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Recent Advances in Joubert Syndrome: Genetic Insights, Clinical Management, and Emerging Therapeutic Strategies

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Abstract:

Joubert syndrome (JS) is a rare, genetically heterogeneous autosomal recessive ciliopathy characterized by the pathognomonic molar tooth sign (MTS) on brain magnetic resonance imaging, resulting from cerebellar vermis hypoplasia or aplasia and abnormal superior cerebellar peduncles. Since its first description by Marie Joubert in 1969, substantial advances in molecular genetics have transformed the understanding of JS, with more than 40 disease-causing genes identified to date. These genes encode proteins that are essential for the structure and function of the primary cilium, a highly specialized sensory organelle involved in embryonic development and multiple intracellular signaling pathways. Consequently, JS is now recognized as part of the broader spectrum of ciliopathies, with multisystem involvement including retinal dystrophy, nephronophthisis, congenital hepatic fibrosis, and skeletal abnormalities, collectively referred to as Joubert syndrome and related disorders (JSRD). This review provides a comprehensive overview of recent advances in the molecular genetics, ciliary biology, pathophysiological mechanisms, clinical manifestations, diagnostic strategies, and current multidisciplinary management of JS. Particular emphasis is placed on emerging therapeutic approaches, including adeno-associated virus-mediated gene replacement, antisense oligonucleotide therapy, CRISPR-Cas9 genome editing, pharmacological modulation of Sonic Hedgehog (SHH) and mTOR signaling pathways, and novel small-molecule therapies targeting ciliary dysfunction. This review emphasizes the evolving landscape of Joubert syndrome research and provides a comprehensive framework for understanding its molecular basis, clinical management, and emerging therapeutic strategies, thereby supporting future research and the translation of precision medicine into clinical practice.

Keywords: Joubert syndrome; ciliopathy; primary cilia; molecular genetics; precision medicine; gene therapy; CRISPR-Cas9; antisense oligonucleotides; pharmacotherapy; targeted therapeutics.

1. INTRODUCTION

Joubert syndrome ((JBTS; OMIM 213300) is a clinically and genetically heterogeneous autosomal recessive disorder first described by the Canadian neurologist Marie Joubert and colleagues in 1969, following observation of four siblings exhibiting episodic hyperpnea, abnormal eye movements, ataxia, and intellectual disability [1]. The disorder is universally recognized by its neuroradiological hallmark — the molar tooth sign (MTS) — a distinctive appearance on axial MRI at the level of the isthmus, produced by the combination of cerebellar vermis hypoplasia, elongated and thickened superior cerebellar peduncles, and a deep interpeduncular fossa [2]. Incidence estimates range from 1 in 80,000 to 1 in 100,000 live births globally, although founder effects in specific populations yield substantially higher rates [3].

The conceptual framework surrounding JS has undergone a paradigm shift with the recognition that it belongs to the expanding family of ciliopathies — disorders arising from dysfunction of the primary cilium. The primary cilium is a non-motile, microtubule-based sensory organelle projecting from the surface of virtually all post-mitotic vertebrate cells. It functions as a cellular antenna, transducing extracellular signals from pathways including Sonic Hedgehog (SHH), Wnt, Notch, and platelet-derived growth factor (PDGF), all of which are critical for embryonic patterning and organogenesis. Proteins encoded by JS-causative genes predominantly localize to the cilium, particularly its transition zone — a specialized domain at the ciliary base functioning as a molecular gate to regulate protein access.

To date, mutations in more than 40 genes (designated JBTS1 through JBTS41 and beyond)

have been identified as causative for JS, collectively explaining approximately 60–70% of diagnosed cases. The remaining genetic architecture is incompletely characterized, suggesting further locus heterogeneity. The broader phenotypic spectrum, encompassing retinal dystrophy, nephronophthisis, liver fibrosis, and polydactyly in addition to cerebellar vermis hypoplasia, is now subsumed under the term Joubert syndrome and related disorders (JSRD), reflecting shared ciliary biology across organ systems.

From a pharmacological perspective, JS presents a compelling yet challenging target for drug development. Unlike many single-gene neurological disorders, JS is defined by profound genetic and phenotypic heterogeneity, requiring gene-specific or pathway-targeted therapeutic strategies. Advances in antisense oligonucleotide (ASO) technology, adeno-associated virus (AAV)-mediated gene delivery, and CRISPR-Cas9 genome editing have opened novel avenues for ciliopathy therapeutics. Simultaneously, a growing understanding of disrupted signaling cascades has identified druggable targets amenable to small-molecule intervention. This review synthesizes developments across the molecular biology, genetics, clinical medicine, and pharmacology of JS. The discussion is structured to provide clinicians and researchers with an updated understanding of pathogenic mechanisms, current standard of care, diagnostic tools, genotype-phenotype correlations, and the therapeutic pipeline approaches for this orphan disease.

2. PATHOPHYSIOLOGY: THE CILIARY BASIS OF JOUBERT SYNDROME

Primary Cilia: Structure and Function: The primary cilium is an evolutionarily conserved organelle assembled from a basal body derived from the mother centriole. Its axoneme consists of nine peripheral microtubule doublets arranged in a 9+0 configuration, distinguishing it from motile cilia (9+2). The transition zone, located immediately distal to the basal body, is characterized by Y-shaped connectors and transition fibers that form a diffusion barrier critical for compartmentalizing ciliary proteins. Intraflagellar transport (IFT) — the bidirectional movement of protein complexes along the axonemal doublets driven by kinesin-2 (anterograde) and dynein-2 (retrograde) motors — is essential for ciliogenesis and ciliary signaling [4]. Disruption of IFT, transition zone function, or basal body integrity destabilizes ciliary architecture, impairing SHH signaling (whose pathway components, including Smoothened and GLI transcription factors, traffic through the cilium), Wnt pathway modulation, and other developmental cascades. In neuronal contexts, these disruptions profoundly affect cerebellar development, particularly the specification, migration, and survival of granule cell precursors and Purkinje cells, explaining the cerebellar vermis hypoplasia that defines JS.

Transition Zone Dysfunction as a Unifying Mechanism: A compelling mechanistic convergence is emerging around transition zone dysfunction in JS. Proteins encoded by JBTS genes including RPGRIP1L (JBTS7/NPHP8), CC2D2A (JBTS9), TCTN1/2/3 (JBTS13/24/14), B9D1/B9D2 (JBTS27/34), and MKS1 (JBTS28) form discrete protein complexes within the transition zone. These "NPHP," "MKS," and "TCTN" modules physically interact and cooperate to maintain the selective permeability of the ciliary gate. Loss-of-function mutations in any component can destabilize the entire network, illustrating why phenotypically overlapping ciliopathies (Meckel-Gruber syndrome, nephronophthisis, Bardet-Biedl syndrome) share molecular machinery with JS. Furthermore, the transition zone regulates hedgehog signaling by controlling the ciliary entry of Smoothened. In the absence of SHH ligand, Patched-1 prevents ciliary entry of Smoothened. SHH binding releases this inhibition, enabling Smoothened accumulation at the cilium and activation of GLI transcription factors. Disruption of transition zone integrity in JS impairs SHH signal transduction, with downstream effects on neural tube patterning and cerebellar foliation. Pharmacological rescue of SHH signaling through Smoothened agonists has demonstrated partial restoration of cerebellar phenotypes in JS mouse models, representing a compelling early therapeutic proof-of-concept. [5]

Ciliopathy Signaling Crosstalk and mTOR Pathway: Emerging research has illuminated extensive crosstalk between ciliary signaling and the mechanistic target of rapamycin (mTOR) pathway. mTOR complex 1 (mTORC1) activity is negatively regulated at the primary cilium; loss of ciliation or transition zone integrity has been associated with upregulated mTOR signaling in renal tubular cells, contributing to nephronophthisis

and cyst formation in JS. Rapamycin and its analogues (rapalogs) have demonstrated efficacy in attenuating renal cystic disease in rodent models of JS-related nephronophthisis, though extrapolation to human trials requires careful consideration of the immunosuppressive profile and off-target effects. The dual role of mTOR in neuronal survival and renal pathology positions it as a pharmacologically relevant, if complex, target in JSRD. [6]

3. MOLECULAR GENETICS OF JOUBERT SYNDROME

Overview of Known Causative Genes: The genetic landscape of JS is characterized by remarkable locus heterogeneity. Since the identification of INPP5E mutations as causative for JBTS1 and the subsequent mapping of TMEM216 (JBTS2), AHI1 (JBTS3), NPHP1 (JBTS4), and CEP290 (JBTS5/NPHP6), the catalogue of JBTS genes has expanded rapidly through whole-exome and whole-genome sequencing strategies. CEP290, encoding a centrosomal protein essential for ciliogenesis, is among the most frequently mutated genes, particularly in JS with retinal involvement, accounting for approximately 10–15% of cases with ocular phenotypes. TMEM67 (JBTS11) is strongly associated with the hepatorenal subtype of JSRD, while AHI1 mutations frequently underlie JS with retinal dystrophy and cognitive impairment. Recent genome-wide association studies and next-generation sequencing cohorts have identified novel causative variants in genes including KIAA0586 (JBTS23), CSPP1 (JBTS21), IFT172 (JBTS29), ARMC9 (JBTS30), TOGARAM1 (JBTS35), and ADAMTS9 (JBTS37), substantially broadening the mutational spectrum. A subset of these genes, including TOGARAM1 and ARMC9, encode proteins governing the tubulin glycylation status of axonemal microtubules, providing novel insight into how post-translational modifications of tubulin impact cilia length and function. [7]

Genotype-Phenotype Correlations: Establishing reliable genotype-phenotype correlations in JS is confounded by variable expressivity, incomplete penetrance, and the influence of genetic modifiers. Nonetheless, certain gene-phenotype associations are sufficiently robust to guide clinical surveillance. Mutations in CEP290 and AHI1 are strongly associated with retinal dystrophy, often presenting as Leber congenital amaurosis; thus, patients harboring these variants warrant early ophthalmological screening. TMEM67 mutations are the primary genetic cause of the hepatorenal phenotype (JSRD with congenital hepatic fibrosis and nephronophthisis), necessitating hepatic and renal function monitoring from diagnosis. INPP5E mutations tend to associate with relatively isolated neurological phenotypes with fewer extracerebral complications. The phenomenon of "ciliopathy spectrum shifting" — where the same gene mutation can cause phenotypes ranging from JS to the more severe Meckel-Gruber syndrome or the milder Bardet-Biedl syndrome — depends on allele-specific effects, with truncating mutations generally producing more severe phenotypes than missense variants. This spectrum explains why careful allele-level analysis is essential in genetic counseling and supports the emerging concept of precision genotyping for prognostication. [8]

Digenic and Oligogenic Inheritance: Accumulating evidence supports the existence of digenic or oligogenic inheritance in a subset of JS patients, wherein mutations in two or more ciliary genes collectively determine disease expression and severity. Studies in zebrafish and murine models have demonstrated that heterozygous mutations in two JBTS genes can recapitulate full ciliopathy phenotypes that neither mutation alone produces. This oligogenic architecture complicates standard Mendelian diagnostic frameworks and highlights the necessity of comprehensive panel-based or genome-wide genetic analysis rather than single-gene testing. Clinically, it suggests that identifying one pathogenic variant in a known JBTS gene should prompt continued sequencing of the entire ciliopathy gene panel rather than concluding the diagnostic workup. [9]

Variant Classification Challenges: A persistent challenge in JS molecular diagnosis is the classification of variants of uncertain significance (VUS). Missense variants, particularly in genes encoding multi-domain transition zone scaffold proteins, frequently pose interpretive difficulties due to limited functional data and inadequate representation of certain ethnic groups in variant databases. The ClinVar repository contains a substantial proportion of JBTS gene variants classified as VUS, creating diagnostic uncertainty that complicates clinical decision-making and genetic counseling. Efforts by international consortia including EURO-RDI and the Ciliopathy

Alliance to develop functional assays — including high-throughput ciliogenesis assays in patient-derived fibroblasts and CRISPR knock-in cell lines — are beginning to provide evidence bases for reclassification. [10]

4. CLINICAL FEATURES AND DIAGNOSTIC CRITERIA

Core Neurological Features: The cardinal clinical features of JS reflect the underlying cerebellar and brainstem malformation. Hypotonia is nearly universal in the neonatal period, often prompting the initial clinical evaluation. Abnormal respiratory control, manifesting as episodic hyperpnea alternating with apnea in the neonatal and early infantile period, reflects disrupted rhythm generation in the brainstem reticular formation and is a characteristic — though not pathognomonic — feature. Ocular motor abnormalities, including oculomotor apraxia and nystagmus, result from cerebellar vermis and floccular hypoplasia affecting conjugate gaze pathways. Developmental delay and intellectual disability occur on a broad spectrum, from severe global developmental delay to near-normal cognitive function, and do not reliably predict underlying genotype. Ataxia, when present and assessable, is typically non-progressive, though motor skill acquisition is uniformly delayed. Brain MRI demonstrating the molar tooth sign — comprising a deepened interpeduncular fossa, elongated horizontally-oriented superior cerebellar peduncles, and cerebellar vermis hypoplasia — remains the diagnostic gold standard. [11]

Extracerebral Organ Involvement: The multi-organ phenotype of JSRD reflects the ubiquitous distribution of primary cilia. Retinal dystrophy, occurring in 30–40% of JS patients, presents variably as Leber congenital amaurosis, cone-rod dystrophy, or atypical retinitis pigmentosa, and frequently leads to significant visual impairment by the second or third decade. Early electroretinography and optical coherence tomography (OCT) are recommended for all genetically confirmed JS patients to detect subclinical photoreceptor degeneration amenable to low-vision intervention. Nephronophthisis — the leading genetic cause of end-stage renal disease in children — occurs in approximately 25% of JSRD patients, typically presenting as tubulointerstitial nephritis with progressive renal impairment that may not manifest until the second decade. Regular urinalysis, creatinine monitoring, and renal ultrasonography are essential components of longitudinal management. Congenital hepatic fibrosis occurs in a subset, most commonly associated with TMEM67 mutations, and may progress to portal hypertension requiring hepatological intervention. Polydactyly, coloboma, and — rarely — oral-facial-digital anomalies represent additional phenotypic extensions that further underscore the breadth of primary cilium involvement in mammalian development. [12]

Diagnostic Workup and Criteria: Diagnosis of JS is established on clinical and radiological grounds, anchored by MRI demonstration of the molar tooth sign. The 2022 consensus diagnostic criteria proposed by the International Joubert Syndrome Research Consortium recommend confirmation of MTS as the obligate criterion, supplemented by at least two of the following: hypotonia in infancy, oculomotor apraxia, nystagmus, developmental delay, episodic breathing abnormalities, or a positive family history with prior confirmed JS. Genetic confirmation, while not required for diagnosis, is strongly recommended for prognostication, family counseling, and research enrollment. Next-generation sequencing panels encompassing all known JBTS genes achieve molecular diagnoses in approximately 60–70% of clinically confirmed cases. Whole-exome sequencing (WES) as a first-tier diagnostic tool is increasingly recommended by rare disease diagnostic guidelines, particularly in cases with atypical or complex phenotypes. Whole-genome sequencing (WGS) adds value in detecting non-coding variants and structural rearrangements missed by WES. Trio analysis (proband and both parents) improves diagnostic yield by facilitating de novo variant detection and phasing of compound heterozygous variants. [13]

5. CURRENT CLINICAL MANAGEMENT

Current clinical management of Joubert syndrome is centred on multidisciplinary, symptom-directed care aimed at addressing multisystem involvement, preventing disease-related complications, and improving long-term functional outcomes and quality of life. [14]

Multidisciplinary Care Framework: Given the multi-organ nature of JSRD, clinical management requires coordinated multidisciplinary involvement

of pediatric neurology, genetics, ophthalmology, nephrology, hepatology, physiotherapy, occupational therapy, and speech and language therapy. No disease-modifying therapy currently exists; management is therefore supportive, symptom-directed, and organ-specific. The overarching goal is to maximize functional independence, prevent complications, and optimize quality of life across the lifespan. Annual or biannual surveillance protocols tailored to genotype where feasible — with more intensive monitoring for CEP290-related retinal disease or TMEM67-related hepatorenal disease — represent best clinical practice.

Respiratory Management: Neonatal and infantile respiratory abnormalities may necessitate monitoring in intensive care settings with pulse oximetry and, in severe cases, respiratory support. Caffeine citrate has been employed as a respiratory stimulant to address apneic episodes in analogy with its application in apnea of prematurity, exploiting adenosine receptor antagonism to stimulate brainstem respiratory centers. As children age, respiratory dysregulation typically improves spontaneously, though sleep-disordered breathing warrants polysomnographic assessment and may require non-invasive positive pressure ventilation.

Neurodevelopmental Rehabilitation: Early intervention with structured physiotherapy, speech therapy, and occupational therapy is the cornerstone of neurodevelopmental management. Physical therapy targets hypotonia, ataxia, and delayed gross motor acquisition through strengthening exercises, balance training, and hydrotherapy. Augmentative and alternative communication devices are often employed in children with severe verbal dyspraxia. Educational support services adapted to intellectual ability and attentional difficulties, guided by formal neuropsychological assessment, are essential components. Psychosocial support for families, including genetic counseling and peer support networks, is equally critical given the chronic, rare disease context.

Renal and Hepatic Surveillance and Intervention: Nephronophthisis management in JSRD currently lacks nephroprotective pharmacological interventions beyond blood pressure optimization and avoidance of nephrotoxic agents. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are employed when proteinuria or hypertension are identified, following general pediatric nephrology guidelines. Renal replacement therapy — dialysis and ultimately renal transplantation — may become necessary as renal disease progresses. Renal transplantation outcomes in JS are generally favorable, with the transplanted kidney not subject to disease recurrence. Hepatic fibrosis monitoring employs liver function tests, imaging, and Fibroscan elastography; cholangitis episodes may require antibiotic prophylaxis, and progressive portal hypertension may necessitate endoscopic or surgical intervention.

6. EMERGING THERAPEUTIC STRATEGIES

Despite significant advances in supportive care, no curative therapy currently exists for Joubert syndrome (JS), underscoring the urgent need for disease-modifying interventions that target its underlying genetic and molecular defects. Recent progress in molecular genetics, gene editing technologies, RNA-based therapeutics, and targeted pharmacological approaches has accelerated the development of innovative treatment strategies aimed at restoring ciliary function, correcting pathogenic variants, and preventing multisystem disease progression. [15-17]

Gene Replacement Therapy: Adeno-associated virus (AAV)-mediated gene replacement therapy represents one of the most actively pursued strategies in JS research, particularly for CEP290-related retinal degeneration. The retinal photoreceptor, given its post-mitotic nature, immune privilege, and accessibility, is an attractive target for viral gene delivery. EDIT-101, a subretinally delivered CRISPR-Cas9-based therapy targeting the intronic IVS26 CEP290 mutation (c.2991+1655A>G) — the most common CEP290 allele causing Leber congenital amaurosis type 10 (LCA10) — has progressed to Phase 1/2 clinical evaluation (NCT03872479), with interim data suggesting acceptable safety and signals of visual function improvement in treated patients. While this is specifically for LCA10 rather than JS with retinal dystrophy per se, the mechanistic overlap strongly informs JS therapeutic translation. For central nervous system delivery in JS, the blood-brain barrier presents formidable obstacles to systemic AAV administration, necessitating intrathecal, intracerebroventricular, or direct parenchymal

delivery routes. Preclinical studies in Ahi1 knockout mice, a well-characterized JS model exhibiting cerebellar hypoplasia and behavioral deficits, have explored neonatal AAV9-mediated gene reconstitution with partial rescue of cerebellar foliation, supporting in-principle feasibility. Critical challenges include the large coding sequences of several JBTS genes (e.g., CEP290 at approximately 7.4 kb, exceeding standard AAV packaging capacity), necessitating dual-vector trans-splicing or mini-gene approaches.

Antisense Oligonucleotide Therapy: Antisense oligonucleotides (ASOs) are chemically modified single-stranded nucleic acids capable of modulating gene expression through RNase H-mediated RNA degradation, exon skipping, or splice modulation. The success of ASO therapies in spinal muscular atrophy (nusinersen) and Duchenne muscular dystrophy (eteplirsen) has catalyzed interest in applying this platform to ciliopathies. A landmark study demonstrated that the deep-intronic CEP290 c.2991+1655A>G mutation, which creates a cryptic splice donor and inserts a premature stop codon, can be corrected by intravitreally injected ASOs (sepofarsen/QR-110) that block the aberrant splice site and restore full-length CEP290 protein. Phase 2/3 clinical trials of sepofarsen are ongoing, and positive outcomes would validate the ASO platform for ciliopathy treatment beyond retinal disease.
ASO delivery to the CNS is achievable through intrathecal administration, exploiting cerebrospinal fluid distribution. For JS-specific CNS targets, proof-of-concept studies targeting AHI1 and RPGRIP1L splice site mutations with ASOs have been initiated in cell-based models, with plans for murine validation. The pharmacokinetic and safety profile of intrathecal ASOs is reasonably well characterized from experience in neurological diseases, supporting the translational pathway. However, the mutation-specificity inherent in ASO design means each therapeutic candidate addresses only a narrow variant subset, requiring population-level frequency analyses to prioritize development programs.

Sonic Hedgehog Pathway Modulation: Given the established role of primary cilia in SHH signal transduction and the disruption of this pathway in JS, pharmacological modulation of SHH signaling represents a rational strategy. Smoothened agonists (SAG, purmorphamine) activate the SHH pathway downstream of Patched-1, bypassing the requirement for intact ciliary SHH reception. In Rpgrip1l and Cc2d2a mouse models, neonatal administration of SAG during critical windows of cerebellar development partially restored granule cell precursor proliferation and cerebellar foliation. Importantly, the cerebellum undergoes its primary postnatal growth phase in rodents (analogous to third trimester in humans), suggesting a potential therapeutic window between prenatal diagnosis and birth in JS. However, the oncogenic potential of SHH pathway agonism — given that aberrant SHH activation drives medulloblastoma and basal cell carcinoma — demands stringent safety evaluation of any SHH-modulating therapeutic strategy, particularly for long-term neonatal administration. The development of pathway modulators with tissue-restricted activity or transient exposure protocols that achieve developmental correction without sustained oncogenic risk represents an active area of pharmaceutical research.

mTOR Pathway Inhibitors: The mTOR pathway's role in JS-related nephronophthisis and possibly in neuronal survival has motivated evaluation of rapamycin (sirolimus) and rapalogs (everolimus, temsirolimus) in preclinical JS models. In murine models of nephronophthisis related to NPHP1 and NPHP3 mutations, rapamycin significantly reduced cyst formation and preserved renal function, establishing mechanistic proof-of-concept. Clinical translation, however, has been constrained by the potent immunosuppressive effects of rapamycin, its metabolic complications (dyslipidemia, impaired glucose tolerance), and concerns regarding inhibition of tubular regeneration. Next-generation mTORC1-selective inhibitors and catalytic mTOR kinase inhibitors are under preclinical evaluation for improved therapeutic windows. The anti-fibrotic properties of mTOR inhibition may additionally benefit JSRD-associated hepatic fibrosis, providing a potential dual-organ rationale for targeted use.

CRISPR-Cas9 Genome Editing: CRISPR-Cas9-based genome editing has demonstrated extraordinary precision in correcting pathogenic variants in disease-relevant cell types. For JS, patient-derived induced pluripotent stem cells (iPSCs) provide a renewable substrate for both mechanistic studies and therapeutic development. Correction of CEP290 and TMEM67 pathogenic variants in iPSC-derived retinal organoids and

kidney organoids has been achieved with high efficiency, with corrected organoids demonstrating restored ciliogenesis, normal transition zone architecture, and appropriate organ-specific differentiation. The path from organoid rescue to in vivo therapeutic application remains long, encompassing delivery challenges, off-target editing safety, and immunogenicity of Cas9 in humans. Base editing and prime editing — successor technologies offering single-nucleotide precision without double-strand breaks — offer improved safety profiles and are actively being explored for JS-relevant mutations.

Small Molecule Approaches: Proteostasis and Ciliary Biology: For JS variants resulting in protein misfolding and premature degradation rather than complete loss of function, pharmacological chaperones and proteostasis regulators represent attractive therapeutic approaches. Specific missense variants in TMEM67, CC2D2A, and RPGRIP1L produce proteins that are structurally near-native but prematurely ubiquitinated and degraded; in such cases, small molecules stabilizing the mutant protein could restore partial function. HSP90 inhibitors and proteasome modulators have shown in vitro activity in stabilizing ciliary transition zone proteins bearing destabilizing missense mutations. Aminoglycoside antibiotics and PTC124 (ataluren) enable read-through of premature termination codons (PTCs) and have been explored for nonsense variants in JBTS genes, with modest effects in cell models. Ataluren's established clinical use in Duchenne muscular dystrophy provides regulatory precedent and clinical safety data supporting its evaluation in JS nonsense variant cohorts. Cilia-enhancing small molecules represent another pharmacological frontier. Compounds that promote ciliogenesis — including HDAC6 inhibitors (tubastatin A), which deacetylate alpha-tubulin and modulate ciliary dynamics — have demonstrated activity in enhancing ciliary length and function in patient-derived cells harboring hypomorphic JBTS mutations. While translational distance remains substantial, these proof-of-concept findings identify tubulin acetylation homeostasis as a potentially druggable node in JS pharmacology.

CONCLUSION:

Joubert syndrome is a complex multisystem ciliopathy in which advances in molecular genetics, ciliary biology, and precision diagnostics have significantly improved the understanding of disease mechanisms and clinical management. Although treatment remains predominantly supportive, emerging gene-based therapies, RNA therapeutics, genome editing, and targeted pharmacological approaches offer promising prospects for disease-modifying interventions and personalized medicine in the future.

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