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REVIEW

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Monogenic diseases in respiratory medicine: Clinical perspectives

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Abstract

With the increasing awareness of genetics in respiratory medicine and improvements in molecular diagnostic techniques, many complicated and rare diseases in respiratory medicine can be diagnosed. Most respiratory diseases have no specific phenotype. However, the clinical spectrum of monogenic diseases in respiratory medicine varies, from pulmonary disease to other inherited disorders that involve the lung. The genes that mediate some of these diseases have been identified. Certain monogenic diseases remain poorly characterized clinically. Because of the specificity of the phenotype of respiratory disease, a future challenge will be to correlate the phenotype and genotype and understand its phenotypic variability. With the development of precision medicine, research on monogenic disorders has been intensive and vigorous. In this article, we provide a brief clinical introduction to monogenic diseases in pediatrics.

KEYWORDS
monogenic diseases, pediatrics, respiratory medicine

1 | INTRODUCTION

Rooted in genomics, precision medicine is different from conventional medicine, which is based on clinical symptoms, signs, and investigations. With the development of molecular diagnostic techniques, precision medicine can help one make early diagnoses of a disease, which can guide the effective treatment and improve the prognosis.

With the increasing awareness of genetics in respiratory medicine and improvements in molecular diagnostic techniques, many diseases can now be diagnosed, particularly complicated and rare diseases in respiratory medicine. Cystic fibrosis (CF) has been considered rare in the Asian population, with phenotypic features differing from those in Caucasian patients. The final diagnosis is often delayed in China because of the lack of newborn screening, the atypical phenotype, and its low frequency in the population, which ultimately results in serious complications and severely affects the prognosis. In recent years, more CF cases have been diagnosed in China. Patients with primary immunodeficiency disease (PID) commonly experience pulmonary involvement as the initial clinical manifestation; this group consists of many monogenic diseases. In addition, with the molecular diagnosis of surfactant metabolism dysfunction, severe complications can be avoided.

This review on monogenic diseases in respiratory medicine is neither exhaustive nor complete but is intended to serve as an introduction to the exponentially growing field of genetics in pediatric pulmonology. We will provide a brief clinical introduction to monogenic diseases in pediatrics. Basic genetic concepts will not be discussed in this article.

2 | MONOGENIC DISEASES IN RESPIRATORY MEDICINE

Monogenic diseases in respiratory medicine are divided into three types: pulmonary disorders, comprising airway disease, pulmonary

parenchymal disease, and pulmonary vascular disease; sleep disorder; and monogenic diseases with respiratory system involvement, including PID, neuromuscular disease, certain syndromes, and inherited metabolic diseases. The exact number of monogenic diseases in respiratory medicine remains unknown. Certain monogenic diseases will be introduced briefly in this article.

2.1 | Primary ciliary dyskinesia (PCD)

PCD (OMIM 244400) is an autosomal recessive disorder. The resulting defect in ciliary motion leads to anomalous mucociliary clearance, causing recurrent or persistent sinorespiratory infections and infertility. PCD occurs in approximately 1 in every 15 000-60 000 individuals.[1] The clinical presentations of PCD are variable. Bronchiectasis, recurrent respiratory infection, rhinitis, sinusitis, otitis media, and infertility can be seen in patients with PCD. In addition, patients can develop neonatal respiratory distress, hydrocephalus, and polycystic kidney disease. Assessment of the ciliary ultrastructure by transmission electron microscopy was considered the standard test for PCD and remains an important tool. Electron microscopy demonstrated that approximately 30% of patients with PCD do not have abnormal ciliary structure.[2] Roughly 20% of patients with a *DNAH11* mutation also lack abnormal ciliary structure.[3] For these patients, genetic testing plays an important role in their diagnosis. It has been reported that 31 genes are associated with PCD, the most common of which are *DNAH5*, *DNAI1*, *DNAAF1*, *CCDC39*, *CCDC40*, *DNAH11*, and *LRRC6*.[4] There is a lack of evidence-based medicine for the management of PCD. Many aspects of patient care are based on other chronic suppurative lung diseases.

2.2 | Cystic fibrosis (CF)

CF (OMIM 219700) is a monogenic autosomal recessive disease that is caused by mutations in *CFTR*, which contains a coding sequence that comprises 27 exons and is located on chromosome 7q31.[5] Because of dysregulation of chloride channel, the surface of exocrine gland cells reduces its permeability.[6] Consequently, dysfunction of the exocrine glands throughout the body leads to elevated sweat chloride, pancreatic insufficiency,[7] pulmonary recurrent infection,[8] hepatobiliary disease, and infertility. The diagnosis of CF relies primarily on clinical evidence and is confirmed by elevated sweat chloride or *CFTR* mutations in two alleles. CF is one of the most frequent lethal disorders in Caucasians. The incidence varies across the globe, from 1 in 2000-3000 newborns to 1 in every 3500 births in the European Union and United States, respectively (data from WHO website: http://www.who.int/genomics/public/geneticdiseases/en/index2.html#CF). In Asians, the prevalence of CF is rare. In Japan, 1 in 350 000 is affected by CF.[9] Thus far, over 2000 mutations have been identified in the *CFTR* that are associated with CF. ΔF508 accounts for approximately 75% of mutant CF alleles. Gene therapies are currently under development. *CFTR* modulators and potentiators are drugs that aim to correct the underlying defect that leads to CF by modifying the function of *CFTR*. Ivacaftor, approved for use by the US Food and Drug Administration in January 2012, targets the specific *CFTR* mutation G551D, improves lung function, and reduces respiratory symptoms and pulmonary exacerbations.

2.3 | Congenital alveolar proteinosis (CAP)

CAP is a group of diseases with characteristics of alveolar and terminal respiratory bronchioles that are rich in periodic acid-Schiff (PAS)-positive phospholipids and proteinlike material deposits. Given the heterogeneity of clinical manifestations, patients can present with respiratory distress, shortness of breath, and failure to thrive or can be asymptomatic. Chest CT often shows interstitial infiltration. CAP has five subtypes. Pulmonary surfactant metabolism dysfunction 1 (SMPD1) (OMIM 178640) is inherited in an autosomal recessive manner and is caused by surfactant protein B gene (*SFTPB*) mutation in 2p12-p11.2, which is usually described as a lethal disease with early onset, usually within hours of birth.[10] Patients with *SFTPB* mutation often have a severe course and survived for merely months after birth.[11] SMDP2 (OMIM 610913) is an autosomal dominant disorder, in which surfactant protein C deficiency is caused by a mutation in surfactant protein C gene (*SFTPC*), located on chromosome 8 (8p21.3). The phenotypic features of *SFTPC* mutations differ, from severe respiratory distress syndrome in neonates to idiopathic pulmonary fibrosis in adults. This condition has variable phenotypes, and some family members may be asymptomatic.[12] SMDP3 (OMIM 610921) is caused by ATP-binding cassette, subfamily A, member 3 (*ABCA3*) mutations in an autosomal recessive manner.[13] SMDP4 (OMIM 300770) and SMDP5 (OMIM 614370) cause impairments in alveolar macrophage development and failure of macrophages to properly catabolize surfactant,[14] owing to mutations in the colony-stimulating factor 2 receptor alpha (*CSF2RA*) gene on Xp22.32 and the granulocyte-macrophage colony-stimulating factor 2 receptor beta (*CSF2RB*) gene on 22q12.3, respectively. It is speculated that SMDP4 is an X-linked recessive disorder. SMDP5 is inherited in an autosomal recessive manner.

2.4 | Pulmonary alveolar microlithiasis (PAM)

PAM (OMIM 265100) is a rare disease. Its diagnosis is commonly made at age 30-50 years. The disease can be seen in children; Yin, et al[15] reported a 6-year-old girl who presented with a 4-year history of recurrent, nonproductive cough and was diagnosed with PAM. The disease can be sporadic or arise in a family. More than one-third of patients have a family history, suggesting that the disease may be autosomal recessive. The clinical manifestations are shortness of breath and exertion or can appear asymptomatically. Diffuse calcific micronodules, known as "sandstorm lung," are a typical sign on chest CT. Analysis of a lung biopsy specimen can reveal microliths in the alveoli. The associated gene is *SCL 34A2*, which encodes a type IIb sodium-phosphate cotransporter that is expressed in type II alveolar cells.[16] No effective therapy for PAM is available.

2.5 | Hereditary hemorrhagic telangiectasia (HHT)

HHT is an autosomal dominant vascular dysplasia leading to telangiectasias and arteriovenous malformations of the skin, mucosa, and viscera. Visceral involvement includes that of the lung, liver, and brain. Patients with pulmonary arteriovenous malformation can present with hemoptysis and cyanosis.[17] There are five subtypes (HHT1-5). HHT1 (OMIM 187300) is caused by a mutation in the gene encoding endoglin (*ENG*) on chromosome 9q34.1, and HHT 2 (OMIM 600376) is caused by a mutation in the gene encoding activin receptor-like kinase 1 (ALK1) (*ACVRL1*) on chromosome 12q11-q14.[18]

2.6 | Primary immunodeficiency disease (PID)

PID is a group of inherited disorders characterized by defects in immunity. The phenotype of PID varies. Patients with PID commonly have recurrent and severe infections. Pulmonary complications are the main manifestation in most cases, even on initial presentation. Many patients with PID experience recurrent respiratory infections and severe pneumonia or respond poorly to routine antibiotics.[19] Recurrent respiratory infections are the major warning signs of PID. In addition, pulmonary complications are significant causes of morbidity in patients with PID. Pediatric pulmonologists should consider PID as an important component for differential diagnosis in order to enable early recognition and improve outcomes. Pulmonary manifestations of PID can be divided into two main groups—infections and noninfectious complications—which differ from recurrent infections affecting various locations and opportunistic or unusual pathogenic infections to malignancy and lymphoproliferative disorders.[20] Findings of PID on imaging range from consolidation, abscess, and empyema to bronchiectasis and interstitial lung disease.[21] The organisms in pulmonary infection differ from defects in immunity—encapsulated organisms are typical pathogens in patients with deficient humoral immunity, and infections by fungal organisms are more typical of cellular immune deficiencies.[22] Over 300 PIDs have been defined and molecularly analyzed,[23] approximately 190 of which have been linked to associated genes. Immunoglobulin replacement therapy and antibiotics are lifesaving options for many patients with PID, and patients with PID can be cured with hematopoietic stem cell transplantation (HSCT) or gene therapy.

2.7 | Congenital central hypoventilation syndrome (CCHS)

CCHS (OMIM 209880) is characterized by hypoventilation during sleep and impaired ventilatory responses to hypercapnia and hypoxemia. It is most commonly caused by pairedlike homeobox 2B (*PHOX2B)* gene mutations.[24] CCHS is an autosomal dominant disease. This disorder is also caused by mutations in several other genes, including *RET*, *GDNF*, *EDN3*, *BDNF*, and *ASCL1*. Evidence suggests that *PHOX2B* is the major disease-causing gene in isolated and syndromic CCHS.

2.8 | Marfan syndrome (MFS)

MFS (OMIM 154700) is an autosomal dominant inherited disorder of connective tissue that results from mutations in the *FBN1* gene (fibrillin-1). This gene encompasses 66 exons and is located on chromosome 15q21.1. The protein product is the extracellular matrix protein fibrillin, which is the major component of both elastin and microfibril. The classical features of MFS are usually seen in the cardiovascular system, the skeletal system, and the eye. Because the connective tissue defect is generalized, multiple organs are often involved. The pulmonary manifestations include subpleural microcysts, emphysema, apical bullae, and spontaneous pneumothorax, but these features are less commonly appreciated.[25] Pulmonary lesions in children are not frequently appreciated and are overshadowed by the cardiovascular abnormalities. MFS has phenotypic diversity and features that gradually evolve during childhood; therefore, the diagnosis is not frequently established in children who lack a family history or typical symptoms of MFS. According to the 2010 revised Ghent Nosology, genetic testing for MFS is crucial to its diagnosis.[26]

2.9 | Primary combined methylmalonic acidemia (MMA) and homocysteinemia

Primary combined MMA and homocysteinemia are a group of autosomal recessive disorders that are caused by inborn errors of cobalamin metabolism, including cblC, cblD, cblF, and cblJ. In addition, one subtype of MMA and homocysteinemia is X-linked, caused by a cblX defect. Because of multisystemic disorder, the central nervous system, retina, liver, kidneys, and bone marrow can be involved in patients with combined MMA and homocysteinemia. Hyperhomocysteinemia leads to pulmonary arterial hypertension (PAH) and pulmonary thromboembolism, damaging blood vessels.[27] It has been reported that patients with combined MMA and homocysteinemia present with diffuse lung diseases and PAH.[28] The mechanisms of pulmonary hypertension in combined MMA and homocysteinemia remain unclear. Oxidative stress, apoptosis, microangiopathy, and thromboembolism can be the underlying elements.[29,30] Subtypes of MMA and homocysteinemia result from different gene mutations in the MeCbl pathway, comprising *MMADHC*, *LMBRD1*, *ABCD4*, and *HCFC1*. Among them, the cblC subtype that is caused by an *MMADHC* mutation is the most prevalent. Liu et al[31] reported that the c.609G > A mutation is a hot spot mutation in *MMADHC* in Chinese patients with the CblC defect. Genotypes vary, as does the severity of the disease and the response to the treatment.[32] Some reports have revealed that the c.484G65 > 65T and c.276G > T *MMACHC* mutations are associated with PAH.[33,34] MMA and homocysteinemia should be considered in the differential diagnosis of PAH in pediatrics. Supplementary treatment is the main regimen, owing to the deficient synthesis of coenzymes that are derived from

vitamin B12. Medications include cyanocobalamin, folate, levocarnitine, vitamin B6, and betaine.

3 | A CLINICIAN'S PERSPECTIVE ON APPLICATIONS OF GENETIC TESTING FOR MONOGENIC DISEASES IN RESPIRATORY MEDICINE

3.1 | The principle of genetic tests

Not all respiratory diseases are suitable for examination by molecular diagnostics. Monogenic diseases, which have an early presentation and a defined single gene mutation, are a good choice for rapid diagnosis by genetic testing. However, clinical phenotyping is a crucial first step in the diagnostic approach. We suggest a gene test with the following conditions to increase positivity rates by molecular diagnosis: (i) similar symptoms in family and consanguineous members; (ii) specific or severe clinical phenotype; (iii) multiple deformities; (iv) specific investigation traits; and 5. exclusion of other factors.[35]

3.2 | Clinical phenotype information

Before establishing the ideal test, a complete characterization of the patient's phenotype needs to be performed. Therefore, phenotyping is a crucial first step before advancing to genetic testing. However, nonstandard phenotypic expression can lead to a misdiagnosis. Human Phenotype Ontology is recommended in the phenotype collection, which can reveal a correlation between the phenotype and potential genotype.[36] Another challenge is the gradual evolution of the phenotype over time. Moreover, many hereditary diseases have certain facial or severe neurological symptoms, but the phenotype of the respiratory system is often nonspecific, necessitating more studies on the phenotype of respiratory diseases.

4 | GENE EDITING FOR MONOGENIC DISEASE

There are about 7000 monogenic diseases, among which 4000 have been connected to specific genes.[37] While each monogenic disease is rare, a large number of the populations are affected, approximately 10 in every 1000 births to be affected (data from WHO website: http://www.who.int/genomics/public/geneticdiseases/en/index2.html). Gene therapy has been used as an innovative tool over the past few decades. Theoretically, it brings significant effect on the therapy of monogenic diseases by the use of normal gene expression replacing the dysfunction of the mutated gene. In 1990, the US Food and Drug Administration approved a clinical trial of the first gene therapy in the world, which were for a 4-year-old girl with severe combined immunodeficiency disease (SCID) due to adenylate deaminase defects. However, there are many problems in classical gene therapy, resulting slow development of gene therapy in recent 10 years. With the rapid development of cell molecular biology, gene editing and iPS cell play an important role in gene therapy. Gene editing can modify genome precisely and help to understand the pathogenesis of monogenic disease and explore the function of the gene, thereby achieve gene therapy. Zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeat-associated RNA-guided Cas9 (CRISPR-Cas9) nucleases are mainly used in gene editing. Gene editing for CF, Duchenne muscular dystrophy, chronic granulomatous disease and certain SCID, were successfully performed in clinical trials or animal models.[38] It is possible that monogenic disease is not rare anymore with gene editing in the next 10 years.

5 | SUMMARY

Approximately 25%-30% of cases of rare diseases can be diagnosed using whole-exome sequencing, which may be related to technical limitations, the data analysis, and the clinical analysis.[39] The spectrum of monogenic diseases in respiratory medicine remains incomplete. Further longitudinal studies in multiple centers on phenotype mining and phenotype-driven genetic analyses would be beneficial in improving the diagnosis of monogenic diseases in respiratory medicine in China.

CONFLICT OF INTEREST

The authors have no conflict of interests relevant to this article.

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