Genetic Counseling and Pulmonary Arterial Hypertension

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INTRODUCTION

As the role of genetics within pulmonary arterial hypertension (PAH) continues to expand, it has become evident over time that there is value and utility in incorporating genetic counseling into this field. Genetic counselors provide a comprehensive service that is tailored to addressing many of the complexities and nuances of genetics and PAH for patients and their families.

WHAT IS GENETIC COUNSELING?

As defined by the National Society of Genetic Counselors, genetic counseling is the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease (Table 1). This process integrates the following: (1) interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; (2) education about inheritance, testing, management, prevention, resources, and research; and (3) counseling to promote informed choices and adaptation to the risk or condition.[1] Genetic counselors have advanced training in human genetics and psychosocial counseling. In the United States, most genetic counselors have a master's degree in genetic counseling from an accredited genetic counseling program. Most employers require their genetic counselors to be certified by the American Board of Genetic Counseling (ABGC), and to maintain their certification by completing ongoing continuing education. In states where genetic counselors are licensed, all genetic counselors with licensure must be ABGC-certified.

ROLE OF GENETIC COUNSELING IN PAH

Genetic counselors play an integral role in multidisciplinary clinics, including pulmonary hypertension clinics. Expert consensus guidelines recommend genetic counseling and genetic testing to patients with familial PAH and idiopathic PAH.[2-5] Current practice guidelines recommend genetic counseling prior to genetic testing, specifically to address the complex genetic basis of PAH, issues of incomplete or variable penetrance, surveillance for at-risk family members, concerns about genetic discrimination, and psychosocial concerns associated with the diagnosis. After genetic testing, genetic counselors can facilitate cascade testing of at-risk family members if a pathogenic mutation is identified and can discuss reproductive testing options if desired.[5]

GENETICS OF HERITABLE PAH

Heritable PAH is inherited in an autosomal dominant manner with reduced penetrance. This means that each child of a parent with PAH due to a gene mutation has a 50% chance of inheriting the genetic mutation that caused the condition. However, not everyone who

Table 1. PAH and Genetics—Important Definitions

Term	Definition
Idiopathic PAH	PAH without an identifiable cause; typically, a diagnosis of exclusion
Familial PAH	PAH that occurs in ≥ 2 family members
Heritable PAH	Includes familial PAH and simplex PAH (ie, a single occurrence in a family) when a pathogenic mutation in one of the known genes has been identified
Penetrance	The proportion of people with a genetic mutation who exhibit symptoms of the disorder
Reduced penetrance	When the penetrance of a mutation is below 100%; that is, when not all individuals carrying a pathogenic mutation develop signs or symptoms of the condition
Variable expressivity	Differing clinical features among individuals carrying the same pathogenic mutation
De novo	Spontaneous genetic mutation not inherited from a parent

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Table 2. PAH Genes

Genes associated with heritable PAH (adapted from Elliott 2021)[10]	
Gene	**% of patients with identifiable mutations**
BMPR2	15.3
TBX4	1.3 (more common in children)
KCNK3	< 1.0
GDF2	< 1.0
KLF2	< 1.0
SMAD4	< 1.0
ATP13A3	< 1.0
BMPR1B	< 1.0
KCNA5	< 1.0
SMAD1	< 1.0
SMAD9	< 1.0
SOX17	< 1.0
AQP	< 1.0
CAV1	< 1.0
ACVRL1	< 1.0
ENG	< 1.0

carries the familial mutation will develop PAH, also known as reduced penetrance. For example, penetrance for *BMPR2* mutations has been estimated at ~20% overall with sex-dependent penetrance due to higher penetrance observed in female (42%) versus male (14%) carriers.[6,7] Penetrance for individuals with hereditary PAH due to mutations in *ACVRL1*, *KCNK3*, *CAV1*, *SMAD9*, or *BMPR1B* is not yet known.

Pathogenic mutations are identified in about 20% to 30% of patients with idiopathic PAH, and in about 75% of patients with familial PAH.[4,8,9] Genetic testing can be useful for familial risk assessment if a pathogenic mutation is identified. However, given the incomplete clinical sensitivity of current genetic testing for familial PAH, a negative result does not rule out a genetic cause of, or contribution to, a patient's PAH (Table 2).

In adult populations, most heritable PAH (~75%) is caused by mutations in the *BMPR2* gene.[11] Other genes associated with hereditary PAH have been identified, but in aggregate account for a very small percentage in adult populations (Table 2).

Table 3. American College of Medical Genetics Variant Classification Categories

Variant	Definition
Pathogenic	Variants or gene alterations that are known to disrupt gene function and cause disease
Benign	Variants in a gene that are found in many unaffected people and do not increase risk for disease
Variant of uncertain significance (VUS)	Gene alterations not commonly found in the general population for which it is unclear whether the variant causes disease or not. Rare genomic variation is extremely common and very difficult to interpret especially in relatively common adult-onset conditions with high clinical variability and incomplete penetrance. In the future, as more is learned about these genes, new information may clarify the risk associated with these specific alterations. The category of VUS has been further divided into subcategories ("*likely pathogenic*" and "*likely benign*") to reflect the substantial difference in variant data affecting interpretation.

Emerging data indicate that there are fundamental differences in the genetics of pediatric-onset versus adult-onset PAH. A greater proportion of patients with pediatric-onset PAH have identifiable genetic mutations as compared to those with adult-onset PAH (35% versus 11%, respectively).[12] While *BMPR2* mutations are the most common cause of heritable PAH in both pediatric and adult populations, the genetics of pediatric-onset PAH are much more heterogenous. In one larger cohort of 412 pediatric- and adult-onset familial PAH and ideopathic PAH cases, rare deleterious *TBX4* variants were reported in 13 cases (3%) with a significant enrichment of variants among pediatric (12/155; 7%) compared to adult-onset (1/257; 0.4%) patients. Variants in the *SOX17* transcription factor have been shown to be similarly enriched in pediatric PAH cases (19/273; 7%), compared with adult-onset PAH (13/3,455; 0.4%).[12] Additionally, de novo genetic variants (spontaneous mutations not inherited from a parent) contribute to a significant proportion, approximately 15%, of pediatric PAH cases.

GENETIC VARIANT CLASSIFICATION

Certain guidelines have been established for the interpretation of genetic variants; specifically, the American College of Medical Genetics has published guidelines that have helped to standardize the classification of genetic sequence variants for the medical community.[13] For clinicians that order genetic testing or those on the clinical team reviewing these results, it is important to know the different classifications of variants. The standard terminology that is used to describe variants identified in genes that cause Mendelian conditions are as follows: "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" (Table 3).

It is important to take into consideration the rapidly changing landscape of genetic testing when ordering PAH genetic panels. For any patient undergoing testing that receives a "negative" result (meaning no pathogenic findings) or a "VUS" (a variant of uncertain significance), we typically recommend that patients check with their genetic counselor or medical care team every 2 to 3 years to inquire about changes, updates, or reclassification regarding their genetic testing results. Some genetic testing laboratories will contact the ordering provider if there is a change to the interpretation of genetic testing results, but not all do, therefore the onus ultimately falls on the patient to recontact their genetic provider to ensure testing is up to date and as comprehensive as possible. Moreover, patients are encouraged to recontact their genetic provider with any subsequent changes to their personal or family's cardiovascular history so that their genetic counselor and care team can assess whether additional testing is recommended.

COORDINATION OF GENETIC TESTING

A critical role of a genetic counselor is to help families coordinate genetic testing. There are various laboratories that

Table 4. PAH Gene Panels Based on Laboratory[a]

Laboratory	GeneDx	Prevention Genetics	Invitae	Blueprint Genetics
Genes	*ACVRL1*	*ACVRL1*	*ACVRL1*	*ACVRL1*
	BMPR2	*BMPR1B*	*AQP1*	*ABCC8*
	CAV1	*BMPR2*	*ATP13A3*	*AQP1*
	EIF2AK4	*CAV1*	*BMPR2*	*ATP13A3*
	ENG	*EIF2AK4*	*CAV1*	*BMPR1B*
	GDF2	*ENG*	*EIF2AK4*	*BMPR2*
	KCNK3	*GDF2*	*ENG*	*CAV1*
	SMAD9	*KCNA5*	*GDF2*	*EIF2AK4*
		KCNK3	*KCNK3*	*ENG*
		SMAD9	*SMAD9*	*FOXF1*
		TBX4	*SOX17*	*GDF2*
			TBX4	*KCNA5*
			KCNA5	*KCNK3*
			BMPR1B	*KLF2*
				NFU1
				NOTCH3
				RASA1
				SARS2
				SMAD4
				SMAD9
				SOX17
				STRA6
				TBX4

[a]Gene panels are subject to change, please refer to each laboratory for updates.

offer clinical genetic testing for PAH; however, not all panels include the same genes, and thus it is paramount for the genetic provider to critically assess and determine which laboratory and/or gene panel will provide the highest yield. For example, an important consideration is whether the panel encompasses genes that target pediatric or adult-onset PAH; specifically, not all panels include the *TBX4* or *SOX17* genes, both of which are enriched in pediatric cases (Table 4).[12] Turnaround time can also vary between laboratories, generally from 14 days to 1 month or greater. Most laboratories perform genetic analysis on blood, saliva, or buccal specimens, but for it is important to check with specific labs should testing be done on any other specimen types (ie, postmortem, blood spot, skin punch) as not all labs have the same capabilities. Cost can also vary among laboratories. Not all accept insurance and patient self-pay pricing can vary from $250 to ~$900. Lastly, there are certain laboratories that offer family-variant testing options (typically for pathogenic or likely pathogenic variants), so it is recommended to inquire with the specific laboratory about options for follow-up testing of at-risk relatives.

RESOURCES FOR GENETIC COUNSELING

Even though the field of genetic counseling is growing, there still may be difficulty in finding a genetics provider to coordinate counseling or testing in your geographical area. If you do not have access to a cardiovascular genetic counselor within your hospital or clinic, here are some resources that can be used to either find a genetic counselor in your area or solicit commercial telehealth genetic counseling services which can be accessed from anywhere in the country:

https://findageneticcounselor.nsgc.org/
https://informeddna.com/
https://www.genomemedical.com/
https://www.gene-matters.com/

CONCLUSION

A genetic counselor is a master's-level trained clinical provider that can help facilitate genetic testing for patients and their families with heritable PAH. As genetic testing for PAH continues to rapidly expand, genetic counselors' skill-set and knowledge of the complexities, nuances, and new technologies available are well suited to assist PAH clinical teams and their patients. This collaboration helps to ensure informed decision making surrounding genetic testing for patients and their family members who may also be at risk and can subsequently receive surveillance and interventions that could be life-saving.

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