Prevalence and Findings of Genetic Testing in Scimitar Syndrome

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BACKGROUND

- Scimitar syndrome (SS) is a rare congenital heart defect where the right-sided pulmonary veins drain aberrantly to the inferior vena cava instead of the left atrium.
- Several studies have highlighted the genetic implications in total anomalous pulmonary venous return (TAPVR), however the genetics of SS are less well-elucidated.
- Until recently, SS was believed to occur largely in isolation, but recent reports there is an increased prevalence of SS in 22q11 and VACTERL syndrome.

OBJECTIVE

We sought to identify the prevalence of genetic testing, either with chromosomal microarray (CMA) or whole exome sequencing (WES), in a cohort of patients with SS at our institution. We also sought to characterize the results of the studies.

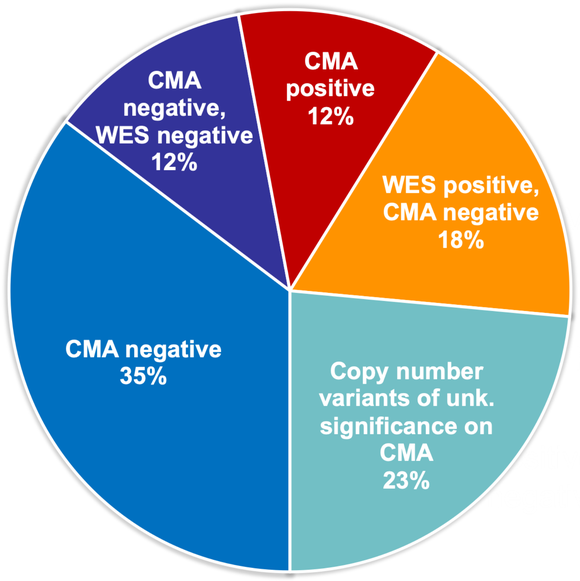
METHODS

- Data Source: Texas Children's Hospital electronic database
- Inclusion criteria: SS, defined as partial anomalous pulmonary venous return of the right pulmonary veins to the inferior vena cava – right atrial junction forming a "Scimitar" vein
- Exclusion criteria: TAPVR
- CMA and WES results were reviewed. Variants noted as pathogenic or likely pathogenic were considered "positive". Additionally, all reported genetic results were reviewed and variants of unknown significance also reported.

RESULTS

Patient Characteristics (N=77)		
	N	Percentage
Sex		
Female	52	68%
Male	25	32%
Testing		
CMA performed	17	22%
CMA positive	2	12%
WES performed	5	6%
WES positive	3	60%

CMA/WES Results in Patients with Genetic Testing



CMA	WES	CMA info	Genes	Interpretation	Other CHD	Extracardiac defects
Y		GAIN 22q11.21	**>20 genes**	**22q11.2 duplication syndrome**	Dextroposition, 2º ASD, RPA narrowing, arch elongation	R lung hypoplasia, AP collateral, absent RUL, CDH, post. rib fusions, hemivertebra,
Y		GAIN 10q21.3q23.1	**>20 genes**	**10q22.3-q23.2 deletion syndrome**	2º ASD, coarctation, pulmonary valve stenosis	CDH, rib fracture, R lung hypoplasia
Y	Y	-	***NAA15***	**Aut. dom. mental retardation, with CHD**	Dextroposition, TOF, mild pulmonary valve stenosis, HCM, 2º ASD	R lung hypoplasia
Y	Y	LOSS 3q13.2; LOSS 8q21.3	***MYRF***	**Cardiac urogenital syndrome**	HLHS (MA/AS), severe coarctation, pulm HTN	R lung hypoplasia, global delay paraesophageal hernia,
Y	Y	GAIN 2q.37.3	***EP300***	**Rubinstein-Taybi syndrome**	Aberrant R subclavian, LSVC	FTT, global delay, laryngeal cleft, CDH
Y	Y	LOSS 16q22.1	-	Unknown significance	TOF, ASD	R lung hypoplasia, R hand ectrodactyly, thoracic vert hypoplasia, scoliosis
Y		GAIN 16p13.11	-	Unknown significance	Dextroposition, ASD, pulm HTN, SVT	FTT, Pyloric stenosis, OSA, bronchomalacia, CDH
Y		LOSS 8p11.21	-	Unknown significance	ASD, VSD	Scoliosis, torticollis, leg-length discrepancy, asthma
Y		DER (X) T (X; 2) (2-6.1 q31.1)	−	Unknown significance	Dextroposition, PDA, VSD	Global delay, thrombocytopenia, scoliosis

CHD = congenital heart disease; HLHS = hypoplastic left heart syndrome; 2º ASD = secundum ASD; PDA = patent ductus arteriosus; VSD = ventricular septal defect; TOF = tetralogy of Fallot; HCM = hypertrophic cardiomyopathy; CDH = congenital diaphragmatic hernia

- An additional patient clinically has Marfan syndrome, but *FBN1* sequencing has not been performed

LIMITATIONS

This was a retrospective study, with non-universal genetic testing, and WES performed only in a fraction of patients. The sample may be biased if testing was conducted in patients with greater degrees of dysmorphology or extracardiac birth defects.

CONCLUSIONS

- 22% of patients had genetic testing performed, and this was predominantly composed of CMA testing.
- Pathogenic variants were found in 5/17 (30%) patients, accounting for at least 6% of our entire cohort.
- Three of the 5 pathogenic variants involved changes in genes related to different phases of cell growth/ proliferation, including TGF-beta, transcription coactivators and post-translational acetylation processing. One involved oligodendrocyte cell proliferation. One involved microduplication of the 22q11.21 region.
- Genetic testing – CMA with reflex to WES if CMA is negative – should be considered in patients with SS.

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