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## Characterisation of Paediatric Hypertrophic Cardiomyopathy Patients with RASopathy Mutations

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**Aim**: To compare clinical characteristics of patients with hypertrophic cardiomyopathy (HCM) and RASopathy or sarcomeric gene mutations.

**Methods**: Retrospective data was collected for paediatric patients seen between 2014-2016, with a diagnosis of HCM (left ventricle (LV) wall thickness ≥ 2 standard deviations above the predicted mean (z-score +2), not explained by abnormal loading conditions) and a 'pathogenic' RASopathy or sarcomeric mutation.

**Results**: 29 patients had RASopathy mutations and 35 patients had sarcomeric. Patients with RASopathy mutations presented younger than sarcomeric patients (median age 4 months vs 9 years). A family history of HCM was uncommon in RASopathy patients (10% vs 66%, P<0.001). Compound mutations were not identified in RASopathy patients but were found in 5 sarcomeric patients.

| RASopathy Gene Mutation | Frequency | Sarcomeric Gene Mutation | Frequency |
|---|---|---|---|
| PTPN11 | 12 | MYH7 | 17 |
| RAF1 | 9 | MYBPC3 | 15 |
| RIT1 | 4 | TNNT13 | 3 |
| HRAS | 2 | TNNT2 | 3 |
| BRAF | 1 | TPMI | 2 |
| SHOC2 | 1 | | |
| Compound | 0 | Compound | 5 |

LV hypertrophy distribution was more variable in RASopathy patients (59% asymmetric septal, concentric 38%), whereas 91% of sarcomeric patients had asymmetric morphology. Maximal wall thickness was lower in RASopathy patients (mean Z score 3.8 vs 4.6, P=0.054). However, LV outflow tract obstruction (LVOTO>30mmHg gradient) and systolic anterior motion of mitral valve were more common in patients with RASopathy mutations (48% vs 15% P=0.005; 76% vs 49% P=0.009 respectively). Structural heart abnormalities were more frequent in RASopathy patients (valvulopathy 52% vs 14%, P=0.002; pulmonary stenosis 28% vs 0%, P<0.001).

The majority (86%) of RASopathy patients were asymptomatic in NYHA class 1. Symptoms reported included: chest pain (17%), palpitations (14%), exertional breathless (48%) and unexplained syncope (7%). No deaths occurred during follow up (median follow up: 4.2 years). Ten sarcomeric patients (29% vs 3%) underwent ICD implantation- 30% for secondary prevention. RASopathy patients were more likely to undergo myomectomy (17% vs 6%, P=0.234).

Compared to other RASopathy patients, RAF1+ mutations were associated with higher ventricular septal thickness and smaller LV diameters (mean z score 11.4 vs 5.5, P=0.009; and -2.2 vs -0.5, P=0.002 respectively).

**Conclusion**: HCM patients with RASopathy mutations were clinically distinct, presenting earlier in childhood with no family history. They had a more variable pattern of LV hypertrophy and a higher prevalence of LVOTO requiring myomectomy. Further studies are needed to characterise this population.