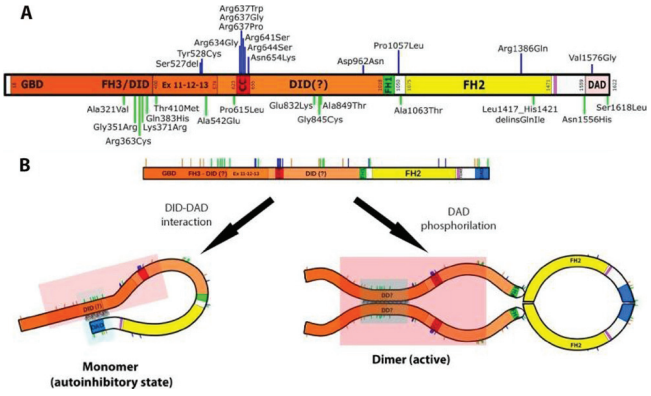
plained in a substantial proportion of cases. Formin homology 2 domain containing 3 (FHOD3) gene is implicated in sarcomere organization, myofibrillogenesis, and maintenance of the contractile apparatus in cardiomyocytes. FHOD3 may have a role in the pathogenesis of cardiac hypertrophy, but has not been implicated in hypertrophic cardiomyopathy.
Purpose: To determine the relation between FHOD3 mutations and the development of Hypertrophic Cardiomyopathy.
Methods: FHOD3 was sequenced by NGS in 3,189 HCM probands; 1,915 patients with other cardiomyopathies or sudden death, and 2,777 disease-controls. We evaluated altering protein candidate variants (minor allele frequency ≤0.005% in controls); carriers of other variants in sarcomeric genes were excluded. We evaluated cosegregation of FHOD3 variants with HCM in families that accepted to participate by calculating the LOD score. Clinical characteristics and outcomes were assessed in carriers of pathogenic or likely pathogenic variants in FHOD3 according to ACMG criteria.
Results: We identified 107 FHOD3 candidate variants in 139 probands. Frequency was significantly higher in HCM probands (76 of 3,189 [2.4%]) than in disease-controls (20 of 2,777 [0.7%]; p<0.001) or in gnomAD database (1,731 of 138,606 [1.2%]; p<0.001). FHOD3 mutations cosegregated with HCM in several families with a combined LOD score of 7.92 (very strong cosegregation). Half of the disease-causing variants were clustered in a narrow conserved coiled-coil domain (amino-acids 622–655); the odds ratio for HCM in this region was 21.8 versus disease-controls (95%IC: 1.3–36.9; p<0.001) and 10.9 against gnomAD (95%IC: 5.6–21.1; p<0.001). Of the rest of the disease-causing variants, the majority were located in the diaphanous auto-regulatory domain (DAD) and inhibitory domains (DID), or their surrounding residues (fig. 1A); these domains have been implicated in the pathogenesis of cardiac hypertrophy induced by angiotensin II (fig. 1B).
Most HCM patients with FHOD3 mutations were diagnosed after age 30 years and two thirds (66%) were males. 82% had asymmetric septal hypertrophy (mean 18.8±5 mm). Left-ventricular ejection fraction <50% was present in 14% and hypertrabeculation in 16%. Annual cardiovascular death incidence between ages 20 to 70 was 0.6%.



Conclusions: FHOD3 is a novel disease causing gene in hypertrophic cardiomyopathy, accounting for at least 1–2% of cases. The phenotype and the rate of cardiovascular events are similar to that described for unselected cohorts. The FHOD3 gene should be routinely included in hypertrophic cardiomyopathy genetic testing panels.

P6321
Clinical presentation and outcomes in paediatric-onset hypertrophic cardiomyopathy associated with MYBPC3 mutations

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Background: Mutations in the MYBPC3 gene are one of the most common causes of hypertrophic cardiomyopathy (HCM). Previous studies have suggested that MYPBC3 mutations are associated with later onset disease and better prognosis than mutations in other sarcomeric genes, but case reports of childhood HCM have also been described. However, the clinical features and outcomes of MYBPC3-related paediatric HCM have not been systematically described. This study aimed to describe the clinical characteristics and outcomes of a large cohort of paediatric HCM cases caused by MYBPC3 mutations.
Methods and results: All children (<18 years) diagnosed with HCM secondary to a MYBPC3 mutation reviewed at a single tertiary centre between 1989 and 2017 were included. Sixty patients from 58 families were identified. Median age at diagnosis was 10 years (IQR: 2–14 years); 12 patients (20%) were diagnosed in the first year of life. Forty-four patients (73.3%) were male. Diagnosis was made through family screening in 19 patients (31.7%), due to symptoms in 14 (23.3%), incidentally in 13 (21.7%) and following an out-of-hospital VF arrest in 6 (10%). Twenty-two patients (36.7%) underwent predictive testing for a familial mutation and 35 (58.3%) underwent diagnostic testing. Forty-two patients (70%) were heterozygous for a single MYBPC3 mutation; 18 patients (30%) carried a second sarcomeric mutation. In 12 patients this was an additional MYBPC3 mutation and in 6 patients the second mutation was in a different gene (MYH6, MYH7, TNNT2 or FLNC). Fifteen patients (35.7%) with a single MYBPC3 mutation were probands, compared to 10 (83.3%) of those with double MYBPC3 mutations.
At the time of baseline assessment, median left ventricular maximal wall thickness was 17mm (IQR = 12–24) and 11 patients (21.6%) had resting left ventricular outflow tract obstruction (>30mmHg). Median follow-up was 3 years (IQR: 1–9 years). At most recent assessment, 42 patients (75%) were alive and well with no adverse outcomes. Nineteen patients (33.3%) underwent implantable cardioverter defibrillator (ICD) implantation (13 for primary prevention and 6 for secondary prevention) with 3 experiencing appropriate ICD therapy during follow-up. Three patients died suddenly and one underwent cardiac transplant. Patients with double mutations in MYBPC3 were significantly more likely to experience adverse outcomes (sudden cardiac death, appropriate ICD therapy or cardiac transplantation) than those with a single mutation (p=0.024).
Conclusion: MYBPC3 mutations are a cause of paediatric-onset HCM, which may present with a severe phenotype and can develop in the first year of life. Children with compound MYBPC3 mutations are at an increased risk of adverse events when compared to those with a single mutation.

P6322
Genotype phenotype relation in patients with hypertrophic cardiomyopathy: development of a model to predict the genetic yield

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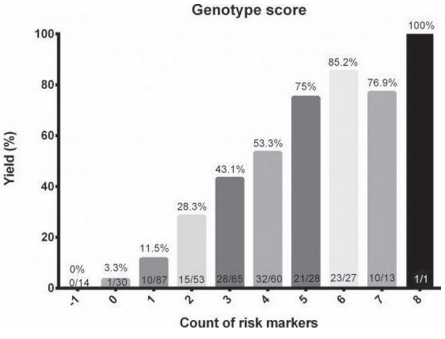
Background: Knowledge on the influence of specific genotypes on the phenotypic expression of hypertrophic cardiomyopathy (HCM) is emerging.
Purpose: The objective of this study was to evaluate the genotype-phenotype relation in a European cohort of HCM patients and to construct a score to predict the genetic yield based on clinical and ECG variables to improve counselling of these patients.
Methods: Unrelated HCM patients who underwent genetic testing were included in the analysis. All identified genetic variants were assessed using the ACMG-AMP criteria. According these criteria, likely pathogenic or pathogenic variants were considered as mutations. A composite endpoint of sudden cardiac death consisted of sudden cardiac death, appropriate ICD shock and sustained ventricular tachycardia. Genotype-phenotype correlation was evaluated between mutation positive and mutation negative patients and between patients carrying mutations in MYBPC3, MYH7 and the troponin complex. Using multivariate logistic regression clinical and ECG variables were identified that predict a positive genetic test. A weighted score was constructed based on the odds ratios.
Results: In total, 378 HCM patients were included of whom 141 carried a mutation (yield 37%), 181 were mutation negative and 56 only carried a variant of unknown significance. There was no difference in survival regarding a composite endpoint of sudden cardiac death, ICD shock and sustained VT between mutation positive and mutation negative HCM patients. However, MYBPC3 mutation carriers (N=80) had worse survival compared to troponin complex mutations carriers (N=24) and a similar trend was observed compared to MYH7 mutation carriers (N=27) and mutation negative patients. We identified age at diagnosis <45 years, familial HCM, familial sudden death, arrhythmic syncope, maximal wall thickness ≥20mm, asymmetrical septal morphology and the absence of negative T waves in the lateral ECG leads as significant predictors of a positive genotype (figure). A weighted score had a very high correlation with the observed genetic yield (Pearson r=0.98).

Variable	Points
Age Diagnosis < 45 years	2
Familial HCM	2
Familial SD	1
Maximal wall thickness ≥20 mm	1
Asymmetrical septal HCM	1
Syncope	1
Negative T waves lateral leads	-1



Genotype score

Conclusions: In this cohort, MYBPC3 mutation carriers had a worse survival regarding sudden cardiac death. A simple score system based on clinical variables can predict the genetic yield in HCM index patients, aiding in counselling HCM patients.

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