

Genotypes and Phenotypes: A Review of Pulmonary Hypertension in Genetic Syndromes

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There has been significant advancement in the understanding of the genetics of pulmonary hypertension (PH), particularly in those with heritable or idiopathic pulmonary arterial hypertension. In addition to genetic variants with a primarily pulmonary vascular disease phenotype, the prevalence of PH in other genetic syndromes is increasingly recognized. We will review the current knowledge of PH associated with multisystem genetic syndromes. There is high prevalence of coexisting cardiac and pulmonary disease, making it challenging to discern whether PH is secondary to these processes or underlying genetic makeup. There is a paucity of data on response to PH-targeted therapy and implications on overall prognosis.

INTRODUCTION

Pulmonary hypertension (PH) is a cardiopulmonary disease with diverse etiologies that significantly impact disease progression and long-term outcomes. PH, particularly that related to left-sided heart disease, is common in adult populations.¹ Conversely, PH prevalence is lower in the pediatric population and with a different distribution of disease etiology, including a higher proportion of patients with contributory developmental factors and congenital anomalies.² Since the 1990s, there has been significant advancement in understanding the genetic underpinnings of PH, particularly as it pertains to those with heritable pulmonary arterial hypertension (HPAH). In fact, rare genetic variations (mutations) are now known to contribute to a considerable proportion of PH cases, including over 10% of adult idiopathic pulmonary arterial hypertension (IPAH) cases and over 35% of pediatric IPAH cases.³ The most commonly identified pathogenic variants for IPAH and HPAH cases are within the bone morphogenetic protein receptor type II (*BMPR2*) gene, a member of the transforming growth factor- β

(*TGF- β*) superfamily (recently updated by reference 2).⁴ A multicenter cohort of 1550 pulmonary arterial hypertension (PAH) patients found that 29% possessed pathogenic variants in *BMPR2*. Patients with *BMPR2* mutations had a more severe phenotype with younger presentation, worse hemodynamics, lower response to acute vasodilator testing, and increased risk for death or transplant.⁵ This may relate to the contribution of not only vasoconstriction, but also cell-level irregularities suggestive of alterations in cellular proliferation, migration, and apoptosis.⁶ While genotype-phenotype information would be highly valuable for all relevant genes, such information is lacking due to the relative rarity of other variants.

Pediatric-onset PH has several important differences compared to adult-onset disease, which further complicates the already challenging quest to better classify disease phenotype. Pediatric-onset disease is characterized by more syncope and less right ventricular failure at time of diagnosis.⁷ Important genetic differences have been identified as well. While *BMPR2* remains the

most commonly identified causative gene in pediatric PH patients, variants in T-box 4-containing protein (*TBX4*) and SRY-related HMG box transcription factor (*SOX17*) are more frequently encountered compared to adult-onset disease.^{3,8,9} *SOX17* notably imparts particular risk for both PAH associated with congenital heart disease (CHD) as well as HPAH.⁹ And while targeted therapies have led to improved survival in pediatric patients, PH continues to impart high morbidity and mortality.⁷

In addition to the genetic variants with a primarily pulmonary vascular disease phenotype, recent pediatric registry studies have shed light on the prevalence of other genetic syndromes seen in pediatric PH cohorts. In the Spanish pediatric PH registry, 38% of patients had an underlying chromosomopathy/multiple congenital anomaly syndrome and an additional 17% of patients had trisomy 21.¹⁰ A study from the Dutch national registry identified that outside of PH-specific genetic variants, 17% had a genetic disorder with established association with PH and an additional 23% had genetic disorders or copy number variants without established PH association.¹¹ The largest pediatric registry study to date is from the North American Pediatric PH Network (PPHNet) Registry, which found that 17% of the 1475 patient cohort had

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a genetic syndrome.¹² These patients' pulmonary vascular disease was classified as World Symposium on Pulmonary Hypertension (WSPH) group 1 (PAH), group 3 (associated with lung disease), or group 5 (multifactorial PH), which likely reflects the high prevalence of both CHD and/or lung disease within these diverse genetic syndromes.¹²

While the field is rapidly gaining more understanding of the clinical features of PH-associated genetic variants, there is a paucity of data about the impact of the other genetic syndromes on pulmonary vascular disease phenotype and response to therapies. This review aims to present the available data about PH associated with multisystem genetic syndromes, with focus on chromosomal abnormalities, single-gene-related syndromes, and heterogeneous disease. Because genetic syndromes with multi-organ system involvement are more commonly encountered both clinically and in the medical literature in pediatric patients, the scope of this review is inherently pediatric focused. Phenotypic descriptions for adult populations with the subsequently described genetic syndromes are described as able, based on literature review. For the sake of brevity and due to the paucity of information in many circumstances, unless treatment efficacy or PH-related prognosis is specifically mentioned, the reader can assume that there are no available data on these outcomes.

CHROMOSOMAL ABNORMALITIES

Trisomy 21

Trisomy 21 (TS21) is the most common genetic syndrome associated with PH, with 4% to 17% carrying this diagnosis in the Dutch, Spanish, and North American pediatric cohorts. Several risk factors for PH have been identified in patients with TS21. The presence of TS21 affects both alveolar and pulmonary vascular development. Since first described by Cooney and Thurlbeck in 1982,¹³ histologic examination of lung tissue from TS21 patients has shown decreased alveoli, decreased airway development, thickened alveolar septa with a double capillary layer, and decreased vessel density.¹³⁻¹⁶

The high prevalence of cardiac and pulmonary disease in the TS21 popula-

tion further enhances the risk for PH. CHD is common, occurring in 38% to 58% of patients with TS21.¹⁷ The most commonly encountered CHDs are atrioventricular septal defect, ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus, and tetralogy of Fallot.¹⁷⁻²⁰ Type of CHD and timing of surgical intervention significantly impact the degree to which CHD may impact pulmonary vascular tone and the development of PH. Regardless, there is a higher risk of baseline PH and higher risk of postsurgical PH after cardiac repair (2.2% versus 0.7%) in TS21 patients compared to non-TS21 patients.^{17,19,20} There are multiple pulmonary comorbidities that may contribute to pulmonary vascular disease in TS21, including obstructive sleep apnea, recurrent pneumonia, infection, asthma, and upper and lower airway obstruction.²¹ Obstructive sleep apnea is particularly prevalent in roughly 60% of patients, including those without clinical suspicion.^{22,23} Patients with TS21 and PH may be classified as multiple WSPH groups depending on the presence and severity of these underlying cardiopulmonary processes, which may include WSPH group 1, 2 (secondary to left heart disease), and/or 3.

There are limited data on the response to PH-targeted therapy in TS21. A few small studies assessing the efficacy of bosentan in adults with CHD, PH (including a high number with Eisenmenger syndrome), and TS21 demonstrated that it has both short- and long-term benefits on hemodynamics and 6-minute walk distance.²⁴⁻²⁶ Pediatric data are lacking and it is likely that patients are treated according to existing pediatric PH treatment algorithms, given experience at the authors' PH centers and anecdotally. More granular data from large pediatric cohorts treated at experienced PH centers would be of great benefit.

TS21 health supervision guidelines currently recommend screening echocardiograms after birth and later in childhood if clinical concerns exist as well as a polysomnogram before age 4.²⁷ Houston and colleagues²⁸ more recently published additional screening recommendations to address the cardiopulmonary comorbidities that influence PH development and

advocate for more stringent screening with yearly echocardiograms in patients with underlying respiratory conditions. It is clear that even as the most studied genetic syndrome associated with PH, additional work is needed to better understand disease phenotype in TS21.

Trisomy 13 and Trisomy 18

Trisomy 13 (TS13) and trisomy 18 (TS18) are the next most commonly encountered chromosomal trisomies after TS21. These disorders have high early mortality and prevalence of PH. While a majority of infants with both TS13 and TS18 die within the first month of life, there is a subset that exhibits longer-term survival. In a multistate population study, 5-year survival was 9.7% in TS13 and 12.3% in TS18.²⁹ Multiple congenital anomalies are common in both TS13 and TS18. CHD is present in 60% to 80% of patients, with VSD, ASD, and tetralogy of Fallot being most common.^{30,31} Extracardiac anomalies commonly encountered in TS13 include orofacial anomalies, abdominal wall defects, limb defects, and central nervous system abnormalities.³¹ Extracardiac anomalies commonly encountered in TS18 include tracheoesophageal fistula, cleft lip, diaphragmatic hernia, and spinal dysraphism.³¹

PH is frequently cited as a potential complication of both TS13 and TS18, though data on the prevalence and hemodynamic severity are limited. From clinical experience, we can state the among those with these syndromes, the burden of PH, and its severity, is high and seemingly on the rise. This may be because intensive treatment has improved survival beyond early infancy for more patients; nonetheless, CHD and PH are common contributors to a high burden of morbidity and mortality.³²

A particular challenge with evaluating PH in these disorders is the high prevalence of CHD, which likely plays some role in the development of pulmonary vascular disease. The role of lung parenchymal and vascular development has not been rigorously evaluated. Tahara and colleagues^{33,34} analyzed lung tissue of a small set of patients with TS18 with CHD and found hypoplasia of the small pulmonary arteries, alveolar wall thickening, alveolar hypoplasia, and histologic

findings of mild pulmonary vascular disease. Notably, the role of unrepaired CHD is impossible to ignore when considering these findings. Cardiac surgical intervention in patients with TS13 and TS18 remains controversial due to the short average lifespan of these patients, though care paradigms may be shifting toward more intervention as a subset of patients has longer-term survival. Patients are often considered for surgery on a center- and patient-specific basis for palliative or comprehensive cardiac surgeries. The Pediatric Cardiac Care Consortium demonstrated that in-hospital mortality after cardiac surgery is high in TS13 (28%) and TS18 (13%). However, those who survive to discharge had a median survival of 15 to 16 years.³⁵ Over half of the patients in this cohort with a preoperative cardiac catheterization had PH, though mean pulmonary vascular resistance was higher (5.1 versus 3.5 WU) in those who died during hospitalization.³⁵

Similarly, Kaneko et al³⁶ reported that in a Japanese cohort, PH was present in 78% of hospitalized TS13/TS18 patients.

22q11 Deletion Syndrome

22q11 deletion syndrome (often referred to as DiGeorge syndrome) was reported in 21 (1.4%) of 1475 reported cases in the PPHNet Registry.¹² 22q11 deletion syndrome has a wide spectrum of clinical phenotypes. The most common associated features are facial dysmorphisms, congenital heart disease, thymic hypoplasia, parathyroid hypoplasia, developmental delay, laryngeal abnormalities, renal/urinary tract anomalies, and ophthalmologic abnormalities.³⁷ CHD is present in approximately 80% of patients, most commonly with conotruncal defects, including tetralogy of Fallot, pulmonary atresia with VSD, truncus arteriosus, interrupted aortic arch, and VSD.³⁸ Pulmonary blood flow can range from critically limited to excessive de-

pending on the underlying CHD, which may impact the development of PH. Data on the prevalence of PH in 22q11 deletion syndrome are limited, with 1 case report describing suprasystemic perioperative PH in an infant with truncus arteriosus undergoing repair at 34 days of life.³⁹ There is also possible increased risk for postoperative PH after CHD repair, with a single-center retrospective cohort study identifying postoperative PH in 13% (8/62) of patients with 22q11 deletion syndrome who underwent cardiac surgery.⁴⁰

SINGLE-GENE-RELATED SYNDROMES

There are several genetic syndromes characterized by pathologic variants in single genes which have associations with PH. We selected those with a more robust literature base to highlight, with less well-described syndromes compiled in Table 1.

Table 1. Additional Genetic Syndromes Associated With Pulmonary Hypertension

Syndrome	Gene	Syndrome features	Evidence for PH association
Alveolar capillary dysplasia with misalignment of the pulmonary veins	<i>FOXF1</i>	Diffuse disorder of the neonatal lung with respiratory distress and pulmonary hypertension; CHD (especially misalignment of the pulmonary veins but also may see left ventricular hypoplasia and/or other defects) with varied possible additional anomalies of cardiac, gastrointestinal, and genitourinary systems	41, 42
Adams-Oliver	<i>ARHGAP31, DOCK6, EOGT, RBPJ, NOTCH1, DLL4</i>	Aplasia cutis congenita; limb abnormalities; CHD; vascular anomalies; central nervous system anomalies	43, 44
Alagille	<i>JAG1, NOTCH2</i>	CHD (especially pulmonary arterial anomalies); cholestasis; butterfly vertebrae; ophthalmologic abnormalities ⁴⁵	46, 47
Cantú	<i>ABCC9, KCNJ8</i>	Facial dysmorphism; macrocephaly; CHD; skeletal abnormalities	48
Dursun	<i>G6PC3</i>	Triad of HPAH, leucopenia, and atrial septal defect; also, congenital neutropenia	49, 50
FLNA syndrome	<i>FLNA</i>	CHD; PAH; developmental impairments	51
Gaucher disease	<i>GBA1</i>	Hepatomegaly; splenomegaly; bone abnormalities; cytopenia; potential for neurologic impairment	52
Holt Oram	<i>TBX5</i>	CHD (especially ASD); cardiac conduction abnormalities; hand malformations	53-55
Kleefstra	9q34.3 microdeletion	CHD; developmental delay; seizures; sleep abnormalities	56-58
Klippel-Trenaunay		Capillary malformations; varicose veins; disturbed growth of bone and/or soft tissue	59
POEMS	None	Plasma cell dyscrasia with polyneuropathy (P); organomegaly (O); endocrinopathy (E); M protein (P); skin changes (S)	60-62
Pierre Robin sequence	None	Retrognathia; glossoptosis; airway obstruction; may be associated with other syndromes	63-66
Sickle cell disease	<i>HbS</i>	Red blood cell disorder with ramifications including primary pulmonary vascular disease and diastolic heart failure	67, 68

Abbreviations: PH indicates pulmonary hypertension; CHD, congenital heart disease; HPAH, heritable pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; ASD, atrial septal defect.

TBX4 Syndrome

While *BMPR2* remains the most commonly identified mutated gene in PAH cases (typically but not exclusively in familial PAH or IPAH cases), there is a growing recognition of other pathologic genes, including *TBX4*. *TBX4* is the second most commonly mutated gene in PAH populations.^{3,4} In pediatric patients, up to 8% of cases are associated with *TBX4* mutations, while the proportion is slightly less among adult PAH patients. As with *BMPR2* gene mutations, patients with *TBX4* may present at any age; however, there is an almost bimodal distribution, with a large proportion presenting as young children and another proportion presenting in adulthood after approximately age 40 years.³ Intriguingly, the phenotypic presentations are quite varied, with many young children presenting with some combination of persistent PH of the newborn which may or may not resolve, developmental lung disease, congenital heart defects, neurodevelopmental variation, and skeletal abnormalities.⁶⁹⁻⁷¹ In contrast, while some older children may present with more of a primary pulmonary vascular disease phenotype, this is the more common presentation among adults, who have a much more “pure” PAH phenotype at first evaluation. However, the adults also have syndromic spectrum disease, with skeletal abnormalities (eg, small patella syndrome), parenchymal lung defects, and airway anomalies.^{72,73} As with *BMPR2* and other single-gene mutations associated with PAH, *TBX4* spectrum disease has reduced penetrance and phenotypic variability, although further work is necessary to explore the impact and pathogenesis of mutations in this gene upon the human condition.

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) is characterized by mucocutaneous telangiectasias, recurrent epistaxis, arteriovenous malformations (including pulmonary, gastrointestinal, hepatic, and cerebral locations), and PH. It is inherited in an autosomal-dominant manner due to pathogenic variants in *ENG*, *ACVRL1*, or *SMAD4*.⁷⁴⁻⁷⁶ As with *BMPR2*, these genes are involved in the

TGF- β signaling pathway. There are 2 primary mechanisms for the development of PH in HHT: secondary to the high output state associated with hemodynamically significant arteriovenous malformations or due to the development of intrinsic pulmonary vascular disease as a form of HPAH. HHT-associated genes account for approximately 1% of identified genetic causes of IPAH in both pediatric and adult cohorts.^{3,8,77} While the sequelae of telangiectasias and arteriovenous malformations have a variable time course, PH most commonly develops in adulthood in HHT patients with median age of onset in the fifth to seventh decade of life.⁷⁷ PH is present in approximately 10% to 20% of patients with HHT and imparts significant increase in mortality.^{78,79} As recently reviewed, data on response to therapy and survival are somewhat mixed in the literature to date, with opportunity for enhanced understanding of genotype-phenotype associations.⁸⁰

Pulmonary Veno-Occlusive Disease and Pulmonary Capillary Hemangiomatosis

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are rare pulmonary and pulmonary vascular disorders characterized clinically by hypoxemia, PH, reduced diffusing capacity as measured by pulmonary function testing, and abnormal chest imaging by computed tomography. While classically considered distinct entities, PVOD and PCH have long been suspected to exist as 2 ends of the same spectrum due to their shared and distinct features.⁸¹ Consistent with this, in 2014, investigators separately demonstrated pathogenic biallelic mutations (both copies of the gene have mutations) in the gene *EIF2AK4* among familial cases of PVOD and PCH, helping to cement the pathophysiologic connection between PVOD and PCH.^{82,83} The discovery of *EIF2AK4* was significant not only due to the connection between PVOD and PCH; because of the challenges with diagnosis with both entities, lung biopsy in the setting of relevant clinical findings is often of serious consideration prior to formal diagnosis of PVOD or PCH. However, with the discovery of

EIF2AK4, in some circumstances biopsy may be avoided if biallelic pathogenic *EIF2AK4* mutations are detected.

But it is important to recognize that not all cases of PVOD or PCH associate with *EIF2AK4* mutations, and much room for enhanced understanding remains. In addition, the precise mechanisms of disease onset and progression remain an area of opportunity for discovery, with increasing evidence that both PVOD and PCH may develop in response to some sort of insult, such as enhanced pulmonary venous and capillary pressure, toxic insult, or a combination of factors (recently reviewed by Weatherald et al⁸⁴). While complete phenotype-genotype information is lacking, unfortunately, survival among *EIF2AK4* mutation carriers is poor, often lower than among individuals with *BMPR2* mutation-associated PAH.⁸⁵

Noonan Syndrome

Noonan syndrome is a multisystem disorder with variable phenotype, which includes characteristic facial features, CHD, short stature, hearing loss, and skeletal malformations. This syndrome is caused by mutations in genes within the RAS/mitogen-activated kinase signaling pathway, most commonly *PTPN11*, *SOS1*, and *RAF1*. Between 50% and 80% of patients with Noonan syndrome have cardiac involvement, most commonly with pulmonary stenosis, hypertrophic cardiomyopathy, or ASD.^{86,87} PAH is not a typical feature of this syndrome, though was first described in a 1982 case report of a 2-month-old with Noonan syndrome and PAH without concomitant CHD.⁸⁸ A few other case reports and small case series have since been published describing severe PAH in patients with Noonan syndrome, ranging in age from the neonatal period to early adulthood.^{86,89,90} While specific gene mutations are not described in all reports, it is notable that PH in the setting of *RAF1* mutations were found in the 2 patients described by Hopper and colleagues⁸⁹ and an additional patient in the description of a cohort of *RAF1*-positive patients.^{89,91} This suggests that further investigation in the specific genetic alterations in those with Noonan syndrome and PAH will be

important to best identify patients most at risk.

HETEROGENEOUS DISEASES

Mitochondrial Disease

Mitochondrial disease is a diverse group of diseases caused by dysfunction within the mitochondrial respiratory chain. These rare disorders can affect virtually all organ systems, with variable phenotypes, including liver disease, neurologic impairment, skeletal muscle weakness, acid-base disturbance, and cardiac involvement. The most common cardiac phenotype in mitochondrial disease is hypertrophic cardiomyopathy, though PH was first described in 2005.⁹² PH has been reported in several case reports and small series with a variety of specific mitochondrial disorders.⁹³⁻⁹⁹ The majority of described patients seemingly had PAH, though 1 study describes a patient with an underlying cardiomyopathy with significant biventricular dysfunction and a second describes a patient with severe restrictive lung disease, which suggests the potential for group 2 and group 3 PH in this population.⁹⁶ Few of these studies describe PH-specific therapy, though response to therapy is variable in the few who do describe treatment. Hung and colleagues⁹⁸ describe echocardiographic improvement with treatment with furosemide and mitochondrial supplements, whereas Sproule and colleagues⁹⁵ describe no improvement in PAH despite therapy with inhaled nitric oxide, epoprostenol, and mitochondrial supplements. The potential for improvement with mitochondrial supplements is particularly interesting and warrants further investigation as a potential means to reverse PH in this population.

CONCLUSION

It is evident that PH is encountered in multiple pediatric- and adult-onset genetic syndromes. There is a high incidence of associated lung disease and CHD, making it challenging to discern whether the primary risk for PH is secondary to the underlying genetic syndrome, cardiac and/or pulmonary disease, or a combination of both. Comprehensive human cohort studies are helpful to identify potential genetic associations with PH and relative fre-

quency of these coinciding relationships. With the exception of the chromosomal trisomies, much of the literature describing these associations is comprised of a limited number of case reports. Additional research is needed to better delineate the incidence of PH and its impact on morbidity and mortality in these genetic syndromes.

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