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Prevalence of mutations in the RAS/MAPK signalling pathway in pre-adolescent children with hypertrophic cardiomyopathy

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Introduction: Recent studies have shown that most cases of apparently idiopathic hypertrophic cardiomyopathy (HCM) in children are caused by mutations in cardiac sarcomere protein genes. Noonan syndrome and related malformation disorders are caused by mutations in genes encoding components of the RAS/MAPK signalling pathway and are commonly associated with HCM. Although the diagnosis is based on typical phenotypic features, in some cases the dysmorphic manifestations can be subtle. We hypothesized that mutations in the genes encoding components of the RAS/MAPK pathway cause apparently idiopathic HCM in pre-adolescent children.
Methods and Results: Seventy-eight patients diagnosed with HCM aged ≤13 years underwent clinical and genetic evaluation. The entire protein coding sequence of 9 RAS/MAPK pathway genes (PTPN11, HRAS, BRAF, MAP2K1 (MEK1), MAP2K2 (MEK2), KRAS, SOS1, RAF1 and NRAS), together with CBL (exons 8 and 9) and SHOC2 (4A>G mutation) were screened for mutations. Five probands (6.4%) carried novel sequence variants in BRAF, MAP2K1, MAP2K2 and SOS1 (2 individuals). Two individuals also had mutations in the MYBPC3 sarcomere protein gene.
Conclusions: This study identifies several novel and potentially pathogenic sequence variants in children with non-syndrome HCM. These findings have important implications for the evaluation and management of children with HCM, and provide an insight into the pathogenesis of apparently idiopathic and sarcomeric HCM.