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Genetic Risk for Aortic Aneurysm in Adolescent Idiopathic Scoliosis

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Background: Scoliosis is a feature of several genetic disorders that are also associated with aortic aneurysm, including Marfan syndrome, Loeys-Dietz syndrome, and type-IV Ehlers-Danlos syndrome. Life-threatening complications of aortic aneurysm can be decreased through early diagnosis. Genetic screening for mutations in populations at risk, such as patients with adolescent idiopathic scoliosis, may improve recognition of these disorders.

Methods: The coding regions of five clinically actionable genes associated with scoliosis (*COL3A1*, *FBN1*, *TGFBR1*, *TGFBR2*, and *SMAD3*) and aortic aneurysm were sequenced in 343 adolescent idiopathic scoliosis cases. Gene variants that had minor allele frequencies of <0.0001 or were present in human disease mutation databases were identified. Variants were classified as pathogenic, likely pathogenic, or variants of unknown significance.

Results: Pathogenic or likely pathogenic mutations were identified in 0.9% (three) of 343 adolescent idiopathic scoliosis cases. Two patients had pathogenic *SMAD3* nonsense mutations consistent with type-III Loeys-Dietz syndrome and one patient had a pathogenic *FBN1* mutation with subsequent confirmation of Marfan syndrome. Variants of unknown significance in *COL3A1* and *FBN1* were identified in 5.0% (seventeen) of 343 adolescent idiopathic scoliosis cases. Six *FBN1* variants were previously reported in patients with Marfan syndrome, yet were considered variants of unknown significance based on the level of evidence. Variants of unknown significance occurred most frequently in *FBN1* and were associated with greater curve severity, systemic features of Marfan syndrome, and joint hypermobility.

Conclusions: Clinically actionable pathogenic mutations in genes associated with adolescent idiopathic scoliosis and aortic aneurysm are rare in patients with adolescent idiopathic scoliosis who are not suspected of having these disorders, although variants of unknown significance are relatively common.

Clinical Relevance: Routine genetic screening of all patients with adolescent idiopathic scoliosis for mutations in clinically actionable aortic aneurysm disease genes is not recommended on the basis of the high frequency of variants of unknown significance. Clinical evaluation and family history should heighten indications for genetic referral and testing.

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Adolescent idiopathic scoliosis is a diagnosis of exclusion. Scoliosis is a feature of many genetic disorders, including several that may present with mild phenotypes or incomplete penetrance of typical manifestations despite known disease-causing mutations¹. Diagnosis during childhood or adolescence, when most children with adolescent idiopathic scoliosis

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TABLE I Clinically Actionable Disease Genes Associated with Scoliosis and Aortic Aneurysm

Gene	Types of Mutations	Disorder	Clinical Features	Prevalence
<i>COL3A1</i>	Missense (mainly glycine), nonsense	Type-IV Ehlers-Danlos syndrome (vascular type)	Arterial dissection, rupture, or aneurysm; bowel rupture; pregnancy complications (uterine rupture); clubfoot; hip dysplasia; thin, translucent skin; easy bruising; facial features	1:200,000 ²⁸
<i>FBN1</i>	Nonsense, missense	Marfan syndrome	Aortic aneurysm, joint hypermobility, tall stature, long limbs, pectus deformity, lens dislocation, glaucoma, cataract, facial features	1:5000 to 10,000 ²⁹
<i>TGFBR1</i>	Missense	Type-I Loeys-Dietz syndrome	Aortic aneurysm, arterial tortuosity, atrial septal defect, bicuspid aortic valve, joint hypermobility, long limbs, bifid uvula or cleft palate, craniosynostosis, Chiari malformation, cognitive impairment, hypertelorism	Unknown ³⁰
<i>TGFBR2</i>	Missense, nonsense	Type-II Loeys-Dietz syndrome	Vascular (aortic aneurysm, arterial tortuosity), bifid uvula, translucent skin, velvety skin	Unknown ³⁰
<i>SMAD3</i>	Missense, nonsense	Type-III Loeys-Dietz syndrome	Vascular (aortic aneurysm, arterial tortuosity), early-onset osteoarthritis	Unknown ³⁰

are evaluated, is also problematic for disorders that may not manifest until adulthood^{2,3}. Although positive family histories can aid the diagnosis of some disorders, many individuals do not know their family history, or mutations may arise de novo, making family history less informative.

Marfan syndrome, Loeys-Dietz syndrome, and type-IV Ehlers-Danlos syndrome may be associated with scoliosis⁴⁻⁶ and are important to diagnose because of the high risk of life-threatening aortic aneurysm. Because treatment can prevent the life-threatening consequences of aortic aneurysm, the American College of Medical Genetics and Genomics has included these disease genes among the fifty-six genes considered medically actionable⁷. Reporting of results for these genes is therefore recommended, even when mutations are found incidentally during exome sequencing for unrelated disorders. Mutations in five clinically actionable genes, *COL3A1* (type-IV Ehlers-Danlos syndrome)⁸, *FBN1* (Marfan syndrome)⁹, *TGFBR1* (type-I Loeys-Dietz syndrome), *TGFBR2* (type-II Loeys-Dietz syndrome)¹⁰, and *SMAD3* (type-III Loeys-Dietz syndrome) (Table I)¹¹, are considered here because they have a higher-than-average risk of scoliosis and may be difficult to diagnose clinically (Table I).

Materials and Methods

Patient Samples

Patients with adolescent idiopathic scoliosis were recruited from St. Louis Children's Hospital and St. Louis Shriners Hospital for Children. This study was approved by the institutional review board and all patients and/or parents provided informed consent. All patients had spinal curves of >10° and of unknown etiology, although most patients had curves of 40° to 50°. Patients with developmental delay, multiple congenital anomalies, or known or suspected underlying medical disorders, including Marfan syndrome or Ehlers-Danlos syndrome, were excluded from the study. The systemic features of Marfan syndrome and joint hypermobility were evaluated in some patients with use of the

Ghent criteria² and the Beighton scoring system¹². Patients were recontacted after potentially disease-causing variants were discovered as part of this research study and were referred to clinical geneticists at St. Louis Children's Hospital and St. Louis Shriners Hospital for Children. Echocardiograms and ophthalmological evaluations were often ordered as part of the clinical genetics evaluations.

Sequencing and Analysis

Exome sequencing was performed on 343 unrelated patients with adolescent idiopathic scoliosis. All sequencing reads were aligned to the hg19 human reference sequence (Build 37) with use of Novoalign software (Novocraft, Selangor, Malaysia). Variant calling and annotation were completed with use of SAMtools (<http://samtools.sourceforge.net>) and SeattleSeq Annotation (University of Washington, Seattle, Washington). All variants were defined as extremely rare if they were present at minor allele frequencies of <0.0001 in the NHLBI (National Heart, Lung, and Blood Institute) GO (Grand Opportunity) Exome Sequencing Project (n = 6503)¹³. Analysis was restricted to variants altering the coding sequence (nonsense, splice-site, missense, and insertion or deletion variants). All variants were validated by Sanger sequencing.

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Results

We identified twenty-one extremely rare variants in three genes associated with both scoliosis and aortic aneurysm (*COL3A1*, *FBN1*, and *SMAD3*) in a screen of 343 patients with adolescent idiopathic scoliosis (Table II). No extremely rare variants were identified in *TGFBR1* or *TGFBR2*.

Two pathogenic variants were identified in *SMAD3*, the gene responsible for type-III Loeys-Dietz syndrome, which is

also known as the aortic aneurysm-osteoarthritis syndrome¹¹. Both *SMAD3* mutations are predicted to result in loss of function, with a loss of the transcription start site (p.Met1Thr) in individual 6234001 and a premature termination codon (p.Ser161*) in individual 6281001. Loss of function mutation is one of the most common types of mutation identified in type-III Loeys-Dietz syndrome^{11,14,15}. Neither *SMAD3* mutation had previously been reported. The proband carrying the *SMAD3* p.Met1Thr mutation had an 80° right thoracic curve that failed bracing and was surgically treated. He was evaluated by the clinical genetics team at the age of fourteen years, and, on the basis of clinical examination, there was no suspicion for a diagnosis of type-III Loeys-Dietz syndrome or other connective tissue disorder. His height was 173.5 cm (75th percentile) and his weight was 55.3 kg (97th percentile). His facial features revealed a normal uvula and absent hypertelorism. He had a normal echocardiogram at the age of fourteen years. His maternal grandfather had a history of aortic aneurysm and the proband's mother, who also had the pathogenic *SMAD3* p.Met1Thr mutation, had bilateral knee arthritis diagnosed at the age of forty-two years.

The second patient with adolescent idiopathic scoliosis harboring a pathogenic *SMAD3* loss of function mutation diagnostic of type-III Loeys-Dietz syndrome (p.Ser161*) presented with a 70° right thoracic curve. Her height was 176 cm (97th percentile) and her weight was 61 kg (78th percentile). She had knee pain as a child, but was otherwise healthy. Her examination did not reveal any evidence for a connective tissue disorder except skin stria. There was no family history of aortic aneurysm, heart disease, or arthritis.

Fourteen extremely rare variants in *FBNI* were identified in this cohort of 343 patients, and one was determined to be pathogenic. Although six variants were previously reported in patients with Marfan syndrome or Marfan-like phenotypes and are listed in the Universal Mutation Database¹⁶, we determined that only *FBNI* p.Ile2585Thr should be considered pathogenic. *FBNI* p.Ile2585Thr was previously reported in multiple patients with Marfan syndrome¹⁶⁻¹⁸ and was absent from more than 60,000 individuals in the Exome Aggregation Consortium (ExAC) database¹⁹. Therefore, according to the variant classification criteria of Dorschner et al., the p.Ile2585Thr mutation is pathogenic because its allele frequency is below the incidence of Marfan syndrome, it is present in at least three unrelated affected individuals, and it segregates with disease²⁰. The proband with adolescent idiopathic scoliosis with the p.Ile2585Thr mutation had a 93° right thoracic curve. She was subsequently diagnosed with Marfan syndrome after clinical genetics and echocardiogram evaluations. She had an elevated Ghent systemic feature score (10 points of 22 points total) and a dilated aortic root (a standard deviation of +2.6), consistent with Marfan syndrome. There was no family history of Marfan syndrome or aortic aneurysm. Therefore, overall, we detected two *SMAD3* pathogenic variants and one *FBNI* pathogenic variant in our cohort of 343 adolescent idiopathic scoliosis cases, resulting in a yield of 0.9% (three of 343 cases).

Five additional *FBNI* variants in our patients with adolescent idiopathic scoliosis were previously reported in patients with Marfan syndrome or Marfan-like phenotypes¹⁶, but ac-

cording to the Dorschner criteria²⁰, these missense variants did not meet the criteria to be considered as pathogenic because they had not been reported in at least three individuals with Marfan syndrome and did not segregate with disease in at least one family. Therefore, all five of these *FBNI* variants were considered variants of unknown significance. The *FBNI* p.Met1576Thr mutation was present in ten of 122,930 control alleles and p.Leu1405Arg was present in six of 122,898 control alleles¹⁹. Although these frequencies were less than the incidence of Marfan syndrome (estimated to be 1:5000 to 10,000), the relatively high frequency in ExAC suggests the possibility that these variants may have been benign polymorphisms. However, the p.Met1576Thr variant was highly enriched in our adolescent idiopathic scoliosis cohort because it was identified in three of 343 adolescent idiopathic scoliosis cases. Two patients with adolescent idiopathic scoliosis with the *FBNI* p.Met1576Thr variant underwent clinical genetics evaluations and had a normal range of Ghent systemic features (4 to 5 points) and normal echocardiograms and ophthalmological evaluations. Although they were both tall (height, ≥89th percentile), they did not meet clinical criteria for Marfan syndrome when evaluated at the ages of nineteen and twenty years². There was a family history of tall stature, but no aortic aneurysm or scoliosis. Because the p.Met1576Thr variant had previously been described in two patients with isolated aortic dilation^{17,21}, regular echocardiogram evaluations were recommended for our patients with adolescent idiopathic scoliosis with the p.Met1576Thr variant until further data established its clinical importance. The *FBNI* p.Leu1405Arg variant was seen in a single patient with adolescent idiopathic scoliosis, who was not found to have a dilated aorta or to meet criteria for Marfan syndrome after evaluation by a medical geneticist. She also had tall stature (91st percentile). This variant was also present in her brother, with pectus excavatum and mild scoliosis, and in her mother; both had normal echocardiograms.

Eight additional *FBNI* rare variants of unknown significance that had not previously been associated with Marfan syndrome were identified in adolescent idiopathic scoliosis cases. Four patients were evaluated by a medical geneticist, and none had a family history of Marfan syndrome or met criteria for Marfan syndrome. However, as a group, patients with adolescent idiopathic scoliosis with *FBNI* variants had greater spinal curve severity and higher Ghent systemic feature scores and Beighton joint hypermobility scores compared with patients with adolescent idiopathic scoliosis without variants in *FBNI* (Table III). These patients were also taller, but this was not significant ($p = 0.15$). No differences in sex, weight, or family history were noted.

Three variants of unknown significance were identified in *COL3A1*, the gene responsible for type-IV Ehlers-Danlos syndrome. Although the vast majority of mutations in *COL3A1* in Ehlers-Danlos syndrome consist of splice-site, nonsense, or missense mutations resulting in glycine substitutions within the triple helical domain⁶, these three novel missense variants resulted in non-glycine amino acid substitutions. Because non-glycine amino acid substitutions are rare causes of type-IV Ehlers-Danlos syndrome, the significance of these mutations was unknown. None underwent clinical genetic evaluation.

TABLE II Rare Genetic Variants in *COL3A1*, *FBN1*, and *SMAD3* Identified in Adolescent Idiopathic Scoliosis Cases†

Gene and Case	Genomic Position	Base Change	Protein Change	Frequency in ExAC Database	Sex	Curve‡	Height§	Weight§
<i>COL3A1</i>								
6294001	chr2:189856935	G > A	R326Q	1 of 122,932	F	69	7	67
6292001	chr2:189873814	C > G	N1230K		F	48	38	25
6388001	chr2:189876375	A > G	K1426E		F	50	93	96
<i>FBN1</i>								
6128001	chr15:48902952	T > A	I107L		F	84	20	21
6340001	chr15:48826300	T > G	N280T		M	48	>99	99
6377001	chr15:48795990	T > G	N703H		F	50	57	62
6623001	chr15:48791223	G > T	A709E		F	85	93	>99
6623001	chr15:48791224	C > T	A709T		F	85	93	>99
6683001	chr15:48787732	T > C	P825A	1 of 122,446	F	90	66	44
6556001	chr15:48779275	C > T	V1197I	6 of 122,898	F	77	38	95
6226001	chr15:48764870	A > C	L1405R	6 of 122,898	F	97	91	85
6272001	chr15:48760155	A > G	M1576T	10 of 122,930	F	90	21	40
6418001	chr15:48760155	A > G	M1576T	10 of 122,930	F	65	>99	87
6442001	chr15:48760155	A > G	M1576T	10 of 122,930	F	35	89	89
6320001	chr15:48736768	C > T	G2003R		F	66	7	30
6111001	chr15:48725128	T > A	Y2225F		M	95	93	86
6386001	chr15:48712949	A > G	I2585T		F	93	98	92
6674001	chr15:48073503	T > C	N2767S	4 of 122,914	F	50	42	31
6005001	chr15:48703201	C > T	2868I		M	55	91	95
<i>SMAD3</i>								
6234001	chr15:67457343	T > C	M1T		M	80	75	97
6281001	chr15:67473717	C > A	S161*		F	70	97	78

†NA = not available and VUS = variant of unknown significance. ‡The values are given in degrees. §The values are given in percentiles. #The values are the scores, given in points. **The aorta was dilated on an echocardiogram.

Overall, genetic variants of unknown significance in *FBN1* were identified in fourteen adolescent idiopathic scoliosis cases and variants of unknown significance in *COL3A1* were identified in three adolescent idiopathic scoliosis cases, resulting in a 5.0% (seventeen of 343) frequency of variants of unknown significance in our adolescent idiopathic scoliosis cases screened for mutations in just five genes.

Discussion

This study reveals the complexity of genetic screening for mutations in five clinically actionable genes associated with aortic aneurysm in an adolescent idiopathic scoliosis population. Despite diagnosing 0.9% of patients having adolescent idiopathic scoliosis with either type-III Loeys-Dietz syndrome or Marfan syndrome, a much larger number of patients had variants of unknown significance in these genes, leaving the clinician and the patient in a precarious diagnostic dilemma. Although early diagnosis of Marfan syndrome and related disorders is important because lifestyle modifications, regular echocardiographic evaluations, pharmacological treatments, and prophylactic surgical

procedures can substantially improve outcomes and lifespan²², the lack of clinical information about so many variants will undoubtedly lead to additional, and often unnecessary, cost and anxiety. Universal genetic screening of these five genes in a general adolescent idiopathic scoliosis population may eventually play a role in disease diagnosis, but the large number of variants of unknown significance reduces its current clinical utility.

In this study, two unrelated patients with adolescent idiopathic scoliosis were diagnosed with type-III Loeys-Dietz syndrome, a disorder whose associated craniofacial, skeletal, and cutaneous abnormalities may be mild¹¹. The distinguishing feature of type-III Loeys-Dietz syndrome is the presence of early-onset arthritis, most often affecting the knees, spine, and thumb base at a mean age of forty-two years, although it can be present in childhood¹¹. However, diagnosis is critical because aneurysms occur in >90% of *SMAD3* gene mutation carriers¹⁵. Because of the lifelong risk of aneurysm, our patients with adolescent idiopathic scoliosis who were diagnosed with type-III Loeys-Dietz syndrome, despite having normal echocardiograms, will need continued surveillance. Compared with type-I Loeys-Dietz syndrome (due

TABLE II (continued)

Ghent Systemic Score#	Beighton Score#	Genetics Evaluation and Echocardiogram**	Interpretation	Reference
NA	NA	N	VUS	
1	1	N	VUS	
3	0	N	VUS	
NA	NA	N	VUS	
3	0	Y	VUS	
1	1	Y	VUS	
NA	NA	N	VUS	Single report, no details ¹⁶
NA	NA	N	VUS	
3	1	N	VUS	Patient with aortic dilation, skeletal features, and ectopia lentis ³¹ , patient with isolated ectopia lentis ³²
3	3	N	VUS	
2	4	Y	VUS	Single report, no details ¹⁶
NA	NA	N	VUS	Two patients with isolated aortic aneurysm ^{17,21}
4	1	Y	VUS	Two patients with isolated aortic aneurysm ^{17,21}
5	4	Y	VUS	Two patients with isolated aortic aneurysm ^{17,21}
4	0	N	VUS	
5	2	Y	VUS	
10	2	Y**	Pathogenic	Patients with Marfan syndrome ¹⁶⁻¹⁸
5	2	N	VUS	Single report, no details ¹⁶
6	9	Y	VUS	
NA	NA	Y	Pathogenic	
NA	NA	N	Pathogenic	

to mutations in *TGFBR1*) and type-II Loey's-Dietz syndrome (due to mutations in *TGFBR2*) that have a high rate of associated abnormalities such as bifid uvula and hypertelorism¹⁰, facial dysmorphism occurs in <50% of all patients with *SMAD3* mu-

tations¹⁵, making type-III Loey's-Dietz syndrome more difficult to diagnose. However, screening patients with adolescent idiopathic scoliosis with pertinent family histories is likely to result in a higher diagnostic yield.

TABLE III Clinical Characteristics of Adolescent Idiopathic Scoliosis Cases with Rare Variants in *FBN1*

	No Variant (N = 328)	<i>FBN1</i> Variant (N = 15*)	P Value
Female patients†	277 (84%)	13 (87%)	1
Spinal curve‡	55° ± 16°	72° ± 20°	1.1 × 10 ⁻⁴
Height percentile‡	46 ± 30§	60 ± 32	0.15
Weight percentile‡	57 ± 31§	56 ± 32	1
First-degree relative with treated adolescent idiopathic scoliosis†	44 (13%)	2 (13%)	1
Ghent systemic features score‡ (points)	2.6 ± 1.7#	4.0 ± 2.2**	5.3 × 10 ⁻³
Beighton joint hypermobility score‡ (points)	1.5 ± 1.7††	2.5 ± 2.4**	0.05

*One patient had two mutations. †The values are given as the number of patients, with the percentage in parentheses. ‡The values are given as the mean and the standard deviation. §The values are based on 217 patients. #The values are based on 205 patients. **The values are based on twelve patients. ††The values are based on 204 patients.

Marfan syndrome was diagnosed in one patient with adolescent idiopathic scoliosis after genetic evaluation in this study. In the absence of a family history, the diagnosis of Marfan syndrome often requires examination by a clinical geneticist, slit-lamp examination for ectopia lentis, and echocardiogram evaluation for aortic enlargement to fulfill the revised Ghent diagnostic criteria². Notably, our patient with adolescent idiopathic scoliosis who was subsequently diagnosed with Marfan syndrome had an elevated Ghent systemic feature score. Although systemic features are not routinely evaluated in orthopaedic clinics, Sponseller et al. described several individual features, including thumb and wrist signs, craniofacial features, pectus excavatum, severe hindfoot valgus, dural ectasia, or acetabular protrusion that may be high-yield features for screening²³.

In the current study, 5% of our adolescent idiopathic scoliosis population had gene variants of unknown significance in *FBNI* or *COL3A1*. Even though several *FBNI* variants were present in Marfan syndrome disease mutation databases, not all variants in these databases have been conclusively established as pathogenic with use of new diagnostic criteria²⁴. To avoid Marfan syndrome misdiagnosis, revised Ghent clinical criteria weigh heavily on aortic root dilation or aneurysm, ectopia lentis, *FBNI* mutation, and family history of Marfan syndrome²³. Therefore, expensive additional testing would be required for these patients with adolescent idiopathic scoliosis. In our study, the majority of adolescent idiopathic scoliosis cases with *FBNI* variants of unknown significance who underwent genetic evaluation and echocardiography did not meet criteria for Marfan syndrome; therefore, we believe that *FBNI* rare variants in adolescent idiopathic scoliosis may contribute to a primary skeletal phenotype that is characterized by increased spinal curve severity and tall stature²⁵.

One limitation of the current study was that clinical genetics evaluations and echocardiograms were obtained in only nine of twenty cases. Furthermore, these examinations were done at an age when aortic root dilation may not yet be present. Therefore, longitudinal follow-up of larger numbers of patients with adolescent idiopathic scoliosis and their relatives is needed to better understand any long-term risk. Our genetic study also evaluated only a small subset of connective tissue disease genes, and therefore it is possible that our patients with adolescent idiopathic scoliosis may have mutations in other genes that were not studied that would put them at risk for other complications. Finally, the results of this study may not be applicable to all scoliosis cohorts, as our research protocol excluded patients in whom connective tissue disorders were suspect; therefore, the numbers of patients with pathogenic variants may be much larger in an unselected population.

Genetic screening can be compared with radiographic screening of patients with adolescent idiopathic scoliosis for anatomic abnormalities such as Chiari malformation, syrinx, or a tethered cord that likewise alter patient management. Overall, the yield is similar, with 5% to 10% of patients with adolescent idiopathic scoliosis having central nervous system abnormalities on spinal magnetic resonance imaging^{26,27} compared with ~6% of patients with adolescent idiopathic scoliosis having pathogenic gene variants or variants of unknown significance in the

current study. The cost of genetic testing and imaging studies is also similar. Unfortunately, imaging and genetic screening studies both yield large numbers of variants or lesions of unknown significance that lead to additional testing. For example, most syrinxes and Chiari I malformations found on screening examinations in asymptomatic patients with adolescent idiopathic scoliosis do not warrant intervention yet are often referred for serial evaluations and imaging. In both cases, screening tests increase the cost of health care through additional medical testing and may contribute to psychological stress in cases where the clinical importance remains unknown.

The utility and cost-effectiveness of genetic screening studies are likely to improve as data are generated to allow variants of unknown significance to be more confidently classified as either pathogenic or benign. First, sequencing of larger numbers of population controls, beyond the 66,000 currently available in the ExAC database¹⁹, will better reveal the frequencies of variants in a general population, which is useful as variants that occur at frequencies above the disease prevalence are unlikely to be pathogenic. Second, sequencing patients with isolated skeletal phenotypes may expand the range of phenotypes associated with human disease mutations and may avoid publication bias inherent when all cases are selected from cardiology clinics. Research studies should include the plan to recontact and to study patients with these variants in greater depth. Finally, data curation in publicly available databases is essential to improve universal access and variant interpretation.

In summary, screening patients with adolescent idiopathic scoliosis for mutations in five clinically actionable genes associated with aortic aneurysm revealed pathogenic mutations in a small number of patients but resulted in diagnostically uncertain results in 5% of those screened. Universal genetic screening of these five genes in a general adolescent idiopathic scoliosis population may eventually play a role in clinical care, but the large number of variants of unknown significance reduces its current clinical utility. In the meantime, referral of patients with family history of aortic aneurysm or dissection, or clinical examination findings supportive of Marfan syndrome, Loeys-Dietz syndrome, or Ehlers-Danlos syndrome, is warranted. ■

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