Prenatal Diagnosis

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The Conundrum of Mechanics Versus Genetics in Congenital Hydrocephalus and Its Implications for Fetal Therapy Approaches: A Scoping Review

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ABSTRACT

Recent advances in gene therapy, particularly for single-gene disorders (SGDs), have led to significant progress in developing innovative precision medicine approaches that hold promise for treating conditions such as primary hydrocephalus (CH), which is characterized by increased cerebrospinal fluid (CSF) volumes and cerebral ventricular dilation as a result of impaired brain development, often due to genetic causes. CH is a significant contributor to childhood morbidity and mortality and a driver of healthcare costs. In many cases, prenatal ultrasound can readily identify ventriculomegaly as early as 14–20 weeks of gestation, with severe cases showing poor neurodevelopmental outcomes. Postnatal surgical approaches, such as ventriculoperitoneal shunts, do not address the underlying genetic causes, have high complication rates, and result in a marginal improvement of neurocognitive deficits. Prenatal somatic cell gene therapy (PSCGT) promises a novel approach to conditions such as CH by targeting genetic mutations in utero, potentially improving long-term outcomes. To better understand the pathophysiology, genetic basis, and molecular pathomechanisms of CH, we conducted a scoping review of the literature that identified over 160 published genes linked to CH. Mutations in *L1CAM*, *TRIM71*, *MPDZ*, and *CCDC88C* play a critical role in neural stem cell development, subventricular zone architecture, and the maintenance of the neural stem cell niche, driving the development of CH. Early prenatal interventions targeting these genes could curb the development of the expected CH phenotype, improve neurodevelopmental outcomes, and possibly limit the need for surgical approaches. However, further research is needed to establish robust genotype-phenotype correlations and develop safe and effective PSCGT strategies for CH.

Summary

- **What's already known about this topic?**
  - Congenital Hydrocephalus (CH) is a significant contributor to childhood morbidity and mortality and a driver of healthcare costs.
  - Prenatal ultrasound can readily identify ventriculomegaly as early as 14–20 weeks of gestation, with severe cases showing poor neurodevelopmental outcomes.
  - Pre- and postnatal surgical approaches do not address the underlying genetic causes of CH, have high complication rates, and result in a marginal improvement of neurocognitive deficits.
  - The knowledge gap surrounding the genetic basis of CH may be favoring (fetal/postnatal) surgical procedures instead of molecular approaches that could tackle the genetic cause of CH.
- **What does this study add?**
  - This scoping review aims to better understand the genetic basis and molecular pathomechanisms of CH along with genes and mutations that drive its development.
  - It also aims to evaluate whether early prenatal interventions targeting these genes could curb the development of the expected CH phenotype, improve neurodevelopmental outcomes, and possibly prevent the need for surgical approaches.

1 | Introduction

Recent gene therapy research, particularly for single-gene disorders (SGDs), has resulted in countless investigational drug applications [1–3] (Figure 1). In particular, advances in antisense oligonucleotides (ASO) [5], gene replacement therapies [6, 7], and gene editing technologies, like Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 [8], coupled with innovative delivery modalities [9–12], promise to revolutionize the treatment of SGDs [13, 14], cancer, and immunological diseases. SGDs, including those that affect the central nervous system (CNS), such as Spinal Muscular Atrophy [15], Angelman Syndrome [4], and certain Lysosomal Disorders [16, 17], with or without clinical signs before birth offer opportunities for early diagnosis (carrier screening/fetal genetic/ultrasound) and possibly prenatal somatic cell gene therapy (PSCGT) [2]. For many, the limited understanding of the genetic background may lead to the selection of cases for fetal/postnatal surgical therapies. However, "*time is neurons,*" and initiating a molecular treatment in utero during the presymptomatic phase may yield superior long-term outcomes [18–20].

Hydrocephalus is a heterogeneous condition manifested as increased cerebrospinal fluid (CSF) volume and dilatation of the cerebral ventricles. It can be (a) primary hydrocephalus due to idiopathic or genetic causes (CH) leading to an impaired brain development and (b) secondary hydrocephalus as a result of a brain insult (bleeding, infection, trauma, or tumors). CH is further classified into obstructive and non-obstructive,

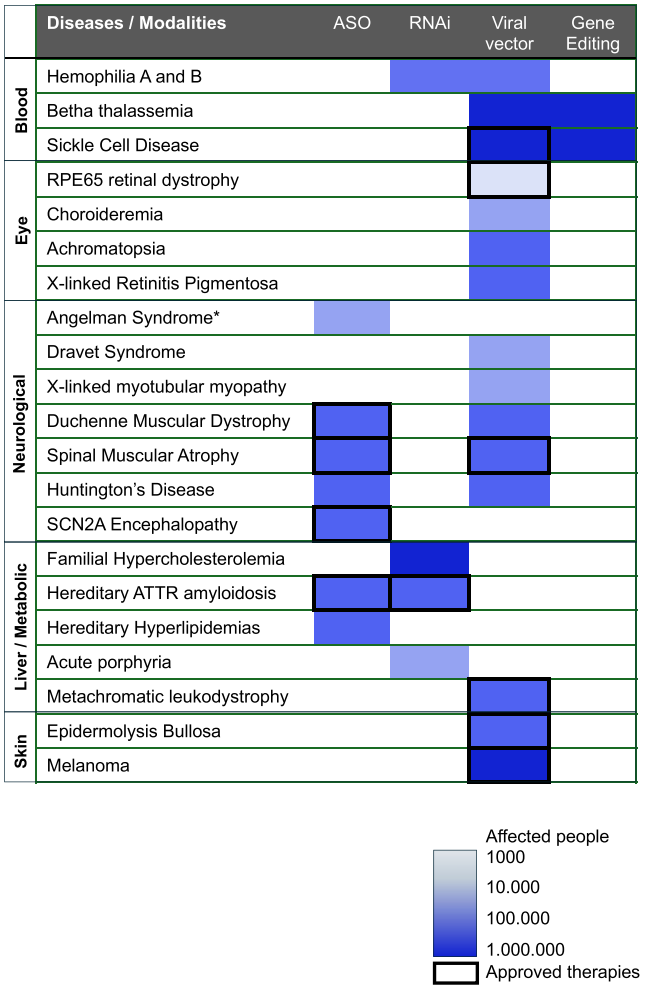

FIGURE 1 | The gene therapy market expanding across therapeutic modalities and areas as of April 2024. *Source:* Fda.gov/McKinsey & Co. [1]/*Clarke et al., *Mol. Ther.*, 2024 [4]. ASO, antisense oligonucleotides; RNAi, ribonucleic acid interference.

depending on whether there are any obstacles to the flow of CSF. While CH is typically non-obstructive [21], a range of complex factors, such as brain compliance, patient age, and brain development, determine whether it is accompanied by elevated intracranial pressure.

CH occurs in 1/1000 live births, is a significant contributor to childhood morbidity and mortality [22], and generates a significant financial burden on healthcare systems [23]. Ventriculomegaly (VM), the enlargement of the ventricular system, is present in up to 2/1000 pregnancies and may be identified prenatally during 14–20 weeks of gestation [24, 25]. While patients with mild (10–12 mm) or moderate (13–15 mm) VM usually have normal neurodevelopment, patients with severe (>15 mm) VM exhibit disrupted neurodevelopment and limited survival [26]. Some 16% of the mild VM cases show in-utero size progression, which is associated with adverse outcomes in >44% of the cases [27, 28], warranting further testing for underlying genetic causes [29].

Although percutaneous fetal endoscopic third ventriculostomy has been promising and has shown successful outcomes in

treating human fetuses with isolated progressive or severe bilateral VM at a median gestational age of 28.7 weeks [30], currently the standard of care for hydrocephalus is the postnatal CSF diversion by surgical placement of a ventriculoperitoneal shunt (VPS) [31]. For CH, while these approaches address the symptoms, they do not treat the underlying genetic pathology [32–34], have high complication rates [35, 36], require ongoing monitoring and revision [37, 38], and do not significantly improve the neurocognitive outcomes [28]. As such, our limited understanding of the molecular underpinnings of CH delays appropriate diagnostic and treatment strategies [39]. Thus, an exhaustive analysis of the pathophysiology and a reappraisal of current diagnostic and therapeutic paradigms is warranted.

2 | Objectives

To better understand the pathophysiology, genetic basis, and molecular mechanisms of CH, we conducted a scoping review of the literature between 1935 and 2023. We focused on identifying potential gene targets amenable to PSCGT to (1) potentially address the molecular causes of CH in utero, before the developmental window closes [40] and (2) achieve a phenotypic rescue by taking advantage of the developmental properties of the fetus [2], namely starting therapy early and in a potentially more efficient way, inducing tolerance to therapeutic transgene-encoded proteins [16] and benefitting from a more permeable blood-brain barrier [41].

3 | Methods

The methodology adhered to previously described frameworks [42, 43]. The initial search in 2022 queried MEDLINE/PubMed and Google.com without restrictions on date, language, subject, or type. Search terms included “hydrocephalus,” “primary,” “congenital,” and “genetic” and expanded to include specific genes and related terms to capture additional studies not initially identified. We used a snowball technique to review the referenced literature. A second search in late 2023 identified new publications. We excluded articles not in English, French, German, or Spanish and those focusing on secondary hydrocephalus or unrelated gene functions, yet we reviewed their citations. We screened titles and abstracts procuring full texts of relevant citations. Data extraction was performed using a customized form (Microsoft Excel for Mac, Version 16.73), with consistency verified in interdisciplinary team meetings ($\kappa > 0.80$). Duplicate entries were manually removed. Data analysis was conducted in GraphPad Prism (GraphPad Software LLC, Version 9.5.1/528) or Circlize (Version 0.4.15) [44], employing descriptive statistics for continuous data and frequencies and percentages for nominal data. Comprehensive reviews of identified genes were conducted in omim.org, proteinaltlas.org, and ncbi.nlm.nih.gov, examining gene location, inheritance patterns, protein expression and localization, RNA expression in tissues, protein functions, molecular functions, biological processes, disease associations, and genotype-phenotype correlation reliability.

4 | Results

4.1 | The Genetic Basis of Primary Congenital Hydrocephalus

Our search identified *38,231* publications on hydrocephalus and yielded *3309* citations for CH, of which *2749* were removed for a lack of relevance. After deduplication and a secondary relevance screening, we included *480* articles that met the eligibility criteria. Four articles that could not be procured were excluded. After data characterization of the full-text articles, *21.8% (104/476)* were excluded as irrelevant to the review question (Figure 2). In the remaining *372 articles,* we identified *167 genes* in relation to CH, showed their citation frequency across the published literature, and highlighted several key genes such as *L1CAM*, *TRIM71*, *CCDC28B*, and *MPDZ* (Figure 3). We categorized these genes based on their molecular functions, such as ciliopathies, neural stem cell/niche maintenance, and other related functions to better understand the different pathways and mechanisms through which they contribute to the development of CH. We also evaluated their dispersion across different chromosomes to potentially identify chromosomal hotspots and patterns relevant in the context of CH. We found that the causative mutations were predominantly loss-of-function mutations (LOF) [45, 46] that disrupt embryonic and fetal brain development, including neural stem cell (NSC) development and the NSC niche architecture [40, 46–48], which occur in early fetal development The severity and presentation of CH varies depending on the specific mutation and its location within the gene. Missense mutations in *L1CAM*, alter the function of cell-cell adhesion proteins and signaling required for normal brain development, whereas frameshift mutations in *TRIM71* result in nonfunctional proteins essential for the maintenance of stemness and the development of the NSC niche [49]. The review captured critical aspects of fetal development and the progression related to CH: (1) the main neurogenic and ventriculogenic events (Figure 4A), detailing their intensities across different fetal developmental periods: neurochemical maturation, myelinization, synaptogenesis, molecular specification, migration, proliferation, pinwheel formation, and ependymal expansion,

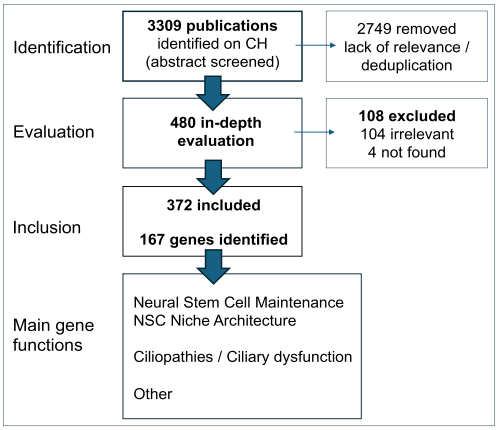

FIGURE 2 | Flowchart delineating the scoping review of the literature aimed at identifying genes, mutations, and genetic mechanisms contributing to congenital hydrocephalus (CH) in humans.

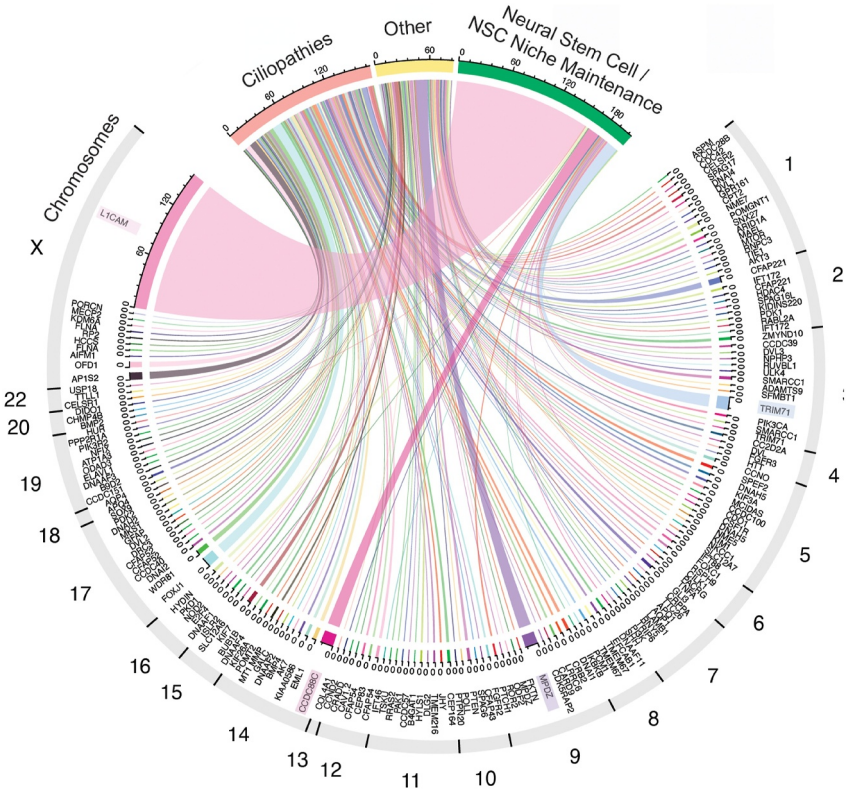

FIGURE 3 | Genes cited in relation to CH. The plot shows the citation frequency of individual genes in publications, their molecular function, and their dispersion on chromosomes [44].

spanning from embryonic stage through early and late fetal development, to birth, and into childhood. This highlights the intricate developmental processes in the brain and ventricles, crucial for understanding the onset and progression of CH. (2) The gene expression levels of *L1CAM* and *TRIM71* show variable expression during embryonic, fetal, and neonatal stages (Figure 4B), revealing the broader impact of dysregulated genes on the precise timing of key neurogenic and ventriculogenic events. (3) Mapping gene activity against the onset of pathology as well as diagnostic and therapeutic windows pinpoints critical periods for intervention, thereby guiding diagnostic and therapeutic strategies for precision medicine approaches that cater to the specific genetic makeup of individual patients (Figure 4C).

Although up to 40% of CH cases are believed to have a genetic basis [48, 51, 52] mutations in the more common genes, such as *L1CAM, MPDZ, CCDC88C, AP1S2, FLNA, PTCH1, SHH,* and *CRB2*, explain only a small percentage of CH cases [53, 54]. Protein-altering de novo mutations in *TRIM71, SMARCC1, PTEN*, and *PIK3CA* account for a significant fraction of the sporadic cases [48]. Almost half of these mutations are inherited in an autosomal recessive manner (56%) and, to a lesser extent, in an autosomal dominant and X-linked recessive manner. Recessive mutations are more structurally perturbing than dominant mutations and are overwhelmingly associated with LOF enriched in 'mutation intolerant' genes [55, 56] stratified by the probability of loss-of-function intolerance (pLI $\geq$0.99) [21]. Truncating mutations are more likely to lead to severe phenotypes (52%) than missense mutations (8%) [57]. Murine knockouts of these genes produce neural tube defects, including exencephaly [58–61] and fatal CH [59, 62].

Some specific gene mutations are linked to distinct clinical and molecular phenotypes, but genotype-phenotype correlations in CH are not yet fully understood. During embryonic and fetal development, mutations in the aforementioned genes result in abnormal proteins, disrupting the ventricular and subventricular zones (VZ) with loss of NSCs or ependyma and disturbing the NSC niche. Based on the specific mutation, this damage occurs in specific regions of the ventricular system and at specific stages of prenatal brain development. Disruption of the VZ of the Sylvian aqueduct leads to aqueductal stenosis and CH, while disruption of the VZ of the telencephalon impairs neurogenesis [34]. Once the appropriate developmental/therapeutic window has closed [63], it is likely that lost functions cannot be restored, emphasizing the importance of timing of diagnosis and early therapeutic intervention.

4.2 | A Novel Approach to Congenital Hydrocephalus

In the neurogenic niches of the mammalian brain, NSCs and ependymal cells (ECs) originate from radial glia, primarily during embryonic development, following a caudo-rostral pattern. However, they remain undifferentiated until the second week after birth, when they develop distinct features, such as motile multi-cilia [64]. In the ventricular wall, the adult NSC niche has a unique pinwheel structure that positions ECs around each NSC [65], allowing each NSC to retain direct contact with the CSF through its apical primary cilium [66]. The correct assembly and integrity of the pinwheel configuration (*L1CAM*) and the proper

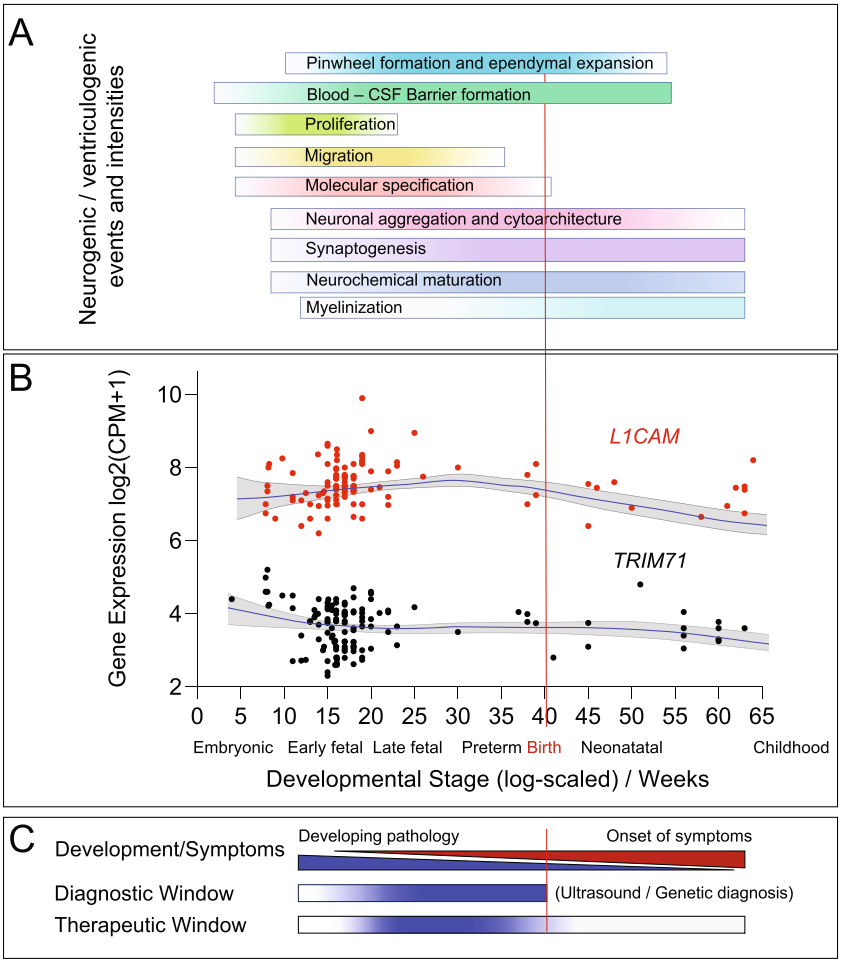

FIGURE 4 | Schematic representation of the (A) main neurogenic and ventriculogenic events and their intensities at different fetal developmental periods (adapted with permission from Kostović, Sedmak, and Judaš, *Neuroimage*, 2019 [50]), (B) *L1CAM* and *TRIM71* gene expression at different developmental stages, and (C) diagnostic and therapeutic windows based on the gene activity and onset of pathology.

regulation of the neurogenesis and differentiation (*TRIM71*) are essential to allow NSCs to proliferate and generate new neurons [67]. Cell adhesion molecules (CAMs) are pivotal in guiding this process by mediating interactions between NSC, EC, and their surrounding matrix. The classic dogma suggests that CH is caused by disrupted ependymogenesis/ciliogenesis, disrupting cilia-driven CSF flow. Although our review found several gene mutations linked to ciliogenesis and ciliary dysfunction (e.g., *EML1*, *AP1S2*, *WDR81*) [46], the development of CH often precedes the maturation of multiciliated EC [40, 68], thus ciliopathies seem unlikely to be the primary cause of CH [69, 70]. Functional genomic analyses rather suggest that risk genes converge in neurogenesis-related cell types [46, 48, 71, 72], indicating that some forms of CH arise from abnormal neural tissue rather than ciliary dysfunction or mechanical issues of the ventricular CSF compartment [46, 72]. Maintaining the structure of the VZ and the proliferative NSCs depends on junctional molecules like *L1CAM* and *MPDZ*. Mutations in these genes, along with mutations in *TRIM71* and *CCDC88C*, disrupt the architectural integrity of the periventricular region. Gene mutations affecting cell junction protein expression (*L1CAM*) and NSC fate (*TRIM71*) result in impaired neurogenesis involving embryonic progenitor cells and their progenies [21, 46, 63, 72], leading to reduced cortical mass, the remodeling of the germinal neuroepithelium, and disrupting ECs, essential for the formation and maintenance of the NSC niche. This leads to a mechanically vulnerable ventricular wall [73], which cannot match the low positive pressure of the CSF in the ventricles [74], deforming the ventricle and disrupting the laminar CSF flow [75].

4.3 | Putative Target Genes for PSCGT

The etiology of CH is complex, and although specific genetic mutations likely play a role in its pathogenesis (Figure 3), verifying a causative relationship is difficult. Nonetheless, the prenatal detection of genetic mutations and clear genotype-phenotype correlations are vital to develop PSCGT. Many genes play a pleiotropic role in the intricate orchestration of fetal brain development, necessitating tight temporal and spatial regulation of cellular connections to ensure proper brain formation and function:

L1CAM (Xq28/XLR): The L1 protein, a CAM, interacts with proteins containing immunoglobulin domains or acts as a ligand for specific tyrosine kinase receptors, playing a crucial role during neural development [76]. It is located on the X

chromosome (Xq28) and is often mutated in CH and X-linked hydrocephalus (HSAS; OMIM #307000) [77]. This protein is highly conserved across species and is essential for neuron adhesion, migration, growth cone morphology [78–82], and synaptic plasticity [83, 84].

Over 200 novel missense mutations have been reported across the entire gene, with a high intolerance to such variations [85, 86]. Most are private mutations unique to a single family [53], and the interfamilial allelic heterogeneity is a well-known feature of the *L1CAM* spectrum diseases [18, 87, 88]. Severe pathogenic mutations in *L1CAM* cause L1 syndrome, characterized by corpus callosum agenesis, intellectual disability, adducted thumbs, spasticity, and hydrocephalus [89–92]. Given that ethanol disrupts L1-mediated adhesion [93], fetal alcohol spectrum disorders could also be implicated in the mutagenesis of this gene [94]. Conversely, the overexpression of L1 is linked to the progression of aggressive gastrointestinal and gynecological [95, 96], breast [97, 98], and other [99–106] cancers, where it contributes to increased cell proliferation, motility, and chemoresistance [107], indicating a poor prognosis.

TRIM71 (Tripartite motif containing 71) (19q13.33/AD) is a gene that encodes for an E3 ubiquitin ligase [108, 109] and mRNA-binding repressor protein [49, 110], playing a vital role in the developing brain by negatively regulating protein expression. It is crucial for controlling stem cell fate [111], fostering proliferation, and inhibiting differentiation [112], thus maintaining pluripotency. *TRIM71* orchestrates the embryonic stem cell proteome as cells transition from pluripotent to differentiated states [109, 113], governing embryonic neurogenesis, neuronal differentiation, and neural tube closure [114–117]. Differentiating stem cells appear to go through phases of simultaneous expression of stemness and differentiation genes [118] with dynamic and temporally controlled *TRIM71* expression levels. These are particularly high in early embryonic undifferentiated stem cells, decreasing as cells differentiate and embryogenesis progresses [110, 119, 120]. This gene is highly intolerant to missense (LOF) mutations [21, 35], which disrupt brain and NSC development, with most children having a confirmed diagnosis of CH before or at birth [121]. This highlights the critical nature of its expression window in the prenatal period and the unique opportunity for PSCGT. *TRIM71* also plays a role in oncogenesis [122, 123] and is involved in miRNA-mediated regulation of cancer genes and pathways. In this context, it suppresses tumorigenesis and invasion [124] but, conversely, is highly expressed in tumors with a poor prognosis [112, 122, 125–128].

MPDZ (a multi-PDZ domain) (9p23/AR) is crucial during neurulation for the apical constriction of neuroepithelial cells and subsequent neural plate bending and proper tissue remodeling during the early stages of neurodevelopment [129]. Mutations or truncated forms of *MPDZ* affect the integrity of the ventricular lining, resulting in severe CH with multifocal rosettes with immature cell accumulation near the ependymal lining, possibly contributing to congenital aqueduct stenosis [130]. LOF mutations in *MPDZ* also increase the permeability of the choroid plexus [131] with CSF proteomic analysis, indicating a 53-fold rise in protein levels, reflecting enhanced transcytosis in MPDZ knockout mice compared to normal mice [131]. Additionally, *MPDZ* is a tumor suppressor that limits cell proliferation, migration, and invasion, and its low expression is a marker for poor prognosis in lung and other cancers [132]. It also suppresses tumor angiogenesis by preventing the formation of vessel tips and branching [133].

CCDC88C (14q32.11–q32.12/AR) codes for Disheveled-associating Protein with a high frequency of leucines (DAPLE), a ubiquitously expressed protein in the fetal brain. DAPLE is a component of cell junctions in epithelial cells, serving as a cellular "compass" for establishing and maintaining contact-triggered planar polarity; it also serves as a platform for signal integration and gradient sensing for tyrosine-based signals within the planar cell polarity pathway [134]. Bi-allelic mutations in the *CCDC88C* gene cause autosomal recessive non-syndromic CH (OMIM #236600) [135]. The mutation in affected patients results in the loss of functional protein in the *Wnt* signaling pathway [136], thereby establishing *CCDC88C* as one of the recessive causes of severe prenatal-onset CH [137, 138].

Notably, CH exhibits a partial overlap in the transcriptional profile of genetic risk factors with neurodevelopmental disorders, including those on the autism spectrum, as well as various other disorders related to brain development [48].

5 | Discussion

5.1 | A Fetal Approach to Treating Congenital Hydrocephalus

Our review suggests that genetic causes leading to impaired neurogenesis and a dysfunctional NSC niche, rather than ciliary dysfunction and active CSF accumulation, are the primary causes of at least some forms of CH [46, 72]. These mutations affect brain development, decrease cortical cell mass, and disrupt the NSC niche architecture and dynamics. Still, pathogenic variants explain only a third of CH cases, and although certain CH gene variants are strongly linked to specific phenotypes, clear gene-phenotype correlations have been delineated only for a handful of genes. For example, fetuses with *TRIM71* pathogenic variants are at a higher risk for isolated CH. In contrast, variants in *L1CAM* are linked to CH of varying severity, often accompanied by intellectual disability, leg spasticity, and adducted thumbs.

This new perspective on the pathogenesis of CH underscores the need for detailed clinical and genetic studies to establish accurate pathogenesis and genotype-phenotype correlations that inform personalized management and therapy. It also highlights the need for prenatal precision approaches targeting affected genes to rescue neurologic function and paves the way for gene-targeted approaches for fetuses diagnosed prenatally. Since *L1CAM* and *TRIM71* are most active during fetal development, early PSCGT has the potential to curb the phenotype and disease progression and significantly improve outcomes [2, 139]. As such ideal candidates for PSCGT are typically fetuses with monogenic diseases that are lethal or cause severe morbidity that are identifiable through prenatal screening and have a clear genotype/phenotype correlation. For PSCGT to be considered,

the fetus should not have abnormalities not correctable by the proposed therapy, which should present a favorable risk-benefit ratio by offering a significant phenotypical rescue or drastically improved function at birth (as opposed to marginal correction) with minimal to no off-target effects such as integration into oncogenic hotspots or overexpression favoring oncogenic events. An adequate (animal/human) model that reproduces the human disease should be available, thereby allowing the evaluation of safety and efficacy [2, 139, 140].

Several techniques could be used for in vivo gene modification (Table 1). These include (a) gene replacement (delivering a functional copy of the mutated gene to restore function), (b) gene editing (using CRISPR/Cas9 to achieve a precise and permanent correction at the DNA level) (c) antisense oligonucleotide therapy (ASO) (short RNA molecules bind to the mutated mRNA transcript offering a precise but temporary modulation of gene expression without altering the DNA or integrating into the genome) [4].

Although for some pathogenic variants in genes with clearer genotype-phenotype correlations (*L1CAM*, *TRIM71*), PSCGT could be a promising approach, some of these genes are implicated in multiple functions and signaling pathways and tumorigenesis [95, 98, 106, 107, 109, 124, 127]. This highlights the importance of matching the necessary level of correction to avoid potential off-target effects in the developing fetus and/or the mother (activation of oncogenes or the disruption of normal developmental pathways). Determining the adequate expression level is a complex and nuanced process that requires careful consideration of the specific variant, the underlying biology of the disease, and a thorough understanding of the potential mechanisms by which protein expression levels could be modulated. It also requires a clear understanding of the genotype-phenotype correlation for the specific mutation, the severity of the expected phenotype, the specific cells or tissues affected, and the potential risks and benefits of modulating protein expression levels. Additionally, gene therapies carry the risk of integrating into the germline [141], immune reactions to the viral vectors [142–144], and other off-target effects.

PSCGT aims to correct or manage genetic anomalies at the molecular level, potentially mitigating the pathological effects of CH on brain structure and function and potentially restoring gene function to normal levels in utero. Furthermore, as some genetic targets of CH gene therapy may overlap with genes implicated in other neurologic disorders (NDs), such as autism spectrum disorder (ASD), intellectual disability (ID), global development delay (GDD), and epilepsy [145], successful PSCGT for CH might directly or indirectly affect the risk or symptomatology of other NDs by (a) *improving neurological function* by preventing or mitigating the structural and functional brain changes associated with those conditions, potentially reducing the risk or severity of ASD in individuals predisposed to hydrocephalus. (b) Reducing the neurological impairment that might exacerbate or contribute to the complexity of ASD symptoms, potentially altering the clinical presentation or the quality of life for ASD patients. (c) *Impact on brain development*: correcting these mutations early may promote more canonic brain development, potentially improving the function of brain areas implicated in ND. (d) *Inflammatory and immune responses*: CH and ASD have been associated with abnormal inflammatory and immune responses, which could be influenced/modulated by gene therapy, potentially affecting ASD development or severity.

6 | Conclusions

PSCGT involves correcting genetic defects in utero, possibly curbing the development of the expected phenotype or preventing disease progression in utero. It has the potential to treat conditions like CH and possibly reduce the need for (fetal/postnatal) surgical interventions. Nevertheless, CH is a complex condition that can occur in isolation or in conjunction with other genetic anomalies. Our review found that over 160 genes have been described to be mutated in syndromic and non-syndromic CH, driving diverse molecular functions and numerous pathways that cause NSC dysfunction and remodeling of the NSC niche [40, 46]. Although certain pathogenic variants of *L1CAM* and *TRIM71* show promising potential for PSCGT, their pleiotropic role might challenge prenatal correction without risking off-target effects (oncogene activation or disruption of developmental pathways). Therefore, further research and a nuanced approach is required for correctly modulating protein expression levels with a comprehensive understanding of genotype-phenotype correlations, disease severity, tissue specificity, and potential risks and benefits.

TABLE 1 | The pros and cons of some putative therapeutic options available to correct mutations in monogenic diseases. ASO, antisense oligonucleotides.

ASO	Gene replacement	Gene editing
Pros:	Pros:	Pros:
• Transitory alteration of gene expression	• Long term correction	• Permanent correction
• Target specificity and flexibility	• Direct solution	• Precision
• Easy delivery (CNS, muscle, amniotic fluid)	• Reduced risk of off-target effects	• Versatility
• Rapid development		
Cons:	Cons:	Cons:
• Temporary effects	• Efficient delivery in some tissues	• Off-target effects
• Off-target effects	• Integration	• Efficient delivery in some tissues
• Immune response	• Immune response	• Ethical and safety concerns

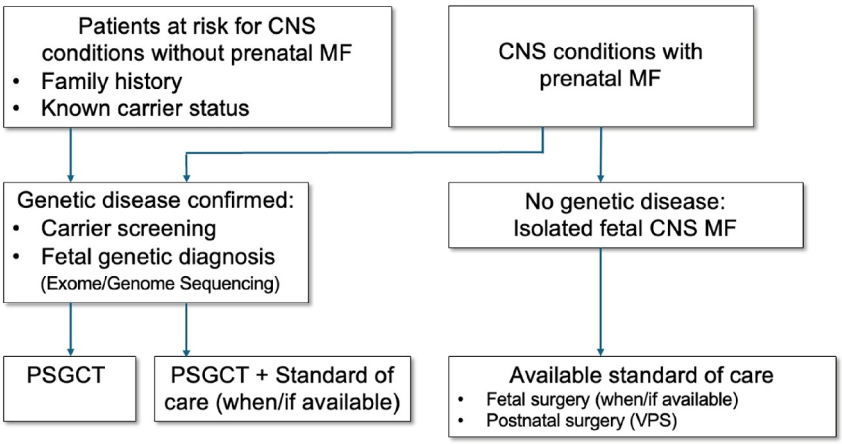

FIGURE 5 | Outlines of a diagnostic and therapeutic cascade should PSGCT become available for in utero SGDs. CNS, central nervous system; MF, malformations; PSCGT, prenatal somatic cell gene therapy; VPS, ventriculo-peritoneal shunt.

However, with known family history/carrier status or when VM is detected prenatally, genetic causes should be investigated whenever a familial recurrence or progressive/unilateral prenatal ultrasound findings occur (Figure 5). As prognosis depends on the underlying cause, genetic screening for *L1CAM* mutations should be carried out for couples experiencing recurrent fetal VM affecting the male gender [146] and/or a history of alcoholism (before/during pregnancy) [147], and screening for *TRIM71* and *CCDC88C* in cases with severe, isolated CH, especially if aqueductal stenosis with or without a medial diverticulum is present [148].

While some SGDs present with anatomical malformations (MF) at diagnosis [16, 46, 72] (ventriculomegaly, hydrops, etc.), many SGDs that may be amenable to PSCGT do not have MFs at the time of in utero diagnosis. These conditions are often diagnosed in families with a known carrier status and although transcriptomic changes [149] or subcellular pathology [16] may occur before the initiation of in utero treatment (typically 20–25 GW), many might not develop anatomic changes [4, 15, 149] that can be diagnosed by ultrasound or present in the 2nd or 3rd trimester, which might compromise actions in the windows of opportunity for gene therapy. In other cases, early VM might resolve during the pregnancy. As such, with a given family history or clinical suspicion, carrier screening and early fetal genetic diagnosis (exome/genome sequencing) allow the selection of CH where PSCGT could rescue the expected phenotype. This can expedite a definitive diagnosis, generate a pool of critical data and raise the threshold for surgical interventions. It also allows for clearer classification schemes to prognosticate neuro-cognitive outcomes and stratify patients more accurately into specific treatment groups, aiding focused problem-oriented counseling. However, in SGDs, where the phenotype is not evident before treatment, we stress the paramount importance of a clear genotype-phenotype correlation before PSCGT.

7 | Challenges and Limitations

This scoping review used rigorous and transparent methods throughout the process. Although our search algorithm included different search terms previously used to describe CH because other terms may also exist, this review may not have identified all articles published despite attempts to be as comprehensive as possible. Searching other bibliographic databases may have yielded additional published articles and articles published in languages not listed in this review.

The broader focus of a scoping review renders it less comprehensive than a systematic review. The lack of critical appraisal of the included articles may have limited our ability to identify gaps in the literature. As such, recommendations for policy or practice should be interpreted as an emphasis on a comprehensive approach rather than a particular standard of evidence. The articles in our review varied in terms of terminology, purpose, methodological rigor, and level of reporting detail, underscoring the somewhat limited knowledge of CH and appropriate pre and postnatal management. Since prenatal molecular therapies are relatively new with limited guidelines, the scope is to steer the clinical and scientific community toward the current optimal assessment and approach.

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Ethics Statement

This scoping review does not require ethical approval. Its data and results are based on peer-reviewed publications.

Conflicts of Interest

A.H., B.B., L.N.D., N.G. declare no conflicts of interest. T.C.M.—Acrigen Consultant, BioMarin Pharmaceutical Inc. Grant/Contract, Novartis Grant/Contract. S.J.S. received research funding from BioMarin Pharmaceutical Inc.

Data Availability Statement

The data that support the findings of this study are located in controlled access data storage at the University of California, San Francisco. Access is available upon written request to the authors.

Permissions

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