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High yield and therapeutic implications justifies genetic investigations in childhood hypertrophic cardiomyopathy

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INTRODUCTION The genetic background of hypertrophic cardiomyopathy (HCM) diagnosed in childhood was earlier considered be characterised by a lower proportion of sarcomeric mutations and a higher proportion of metabolic or storage disorders than HCM diagnosed in adulthood, although lately data from tertiary referral centres has suggested a similar spectrum of sarcomere gene mutations also in childhood HCM. However, geographically-based population data are lacking, particularly in the paediatric age range.

METHODS Patients belonging to the West Götaland region with presentation of non-syndromic HCM either in childhood or in adulthood were offered genetic investigations; only one family declined. In total 47 patients with a childhood presentation, and 55 patients with adult presentation had samples sent for assay at accredited laboratories (in Oxford, Copenhagen and Helsinki). A minimum screen of 13 genes were performed (MYBPC3, MYH7,TNNT2,TNNI3, MYL2, MYL3,TPM1, ACTC1, CSRP3, PLN, FHL1,PRKAG2, and GLA; in patients with marked ECG changes LAMP2 was also analyzed) and in those negative on this screen a 100-gene survey is being undertaken.

RESULTS Causative mutations were identified in a significantly higher proportion of childhood HCM, 38/47 (81%), than in adult HCM, 33/55 (60%; p =0.016). Mutations in MYBPC3 were most common both in childhood (40%) and in adulthood (36%), followed by MYH7 30% in childhood,versus 16% in adults. Further causative mutations found in childhood were ACTC (5%), MYPN, MYL2 and LAMP2 all 2.6%. An additional LAMP2 mutation was found among 9 tertiary referral patients from other regions, so a mutation causing Danon disease was unexpectedly found in a total of 3.6% of paediatric patients with non-syndromic HCM. Among adults mutations were found in TNNI in 5.5%, and MYL2 in 1.8%. 10.6% of childhood HCM and 22.8% of adult HCM had mutations of unknown significance that were not known polymorphisms, and 8.5% of childhood HCM and 17.5% of adult HCM had no identified mutations or known polymorphisms.

CONCLUSIONS Genetic investigation of childhood presentation of non-syndromic HCM has a higher yield than in adult HCM with sarcomere genes dominating, and sometimes has major therapeutic consequences such as the early recognition of Danon disease leading to early consideration of cardiac transplantation.