populations, endocytosis is upregulated where early endosomal dysfunction is interlinked to the amyloidogenic processing of APP, and malformed early endosomes are the earliest pathological change in the endocytic pathway.[130–133] Early endosomes in both populations carry cargoes inclusive of APP, β-APP cleaving enzyme-1, and γ-secretase, along with various insoluble and soluble aggregated forms of neurotoxic Aβ peptides and APP proteolytic transmembrane fragments which subsequently results in the trafficking of Aβ to late endosomes and sEVs.[131,134–136] Interestingly, along with APP and its metabolites, another early-appearing endocytic pathology is enlarged RAS-Associated Protein (RAB5)-positive endosomes in individuals with AD and DS (Figure 3).[131,135,136] RAB5 is a crucial regulator of endosome biogenesis, including early to late endosome maturation, fusion, and trafficking, especially of cell-surface proteins.[137–139] The noted enlargement of RAB5 in early endosomes is due to escalated endocytosis to clear the neuronal waste, eventually leading to endosomal dysfunction and neuronal vulnerability.[135,140] The enlarged RAB5 positive endosomes are detected as early as in DS fetal neurons and almost all the neurons in the preclinical stage of DS individuals.[131,140] Similar endosomal phenotypes were also identified in AD and DS mice models.[130,141,142]

The endocytic pathway is also responsible for sEVs formation and release, and trisomic APP boosts the boosted exosome release in extracellular space. sEVs are believed to have a compensatory and protective function in neurodegeneration by clearing toxic content from neurons. Evidence suggests that approximately 40% more sEVs are released in the DS brain compared to the age-matched non-DS controls, and similar age-related endosome abnormality was observed in the TS2 mouse model of DS.[143,144] Studies suggest neuronal sEVs either conform Aβ to nontoxic amyloid fibrils, facilitating microglial internalization and degradation, or promote Aβ proteolysis via exosome-associated insulin-degrading enzyme.[145–147] As indicated, exosomal release in AD and DS is a potential mechanism to remove Aβ and its metabolites from the neurons. Still, it also presents a potential risk of disease propagation to surrounding neurons and cells across the BBB. Once released, these nanoparticles possess the power to travel both within the brain parenchyma and across the BBB, and other tissue barriers and sEVs cargoes are released in the respective cells.[148,149] The contradicting role of sEVs in the seeding and spreading of misfolded toxic proteins is shown where sEVs cargo proteins are shuttled from one region of the brain to another, as well as varied tissues of AD and DS individuals.[136,150–154] Researchers attribute endo-lyso-recycling defects as a driver for the DS population's progressive neuronal dysfunction and neurodegeneration.[155] In-depth study of highly striking altered endosomal mechanisms in AD and DS could reveal additional insights into the relationship between the primary endo-lysosomal system, APP, OS, and AD, providing an edge to investigate the vital biochemical abnormalities and molecular biomarkers linked to endosomal changes concerning triplication of genes on Hsa21 in DSAD population.

7 | INTRICATE COMPLEXITIES UNDERLYING THE COGNITIVE DECLINE IN T21

As seen so far, a complex interplay of various factors significantly contributes to the early onset of AD-like dementia in DS individuals. It can be noted that genetics, particularly an extra set of chromosome 21, sets the stage for amplified developmental instability and altered neurobiology, predisposing individuals to neurological complications. Still, the overexpression of genes implicated in AD pathology contributes to the increased production of Aβ peptides, a hallmark feature of AD pathology in individuals with DS. Especially the triplication of genes involved in neuroinflammation, oxidative stress, synaptic function, and immune response further exacerbates neuronal vulnerability, predisposing DS individuals to early dementia. Further emerging evidence suggests that the aberrant functioning of the endo-lyso-cycle, impairing the intracellular protein trafficking, degradation, and recycling, leading to the accumulation of toxic protein aggregates and accelerated neurodegenerative process in DS brain. Moreover, aberrant sEVs secretion and cargo trafficking cause disrupted intercellular communication and pathogenesis of AD in individuals with DS. These combined factors synergistically accelerate cognitive decline and the onset of dementia in DS individuals, shedding light on potential targets to either diagnose or mitigate the neurological consequences.

8 | BLOOD-BASED BIOMARKERS

The pre-existing cognitive disability in the DS population makes the evaluation of AD-like dementia extremely difficult by using traditional cognitive screening tools like the Mini-Mental State Examination.[156] Over time, clinicians have developed varied rating scales to diagnose and assess the cognitive decline in populations with lowered intellectual capacity, such as the Brief Praxis Test (BPT), Dementia Scale for Mentally Retarded Persons (DMR), Test of Severe Impairment, the National Task Group (NTG)-Early Detection Screen for Dementia, Down Syndrome Mental Status Exam, the Cambridge Cognitive

Examination for Older Adults with Down Syndrome (CAMCOG-DS), the Cambridge Cognitive Examination for Mental Disorders of Elderly-Down Syndrome (CAMDEX-DS), and the Cognitive Scale for Down Syndrome (CS-DS).[157–164] The subtle changes in cognitive functioning over age in individuals with DS are enveloped by the established ID, making it particularly complex and challenging to diagnose AD.[165] Thereby, clinical dementia assessment and AD diagnosis remain essential in the at-risk DS population. Given the high prevalence of AD in individuals with DS, it makes this population a necessary target for regular screening of AD biomarkers from an early age to monitor the dementia progression to AD, with an outlook to characterize predictive aspects of the biomarkers in DSAD.

Although detecting Aβ and tau in CSF or visualization of deposited toxic misfolded proteins using PET imaging reliably and accurately diagnose AD in at-risk individuals.[166–168] Irrespective of accuracy, these detection methods are expensive or invasive and particularly challenging in at-risk populations with DS. In contrast, screening tools like blood-based biomarkers of AD are significantly easier for individuals with DS, as they are minimally invasive, scalable, and cost-effective. Blood-based biomarkers provide an excellent platform for at-risk DS individuals where appropriate AD screening tools are limited, and often their health history is completed by care providers. Given that blood examination is a routine clinical workup in individuals with DS, blood-based tools could quickly help understand this population's changes throughout the disease progression. Standardization and development of reliable AD-specific blood-based biomarkers would give access to early recognition of AD-like dementia to transition to AD in DS individuals with an option of better treatment monitoring.

Additionally, DS adults have not been included in AD drug trials in the past, as the recruitment and assessment of task completion are additional challenges. Trusted AD biomarkers can provide an edge to streamline the recruitment of individuals with DS in new AD drug clinical trials, eventually aiming to slow the dementia progression and improve the lives of individuals with DS. Also, the characterization of blood-based biomarkers could enable personalized therapy to delay dementia progression in the at-risk DS population.[166–168]

The most studied AD biomarkers in the brain are Aβ, pTau, and tTau in CSF and plasma.[169–173] The importance of CSF markers is apparent, as they indirectly reflect the brain's pathophysiology. Still, the technique is invasive, which limits the CSF collection over a longitudinal span of AD progression in DS population. However, CSF and imaging techniques were developed to characterize the "A/T/N" system for diagnosis. A/T/N system includes seven AD biomarkers, further divided into three categories based on the indicative AD pathophysiology: A represents amyloid pathology, T shows total or phosphorylated (or both) tau, and N indicates neuronal injury and degeneration.[169–174] The plasma A/T/N biomarkers can differentiate AD patients from healthy controls and non-AD dementias.[175] Remarkably, the traditional blood-based A/T/N biomarker platform can successfully classify DS with or without AD.[176,177] The plasma Aβ biomarkers can distinguish DSAD individuals from those without dementia, where higher concentrations of plasma Aβ40 and lower ratios of Aβ42/Aβ40 have been observed. However, some studies have reported that individuals with DS and dementia have higher levels of both Aβ40 and Aβ42 in comparison to their control group DS without dementia, while others reported differences exclusively in either Aβ40 or Aβ42 or Aβ42/Aβ40.[178–182] The cross-sectional and longitudinal studies showed plasma levels of Aβ40 and Aβ42 as a predictor of cognitive decline in the DS population.[181–186] Although, increase or decrease in cognitive ability was shown to be dependent on time point assessment of plasma Aβ measurement, that is, higher baseline concentrations of plasma Aβ42 were associated with poor communication skills, memory, and motor performance and increased AD risk in DS while changes in plasma Aβ across multiple time points associated lower Aβ42 to increased cognitive decline in adults with DS.[181–186]

Another biomarker explored in AD is the tau protein. Reports assessing tau concentrations in the DS population suggested higher tau levels in older DS individuals compared to non-DS controls, and a similar trend was noted in DSAD versus non-DSAD (asymptomatic) population.[177,179,187,188] Although, few researchers showed no differences between DS groups, thus limiting the diagnostic performance of tau to distinguish between DSAD and the control population.[189,190] Although, specific phosphorylation sites of the tau protein (pTau; epitopes localized at positions 181, 199, 217, 231, 396, and 404) have been directly associated with NFTs accumulation in AD.[191] Out of all the pTaus, plasma pTau181, 217, and 231 have been studied extensively, and increased levels of these pTaus can distinguish people with AD from cognitively unimpaired older adults and people with other neurodegenerative disorders.[192–194] Also, a study suggested that individuals positive for pTau231 and pTau181 had a higher amyloid burden, lower hippocampus volume, and worse cognitive performance than individuals positive for only one of these markers in AD versus MCI groups.[195] In the DS population, only one study has investigated plasma pTau181 to detect AD pathophysiology, and higher levels of pTau181 were reported in DS individuals compared to non-trisomy controls.[196]

Neurofilament light chain protein (NF-L), a plasma biomarker abundantly expressed in myelinated axons, is another well-studied plasma biomarker.[197] Researchers have shown that plasma NF-L in the DS population could be detected early, and increasing shifts are noted in NF-L at different age points in the prodromal stage of AD in the DS.[177,189] Also, a significantly higher concentration of plasma NF-L has been reported in symptomatic individuals with DSAD compared to DS individuals without AD-like dementia.[179,198] The quality of plasma NF-L emphasizes its consistency, relevance, and potential clinical applicability as a diagnostic and prognostic biomarker.

sEVs are another promising neurodegenerative biomarker. As discussed earlier, there are escalated releases of sEVs in AD and DS populations, and these nanoparticles can easily be used for "fluid biopsy" to study the specific neuronal populations and their pathophysiology with a dual advantage to be studied in both diagnosis and prognosis of the disease.[199] The protein cargoes of blood-based neuronal and astrocyte-derived sEVs (sN/ADEVs) have been investigated in various neurological conditions.[200–204] The enriched loads in sADEVs versus sNDEVs were distinct in AD or FTD relative to their age-matched controls.[205] Also, sN/ADEVs biomarkers have been examined for AD

and traumatic brain injury groups.[206] Abnormal A/T/N cargoes in sNDEVs (pTau, Aβ1-42, neurogranin, and REST) accurately predicted converting mild cognitive impairment to Alzheimer's.[207] The sNDEVs cargo biomarkers (Aβ42, pTau-181, and p-S396-Tau) evaluated in DS individuals showed significantly higher levels in people with DS than in age- and gender-matched control groups.[129] Although sN/ADEVs are being explored extensively in different neurological disorders not in the DS population, their potential as blood-based biomarkers in the DS population has yet to be explored. Microglial-derived sEVs have also been associated with neurodegenerative disease and have been successfully isolated and characterized from human plasma with the potential to serve as a novel subject of inquiry in the context of AD and DSAD.[200,208]

As discussed earlier in the review, several reports state an altered neuro-inflammatory response in DS as a potential culprit behind AD pathology.[103,104,183,209–212] Hence, inflammatory markers are gaining the focus, although the existing A/T/N framework does not consider the inflammatory and immune markers for AD in the DS population.[174,213] Several researchers have detected a significantly high level of IL-6, IL-22, IFNγ, and TNFα levels in young and adult individuals with DS compared to their age-matched controls.[212,214,215] Future biomarker studies should focus on assessing the role and trajectory of neuroinflammatory markers throughout the lifespan of those with DS.

Irrespective of the nature and robustness of a biomarker, it is recommended to develop a combination of biomarkers to predict the onset and AD prognosis in DS. Moreover, longitudinal assessments of different fluid biomarkers might provide a more substantial clinical value than single time points in individuals with DS.

9 | CLINICAL TRIALS AND FUTURE THERAPIES IN T21

Undoubtedly, advancements in medical care and research have improved and extended the life span of DS individuals. However, an increased life expectancy of individuals with DS pushes the population to a higher risk of AD development. There are no pharmacologic therapies for DSAD that are effective in slowing or stopping neurodegeneration due to the lack of understanding of its etiology and pathophysiology. In clinical practice, AD diagnosis in the DS population solely relies on clinical symptoms, neurological and neuropsychological tests, and the exclusion of alternative dementia or neurological illnesses. Thus, there is a dire need to find therapies that either slow down or prevent AD in DS individuals.

Researchers and clinicians have been working in parallel to find better treatments or targeted therapies to treat or prevent AD in the general population. A wide range of approaches has been implemented to target Aβ, tau, and various neurotransmitters, to name a few.[216] Thus far, most of these trials have been unsuccessful, and there are no effective treatments for changing the course of AD in DS population. Researchers have speculated that the ineffective impacts of the drug trial against AD could be due to the recruitment of individuals post-diagnosis of AD with 10–20 years of neurodegeneration and cognitive decline instead of targeting the preclinical stages of AD. Hence, the recent focus of clinical trials for AD prevention has been on treating individuals at high risk for dementia, that is, at prodromal stages of AD.

Globally, researchers have shown remarkable similarities between AD and DSAD. However, until recently, the at-risk DS population, which requires a regular screening and evaluation of cognitive decline from an early age to monitor the dementia progression to AD, has not been included in AD drug trials. This is thought to be due to the absence of reliable and robust diagnostic and prognostic biomarkers to study the drug response; these clinical trials rely on behavioral, learning outcomes, intellect, and environment, making these outcome measures unsuitable for individuals with DS.[19] Recruiting individuals with ID to clinical trials poses several other challenges, like a formal alliance with individuals with DS and their family members, obtaining informed consent, retention, coordination, safety, research design, and interpretations, which strongly impact clinical trials research in the DS population. In addition, there is often insufficient recruitment to obtain valid and reliable results due to lack of exposure to research benefits and limited community awareness in racially and ethnically diverse populations of DS and their family.

In the past decade, many researchers have focused on understanding DSAD by exploiting the latest AD biomarkers via brain imaging and sensitive assays in CSF. Still, several open-ended questions exist to understand the AD onset and its progression in people with DS, subsequently helping to develop possible treatments to delay or prevent it. Researchers still must develop the best-suited cognitive outcome measures and study the applicability and feasibility of the A/T/N biomarkers in DSAD. Will ongoing interventions targeting Aβ plaques in AD in general populations be well received in the DS population? The clinical trials of disease-modifying AD are generally 18–36 months. Still, it is essential to revisit the trial timeframe for individuals with DS, provided AD-like neuropathology and neuroinflammation begin at a much earlier age than the general AD population. Besides neuroinflammatory proteins, there are varied miRNAs reported to be associated with the dysregulation of proteins involved in AD pathology in the DS population. Opening follow-up questions: at what age shall the trial be targeted, and how early should AD in DS be intervened? Also, how long should drugs be targeted to prevent AD in DS? Would preventive trials in DS, that is, before the appearance of AD neuropathology, be more valuable? If so, what age range should the DS population be recruited for trials? Could prenatal treatment to improve fetal brain growth, connectivity, and neurocognition in DS fetuses be open for discussion in futuristic clinical trials? Could embryonic stem cells or stem cell-derived sEVs treatment effectively mitigate the neuropathology associated with DSAD? Should we use the differentially expressed miRNA signatures parallel to protein markers to reflect the accurate underlying disease pathology to provide evidence for new strategies for designing drugs for DSAD treatment? Hence, there is an extreme necessity for developing research guidelines for defining the preclinical, prodromal, and dementia progression of AD in DS, which could be critical for consideration and trial design in this population.

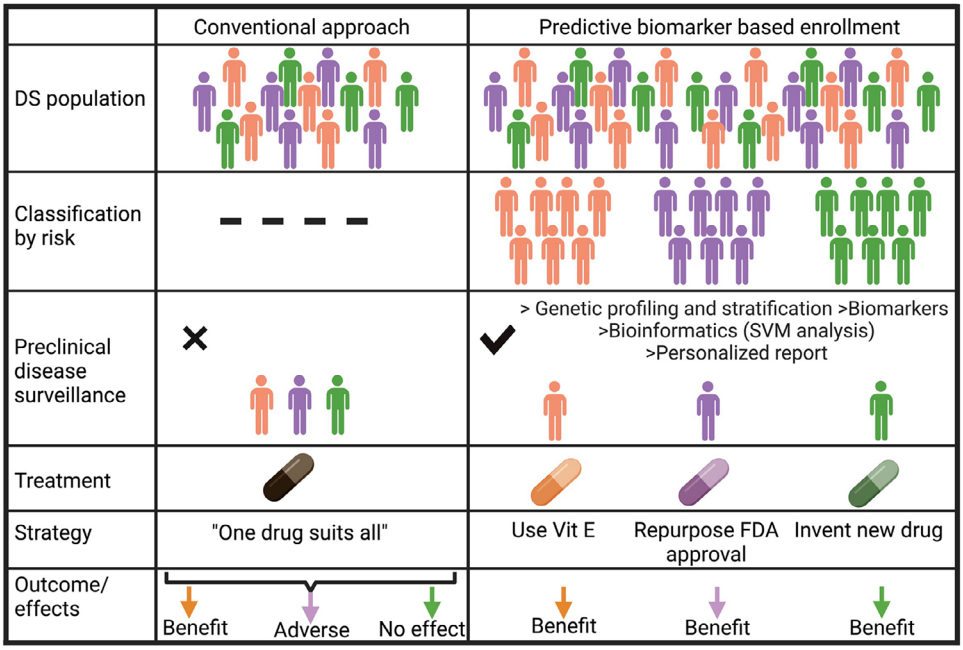

FIGURE 5 Schematic of conventional versus precision medicine in the DSAD population. Hypothetical clinical trial protocol with different levels of selection of patients with DSAD (1) genetic profiling tests to distinguish between types of T21; (2) neuropsychological tests to distinguish non-demented and demented DS; blood-based biomarker analyses to identify subjects with high propensities to convert to AD and (3) assess pro-inflammatory profiles in plasma.

Considering all the points discussed, special cruxes are required for the success of clinical trials for DSAD. First, to achieve the goal of bringing the most innovative and reliable AD therapies to the DS population, the NIH launched ABC-DS for clinical trials in the DSAD population, intending to examine the progression of AD-related biomarkers (Aβ, tau, and FDG-PET, MRI, fluid biomarkers, and neuropathology) as well as cognitive and functional measures in adults with DS.[217] Further, to conduct randomized, multi-center, placebo-controlled clinical trials in individuals with DS, the NIH-funded ACTC-DS was launched in 2018 (https://www.actc-ds.org) and has established a Trial-Ready Cohort (www.trcds.org) of over 150 deeply phenotyped adults with DS in advance of clinical trials for DSAD. Meanwhile, different research teams in Europe formed Horizon 21 Down Syndrome Consortium to study the longitudinal datasets inclusive of cognition change and AD biomarkers in DS cohorts from six countries (a) the Lon Down Syndrome Consortium; (b) the Cambridge Dementia in Down's Syndrome cohort; (c) the Rotterdam Down syndrome study; (d) AD21 study group, Munich; (e) TriAL21 for Lejeune Institute of Paris; and (f) the Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) (https://horizon-21.org).

A potential intervention that needs to be tested under appropriate conditions in the DSAD population is individually tailored biomarker-guided targeted therapies, that is, precision medicine (PM) in the DS population (Figure 5).[218] This is opposed to the one-size-fits-all approach of most ongoing clinical trials, that is, prevention strategies and treatments are directed to all the people in the diseased population, with minimal consideration for the existing differences between individuals. PM in the DS population shall aim to predict AD risk, understand cause and effect, discover subtypes, improve diagnosis, and offer individualized therapies using biological knowledge and health information.

Given that the DS population is genetically homogeneous, it provides a remarkable opportunity to implement preventative interventions by considering individual variability in genotype (complete vs. partial trisomy; Apoe4 +/−), neuroinflammatory protein and miRNA markers, environment, and lifestyle for each DS person to identify the onset and progress of AD. As discussed previously, OS has been identified as the widely accepted cause of neuroinflammation in DSAD. So, a combination of predictive protein and miRNA biomarkers and proinflammatory endophenotypes in the DS population could be a promising tool to predict the efficacy of the drugs in the trial and treatment response by a specific subset of individuals in the DS population. The beauty lies in the fact that we can obtain proof of concept of whether predictive biomarkers are helpful in screening and predicting treatment response by conducting retrospective studies on the failed trials so far, hence holding a tremendous benefit in designing futuristic clinical trials. Taking advantage of genotype-to-phenotype research coupled with a computational biology approach might be the most awaited path to develop individualized treatment strategies to delay the onset or prevent AD in the DS population. Similar processes can be applied to different pharmacological combinations for profiling individually tailored biomarker-guided targeted therapies in individuals with DS. DSAD has a complex molecular connectivity due to an extra copy of chromosome 21, as opposed to AD in the general population. To date, there are no effective interventions available for halting AD-like dementia in DS population. A multifaceted approach is required to

achieve effective anti-dementia results in individuals with DS, which should focus on various targets, such as inflammation, amyloid aggregation, and proteo-endo-lyso-recycling defects causing amyloidogenic processing of APP, with the goal of overall neuroprotection. In clinical trials, drugs with multitarget effects or multiple drugs that act on integrated molecular pathways in the DS population can be tested by assessing treatment efficacy using a range of predictive blood-based biomarkers.

To make it possible, continued research funding and investments to study the genetic and molecular basis of T21 and to design the trials accordingly are only assurances to transform the lives of individuals with DS individuals and the communities in which they live.

AUTHOR CONTRIBUTIONS

Sonal Sukreet and Robert A. Rissman conceived the idea; Sonal Sukreet, Robert A. Rissman, and Michael S. Rafii designed and wrote the paper; Robert A. Rissman had primary responsibility for the final content. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Michael S. Rafii is a consultant to AC Immune, Aptah Bio, Alzheon, Ionis, and Keystone Bio. Sonal Sukreet and Robert A. Rissman have nothing to disclose. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Human consent was not necessary.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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