YIELD OF SYSTEMATIC INPATIENT GENETIC TESTING OF NEONATES WITH CONOTRUNCAL 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. We aimed to describe the diagnostic yield of systematic genetic testing by lesion of infants with conotruncal heart defects.

Materials/Methods: We performed a retrospective cohort study of infants with conotruncal CHD without heterotaxy admitted to either the neonatal or cardiac intensive care units <28 days of age between January 2012 - December 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: A total of 472 subjects met inclusion criteria, with the most common lesion being Tetralogy of Fallot (30%, Table). A total of 93% 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 22% (96/438) for a pathogenic diagnostic finding, with 93% of infants having dysmorphic features and/or other ECA . Aneuploidy was present in 5% (n=24) and pathogenic copy number variants were present in 13% (n=58), with 45 of those being 22q11.2 deletion. Only 10% of the cohort (11% of those with a non-diagnostic CMA) underwent panel or exome sequencing, of which 84% was exome. Yield of sequencing was 29% (14/49) 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.

Images / Graph / Table

	Total N	Any testing N (%)	Total w/ pathogenic testing N (%)	Chrom. anomaly N (%)	CNV Pathogenic N (%)	ES or Panel Done N	ES VUS N	ES/Panel Pathogenic N (%)/% of Sequencing
Truncus	33	32 (97%)	8 (25%)	1 (3%) **T13** (1)	6 (19%) **22q11.2 del** (5) **Other** (1)	6	4	1 (3%)/(17%) **RAB3GAP1** (1)
Truncus/ IAA	6	6 (100%)	2 (33%)	0 (0%)	1 (17%) **8q12.1-2 del** (1)	2	0	1 (17%)/(50%) **CHD7** (1)
TOF Absent PV	17	16 (94%)	3 (19%)	0 (0%)	3 (19%) **22q11.2 del** (3)	3	3	0 (0%)/(0%)
TOF	140	130 (93%)	27 (20%)	15 (12%) **T21** (10) **T18** (4) **T13** (1)	7 (5%) **22q11.2 del** (4) **Xp21.1 dup** (1) **17p12 del** (1) **6q15q21 del** (1)	16	11	5 (4%)/(31%) **CHD7** (2) **JAG1** (1) **SMN1** (1) **NAA15** (1)
IAA Type B	32	31 (97%)	23 (74%)	0 (0%)	21 (68%) **22q11.2 del** (20) **1q21.1 del** (1)	4	1	2 (6%)/(50%) **CHD7** (1) **FGR1** (1)
PA/VSD	58	57 (98%)	18 (32%)	3 (5%) **T21** (3)	14 (25%) **22q11.2 del** (13) **Other** (1)	10	7	1 (2%)/(10%) **SMARCA4** (1)
DORV/PA	23	23 (100%)	10 (43%)	3 (13%) **T13** (3)	4 (17%) **1p36 del** (2) **18p11.2 del** (1) **8q12.1 del** (1)	5	2	3 (13%)/(60%) **CHD7** (1) **BBS12** (1) **GDF1** (1)
DTGA	142	125 (87%)	5 (4%)	2 (2%) **T21** (1) **XYY** (1)	2 (2%) **Xp21.1 del** (1) **1p36 del** (1)	3	1	1 (1%)/(33%) **IFT122** (1)
L-TGA	21	18 (86%)	0 (0%)	0 (0%)	0 (0%)	0	0	0 (0%)
All	472	438 (93%)	96 (22%)	24 (5%)	58 (13%)	49	27	14 (3%)/(29%)

Chrom: Chromosomal, CNV: Copy number variant; T13: Trisomy 13; T18: Trisomy 18, T21: Trisomy 21; VUS: Variant of uncertain significance