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Advances in Prenatal Diagnosis and Genetic Research of Ciliopathies

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Abstract: ***Primary cilium is a kind of organelle that widely exists on the surface of various cells. It is small but complex in structure and has powerful effects. Cilia defects often lead to a series of disorders that are collectively termed "ciliopathies," involving multiple systems. In recent years, it has been found that defects in ciliary morphology and function can lead to genetic diseases in newborns. Since cilia play a rather important role in regulating the balance of development and internal environment in vertebrates, the loss of genes related to cilia is associated with a range of diseases. Prenatal detection of renal abnormalities associated with skeletal or cerebral abnormalities should raise suspicion of multisystem ciliopathy, which is often associated with a variety of syndromes, including Meckel-Gruber syndrome, Joubert syndrome, Nephronophthisis, and Bardet-Biedl syndrome. Combined with recent studies, this article mainly summarizes four categories of cilia-related diseases in order to provide references for clinical diagnosis.***

Keywords: Ciliopathies, Prenatal disgnosis, Meckel-Gruber syndrome, Joubert syndrome, Nephronophthisis, Bardet-Biedl syndrome.

1. Introduction

Primary cilia are small but complex organelles that widely exist on the surface of various cells. They are powerful and have important sensory functions. They can sense extracellular mechanical and chemical signals and assist their transduction into the cell interior, thereby causing cellular responses. Primary cilia play a role in signal transduction, which affects the growth and development of animals and the normal physiological function of various organs [1]. The ependymal cilia in the brain are responsible for cerebrospinal fluid circulation; olfactory cilia enable people to further sense the external environment. The surface of the cell membrane is filled with olfactory receptor proteins, which can find chemicals in the environment and send signals to the brain, which is processed and converted into people's sense of smell. Retinal rods and cones sense light through membrane-associated molecules concentrated in the outer segment, called mutant cilia. Respiratory cilia remove respiratory mucus and inhaled particles. Cilia of the renal collecting duct and tubular epithelium can detect the fluid flow in the tubule and help to maintain the normal pattern of cell division. Cilia on the surface of developing heart cells play an important role in the formation of cardiac morphology. Ciliary defects often lead to a series of symptoms, that is, abnormalities in ciliary structure and function often lead to diseases involving multiple systems [1-3].

In recent years, it has been found that defects in ciliary morphology and function can lead to genetic diseases in newborns. Since cilia play a rather important role in regulating the balance of development and internal environment in vertebrates, the loss of genes related to cilia is associated with a range of diseases. A review of cases of prenatal diagnosis of suspected multisystem ciliopathy in a single center has found that prenatal detection of renal abnormalities related to skeletal or cerebral abnormalities should raise suspicion of multisystem ciliopathy, which is associated with a variety of syndromes, including: Meckel-Gruber syndrome, Joubert syndrome, Nephronophthisis and Bardet-Biedl syndrome, etc. Combined with recent studies, this article mainly summarizes four categories of cilia-related diseases in order to provide references for clinical diagnosis [2-3].

2. Meckel-Gruber Syndrome

Meckel-Gruber Syndrome (MKS) is a rare autosomal recessive primary ciliopathy. The main manifestations are central nervous system malformations, renal malformations and limb malformations, often accompanied by intracranial, facial, spinal, urogenital, cardiac system and other abnormalities. It is a fatal deformity. The incidence in China is unknown, and only a few sporadic cases have been reported. Early prenatal detection and accurate diagnosis are of great significance [4].

In the early and middle stages of fetal development, MKS can present with typical clinical phenotypes, including meningoencephalocele, postaxial polydactyly, polycystic renal dysplasia, etc., which is called Meckel-Gruber syndrome triad. Some studies believe that the diagnosis can be made if two of them are found. Prenatal ultrasound is currently the best method for the diagnosis of MKS, so that the disease can be diagnosed as early as 10 weeks of gestation.

MKS has a high genetic heterogeneity. The known pathogenic genes associated with this disease include MKS1, TMEM216, TMEM67, CEP290, RPGRIP1L, CC2D2A and NPHP3, which are located on different chromosomes. Among them, transmembrane proteins TMEM67 and TMEM216 are relatively well studied. Studies have found that cells from patients with Meckel-Gruber syndrome carrying pathogenic mutations in the TMEM67 or TMEM216 genes often show defects in actin or ciliation in the cytoskeleton. For other Meckel-Gruber syndrome related proteins, the use of model biological research found that some of them are indispensable for ciliogenesis [5]. Mutations result in an increased risk of impairment of processes such as microtubule formation, vesicle trafficking, and signal transduction.

Genetic diagnosis is the means of definite diagnosis of Meckel-Gruber syndrome. As imaging abnormalities can be found in the first and second trimesters, DNA can be extracted from the highly suspected MKS fetuses and their parents. Primers for known pathogenic genes of MKS can be designed and Sanger sequencing technology can be used for mutation detection. With the development of molecular genetics, whole exon sequencing (WES) technology can also be used to obtain the sequences of all exons, and then analyze the related gene information. Whole exome sequencing was performed on the proband, and the suspected pathogenic variants were verified by Sanger sequencing after PCR amplification. The proband carried compound heterozygous variants of CEP290 gene, c.2743G>T(p.E915X) and c.2587-2A>T, which had not been reported previously. After the pathogenic variant was identified, placental villus tissue was extracted for prenatal diagnosis, which provided a basis for genetic counseling and prenatal diagnosis of the family, and enriched the CEP290 gene mutation spectrum [6]. However, Hong et al. [7] identified compound heterozygotes of two new variants of CEP290 and heterozygotes of a new variant of CC2D2A by whole exome sequencing, and showed that ZNF77 may promote the expression of CC2D2A and regulate the amount of SHH. The current low sensitivity of single-gene testing is due to the lack of a clear genotype-phenotype correlation; however, as soon as a new gene mutation occurs in a family, prenatal diagnosis in the next pregnancy can be performed.

3. Joubert Syndrome

Joubert syndrome (JS) is a rare congenital malformation of brain, which belongs to autosomal recessive genetic disease. Its main feature is congenital cerebellar vermis hypoplasia. The incidence of JS in newborns is about 1/80 000 to 1/10 000. The clinical manifestations of JS are hypotonia, ataxia, developmental delay, often combined with intellectual disability. Such as microcephaly, tongue extension, polydactyly, retinal dystrophy, sacral dermal sinus, corpus callosum dysplasia and congenital heart disease, a few cases of cerebellar hemisphere enlargement, posterior cranial fossa widening, lateral ventricle widening and corpus callosum dysplasia [8-9].

The imaging features of JS are partial or complete absence of cerebellar vermis, abnormal development of the brainstem, thickened and shifted superior cerebellar crus, perpendicular to the brainstem, clearly displayed in sagittal plane, and abnormal morphology of the fourth ventricle. The imaging manifestations of JS reported in foreign literature include “midline fissure”, “bat wing” shape and “triangular” fourth ventricle, “molar tooth sign” and other characteristics. MRI is superior to ultrasound, which can make up for the deficiency of ultrasound [8,10].

At present, at least 40 pathogenic genes have been found to cause JS, which all encode primary ciliary proteins and related genes include NPHP1, AHI1, CEP290, TMEM216, OFD1, CC2D2A, C5orf42, INPP5E and so on [10]. However, due to the heterogeneity of clinical manifestations and gene ambiguity of JS, Sanger sequencing cannot make a good genetic diagnosis of JS. First, whole exome high-throughput sequencing technology was used to detect the mutation genes of suspected JS families, and the detected mutation sites were verified by Sanger sequencing again. It is expected to further enrich the etiological information of JS and provide a feasible new method for prenatal diagnosis of rare diseases [11]. In the case reported by foreign scholars, the importance of fetal exome was shown. Among them, the parents were carriers of two ciliopathy genes (TMEM138 and SDCCAG8), and the diagnosis of JS of the case was confirmed by fetal exome sequencing. The genetic variation spectrum of JS caused by CPLANE1 was updated [12]. Fei et al. first found two novel CPLANE1 heterozygous variants in the proband, including c.4459del (frameshift variant) and c.7534-14G > A (intron variant). The clinical phenotype of JS patients and CPLANE1 variants were analyzed and proved to be consistent. These two novel variants confirm the importance of diagnostic whole-exome sequencing [13]. Similarly, Chinese scholars confirmed that the fetus induced by JS was JBTS17 caused by c.7978C>T and c.7169delT compound heterozygous variants of CPLANE1 gene based on gene analysis [14]. We previously reported a fetus with cerebellar hypoplasia and polydactyly detected by prenatal ultrasound. Whole-exome sequencing detected an unknown missense variant in TMEM231 gene (c.19C>T; p.R7W). Considering that TMEM231 gene mutation may be related to Joubert syndrome or Meckel-Gruber syndrome, this study not only provides data for genetic counseling and prenatal diagnosis of the family, but also broads the understanding of TMEM231 [15].

4. Nephronophthisis

Nephronophthsis (NPHP) is an autosomal recessive cystic kidney disease that can lead to renal failure in childhood or adolescence. It is the most common genetic cause of renal failure in children. The age of onset, disease progression and clinical manifestations of NPHP are nonspecific, and even similar to other types of nephropathy, such as primary hyperoxaluria. The main clinical manifestations of NPHP are impaired renal tubular function. The common clinical manifestations include low birth weight, polydipsia, polyuria, polydipsia, growth retardation, metabolic acidosis, anemia, and renal failure. Although the clinical manifestations of NPHP are lack of specificity, the clinical manifestations of NPHP are mostly solitary renal phenotypes, and about 10%-15% of NPHP are accompanied by extrarenal phenotypes. The main organs involved are the eye, nerve, bone, and liver [16].

B-ultrasound or MRI showed that the shape of bilateral kidneys was not significant, and could be normal or slightly reduced. The boundary between cortex and medulla was not clear, and there were multiple small cysts at the junction. Sometimes the existence of cysts could not be found by early imaging examination. Typical renal pathological changes were: focal atrophy of renal tubules, significant structural changes of tubular basement membrane (stratification, tearing, thickening or thinning); diffuse renal interstitial fibrosis with a small amount of lymphocyte infiltration and prominent peritubular fibrosis was observed. Cystic dilatation or cyst formation of the distal convoluted tubules and collecting ducts [17].

At present, the clinical features of NPHP and renal biopsy only have suggestive value, while genetic testing has early prediction and good diagnostic value. NPHP is a genetically

heterogeneous disease, and more than 20 pathogenic genes have been identified, including NPHP1-20, NPHPL1, NPHPL2, etc. In recent years, high-throughput sequencing technology has become an important method for the diagnosis of NPHP, which can not only avoid invasive examination of renal biopsy, but also provide more accurate subtyping of NPHP, and help genetic counseling and reproductive evaluation. Tang et al. conducted a multicenter cohort in China to study the phenotypic and genotypic profiles of NPHP. Cross-sectional and longitudinal data on 60 patients with NPHP pathogenic gene mutations from 57 families distributed in 22 regions of China were collected into a unified anonymous database. Finally, it was found that NPHP1 and NPHP3 were the most common pathogenic genes, and patients with NPHP3 mutations progressed to ESRD and liver involvement more rapidly [18]. Wu et al. conducted genetic analysis on a fetus with bilateral polycystic renal dysplasia and oligohydramnio at the 16th week of pregnancy. The pregnant woman had a previous history of fetal renal abnormalities. After genetic counseling, the parents decided to terminate the pregnancy, and histological examination of the fetal kidney showed cystic changes without cortical, medullary or normal renal structures [19]. NGS had identified A heterozygous c.100 1G> A variant from the mother and a deletion of exon 3 of the INVS gene from the father, respectively. Through NGS and Sanger sequencing, the fetus was diagnosed with NPHP2 [20]. The above results may provide guidance for further pregnancy and enhance the understanding of the clinical features and genetic etiology of NPHP.

5. Bardet Biedl Syndrome

Bardet-Biedl syndrome (BBS) is a rare autosomal recessive genetic disease characterized by mental retardation, pigmentary retinopathy, polydactyly, congenital obesity, gonadal dysgenesis, and renal malformations. And a variety of secondary features such as language delay, developmental delay, diabetes, hearing loss, hyposmia, asthma, etc. The incidence of BBS is very low (1/13,500 to 1/160,000) [2,21].

Molecular genetic studies have found that BBS has genetic consistency, and at least 27 pathogenic genes have been identified, with BBS1 and BBS10 being particularly closely related to BBS. The clinical manifestations of different mutations are basically no difference, and the pathogenic mechanism is not clear. However, the detection rate of potential genetic causes for BBS ranged from 48% to 80%, depending on the scope of genetic analysis and the methodologies employed. [21]. Therefore, there is still a long way to go to screen the pathogenic genes of BBS.

6. Conclusion

In summary, ciliopathies affect almost every system of the body, and the study of ciliary biology helps to understand the integrated features of these specific diseases. The deletion of cilia-related genes is associated with a series of diseases. For some cases with specific abnormal ciliopathy, prenatal ultrasound screening can indicate the possibility of disease as early as possible, and corresponding genetic screening measures can be taken to achieve early diagnosis of eugenics and eugenics. In addition, it is necessary to further understand the molecular mechanisms of how cilia lead to organ formation and maintenance, which may enable personalized treatment for patients with different gene mutations.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

References

[1] Despotes KA, Zariwala MA, Davis SD, Ferkol TW. Primary Ciliary Dyskinesia: A Clinical Review. Cells. 2024 Jun 4;13(11):974.

[2] Orlova M, Gundorova P, Kadnikova V, Polyakov A. Spectrum of pathogenic variants and high prevalence of pathogenic BBS7 variants in Russian patients with Bardet-Biedl syndrome. Front Genet. 2024 Jul 18; 15: 1419025.

[3] Zhang R, Pan S, Zhao J, Wang J, Yang X, Qi Z. Primary cilia in neural development and disease. Neurobiol Dis. 2025 Dec; 217: 107184.

[4] Hartill V, Szymanska K, Sharif SM, Wheway G, Johnson CA. Meckel-Gruber Syndrome: An Update on Diagnosis, Clinical Management, and Research Advances. Front Pediatr. 2017 Nov 20; 5: 244.

[5] Zhang M, Cheng J, Liu A, Wang L, Xiong L, Chen M, Sun Y, Li J, Lu Y, Yuan H, Li Y, Lu Y. A missense mutation in TMEM67 causes Meckel-Gruber syndrome type 3 (MKS3): a family from China. Int J Clin Exp Pathol. 2015 May 1;8(5):5379-86.

[6] Srivastava S, Manisha R, Dwivedi A, Agarwal H, Saxena D, Agrawal V, Mandal K. Meckel Gruber and Joubert Syndrome Diagnosed Prenatally: Allelism between the Two Ciliopathies, Complexities of Mutation Types and Digenic Inheritance. Fetal Pediatr Pathol. 2022 Dec;41(6):1041-1051.

[7] Hong Z, He X, Yu F, Liu H, Zhang X, Zhang Y. Three Novel Variants of CEP290 and CC2D2DA and a Link Between ZNF77 and SHH Signaling Pathway Are Found in Two Meckel-Gruber Syndrome Fetuses. Reprod Sci. 2022 Aug;29(8):2322-2332.

[8] Tran AM, Jnah AJ, De Castro Pretelt MJ. Genetics Review: Joubert Syndrome. Neonatal Netw. 2025 Jun 1;44(3):159-166.

[9] Kumasaka I, Takushi H, Watanabe T, Ota C. Challenges in postoperative management of a patient with primary ciliary dyskinesia and Joubert syndrome and related disorders with congenital heart disease. BMJ Case Rep. 2025 Oct 23;18(10): e267389.

[10] Gana S, Serpieri V, Valente EM. Genotype-phenotype correlates in Joubert syndrome: A review. Am J Med Genet C Semin Med Genet. 2022 Mar;190(1):72-88.

[11] Fei H, Wu Y, Wang Y, Zhang J. Exome sequencing and RNA analysis identify two novel CPLANE1 variants causing Joubert syndrome. Mol Genet Genomic Med. 2022 Mar;10(3):e1877.

[12] Li MM, Datto M, Duncavage EJ, Kulkarni S, Lindeman NI, Roy S, Tsimberidou AM, Vnencak-Jones CL, Wolff DJ, Younes A, Nikiforova MN. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular

Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

[13] Cui S, Lou H, Yin H, Geng F, Li N, Ma L. [Phenotype and genotype analysis of a pedigree affected with Joubert syndrome due to variant of TMEM237 gene]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2021 Dec 10;38(12):1211-1215.

[14] Du E, Li H, Jin S, Hu X, Qiu M, Han R. Evidence that TMEM67 causes polycystic kidney disease through activation of JNK/ERK-dependent pathways. Cell Biol Int. 2013 Jul;37(7):694-702.

[15] Wang T, Liu YX, Luo FM, Dong Y, Li YL, Fan LL. A Novel Homozygous Variant of TMEM231 in a Case with Hypoplasia of the Cerebellar Vermis and Polydactyly. Front Pediatr. 2021 Nov 29; 9: 774575.

[16] Stokman MF, van der Zwaag B, van de Kar NCAJ, van Haelst MM, van Eerde AM, van der Heijden JW, Kroes HY, Ippel E, Schulp AJA, van Gassen KL, van Rooij IALM, Giles RH, Beales PL, Roepman R, Arts HH, Bongers EMHF, Renkema KY, Knoers NVAM, van Reeuwijk J, Lilien MR. Clinical and genetic analyses of a Dutch cohort of 40 patients with a nephronophthisis-related ciliopathy. Pediatr Nephrol. 2018 Oct;33(10):1701-1712.

[17] Wolf MT. Nephronophthisis and related syndromes. Curr Opin Pediatr. 2015 Apr;27(2):201-11.

[18] Tang X, Liu C, Liu X, Chen J, Fan X, Liu J, Ma D, Cao G, Chen Z, Xu D, Zhu Y, Jiang X, Cheng L, Wu Y, Hou L, Li Y, Shao X, Zheng S, Zhang A, Zheng B, Jian S, Rong Z, Su Q, Gao X, Rao J, Shen Q, Xu H; Chinese Children Genetic Kidney Disease Database (CCGKDD); "Internet Plus" Nephrology Alliance of the National Center for Children's Care. Phenotype and genotype spectra of a Chinese cohort with nephronophthisis-related ciliopathy. J Med Genet. 2022 Feb;59(2):147-154.

[19] Wu Q, Yang S, Wang C, Shi H, Ren S, Jiao Z, Kong X. [Ultrasonographic manifestation and genetic analysis of a fetus with nephronophthisis type 2]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2020 May 10;37(5):559-562.

[20] Macia MS, Halbritter J, Delous M, Bredrup C, Gutter A, Filhol E, Mellgren AEC, Leh S, Bizet A, Braun DA, Gee HY, Silbermann F, Henry C, Krug P, Bole-Feysot C, Nitschké P, Joly D, Nicoud P, Paget A, Haugland H, Brackmann D, Ahmet N, Sandford R, Cengiz N, Knappskog PM, Boman H, Linghu B, Yang F, Oakeley EJ, Saint Mézard P, Sailer AW, Johansson S, Rødahl E, Saunier S, Hildebrandt F, Benmerah A. Mutations in MAPKBP1 Cause Juvenile or Late-Onset Cilia-Independent Nephronophthisis. Am J Hum Genet. 2017 Feb 2;100(2):323-333.

[21] Rustad CF, Bragadottir R, Tveten K, Nordgarden H, Miller JU, Åsten PM, Vasconcelos G, Kulseth MA, Holla ØL, Olsen HG, von der Lippe C, Sigurdardottir S. Clinical and genetic aspects of Bardet-Biedl syndrome in adults in Norway. Orphanet J Rare Dis. 2025 Mar 14;20(1):127.