Yield of Systematic Inpatient Genetic testing of Neonates with Conotruncal and Laterality Heart Defects

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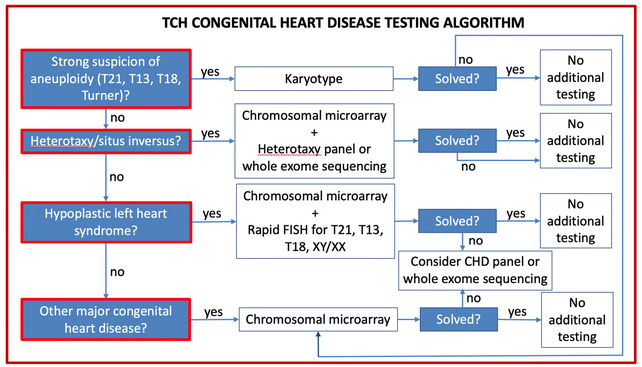
BACKGROUND

Many studies have demonstrated a high yield of genetic testing in congenital heart disease (CHD); however, to date, testing in most centers is not systematic and performed in a clinical setting.

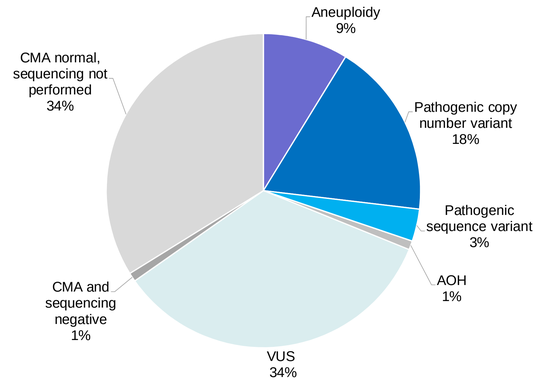
METHODS

- Retrospective cohort study of neonates with conotruncal and/or laterality CHD admitted to either the neonatal or cardiac intensive care units <28 days of age between Jan 2012 - Dec 2019.
- During this time, institutional recommendations were for a chromosomal microarray (CMA) for all children with conotruncal heart defects if a clear diagnosis of aneuploidy was not present. If negative, gene panel or exome sequencing was considered for infants with dysmorphic features, extracardiac defects (ECA), or a family history of CHD.
- Results of prenatal and postnatal genetic testing were reported by CHD lesion, and by testing modality.



RESULTS

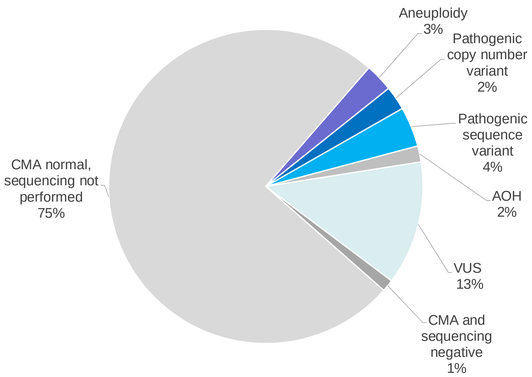
Fig 1: Conotruncal CHD Testing Results



Most Common Variants		
Variant	Variant type	N (%)
22q11.2 deletion	CNV	47 (14%)
T21	Aneuploidy	15 (5%)
T13	Aneuploidy	6 (2%)

Pathogenic Sequence variants		
Variant	N (%)	Associated Syndrome
CHD7 het	5 (9%)	CHARGE
JAG1 het	1 (2%)	Alagille
SMN1 het	1 (2%)	Spinal Muscular atrophy
SMARCA4 het	1 (2%)	Coffin Siris
EVC2 homozyg. variant	1 (2%)	Ellis Van Creveld
KMT2D het mosaic	1 (2%)	Kabuki
NAA15 het	1 (2%)	

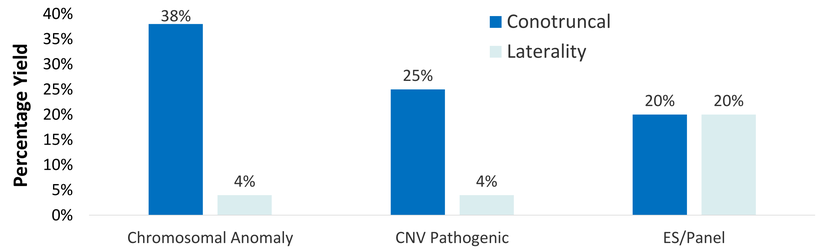
Fig 2: Laterality CHD Genetic Testing Results



Most Common Variants		
Variant	Variant type	N (%)
T21	Aneuploidy	9 (3%)
NODAL het	Sequence	9 (3%)
22q11.2 deletion	CNV	4 (1%)

Pathogenic Sequence variants		
Variant	N (%)	Associated Syndrome
NODAL het	2 (4%)	Heterotaxy, type 5
EFTUD2 het	1 (2%)	Mandibulofacial dysostosis w/ microcephaly
RPL5 het	1 (2%)	Diamond-Blackfan anemia 6
AVCR2B het	1 (2%)	Heterotaxy, type 4
CCDC103 homo	1 (2%)	Primary Ciliary Dyskinesia
DNAH5 homo	1 (2%)	Primary Ciliary Dyskinesia
MMP21 comp het	1 (2%)	Heterotaxy, type 7
MKKS comp het	1 (2%)	McKusick-Kaufman
PKHD1 comp het	1 (2%)	Autosomal recessive polycystic kidney disease
FBLN2 het	1 (2%)	AVSD candidate gene in T21

Fig 3: Pathogenic Yield per CHD type



- A total of 697 subjects met inclusion criteria, with 51% of those with laterality CHD.
- A total of 94% underwent at least one form of genetic testing, with 97% of those having had a CMA prenatally or postnatally.
- Overall yield of systematic genetic testing was 19% (122/654) for a pathogenic diagnostic finding, with 30% and 7% in conotruncal and laterality CHD respectively.
- Chromosomal anomalies and copy number variants were present in 27% of conotruncal anomalies, and 4% of laterality CHD.
- Only 16% of the cohort underwent panel or exome sequencing, of which 84% was exome.
- Yield of sequencing was 20% (21/105) which was diagnostic in 3% of the total cohort.

CONCLUSIONS

- Systemic genetic testing of neonates with conotruncal heart defects results in a high diagnostic rate for pathogenic genetic conditions.
- Given the high yield of exome sequencing in the minority of subjects tested, increased use of exome sequencing when CMA is negative is likely to provide even higher diagnostic rates.