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High Prevalence of Sarcomeric Mutations in a Pediatric Cohort of Hypertrophic Cardiomyopathy

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Introduction:
Hypertrophic cardiomyopathy (HCM) is, in most adults and adolescents, a genetic disorder of sarcomeric proteins inherited as an autosomal dominant trait. In contrast, a genetic origin of the disease in infants and children is considered unusual (commonly associated with metabolic disorders, neuromuscular diseases and congenital malformation syndromes). The objective of this study is to describe the genetic origin and clinical characteristics of a cohort of pediatric patients with HCM.

Methods:
Prospective observational cohort study from June 2010 to November 2011 of children with idiopathic HCM. Demographics, family tree, genetic test for sequences of sarcomere protein genes (MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, ACTC and TNNC1), ECG and echocardiography were performed.

Results:
15 patients were included in the cohort. 73,3% were male. Mean age 10,7 years (2,3 months to 17,7 years), being 9 (60%) under 13 (Mean age 7,1 years ±3,5). 66,7% of the patients included (10/15) were positive for a mutation, this proportion was equal in both age groups. A patient had 2 concurrent mutations in 2 different genes. The mutations were found in 5 different genes (see table). Three mutations (30%) had never been described before. At present, 7 of the 10 positive families have been studied, 2 being denovo mutations and 5 inherited mutations. The interventricular septum thickness was similar in both mutation and no-mutation groups. 3 patients with mutations had an ICD implantation. 1 patient with mutation was diagnosed after an aborted sudden death episode, and died for severe neurological complications. 1 patient with no mutations has a myomectomy performed. The youngest patient, with MYL3 mutation, was a prenatal HCM diagnosis and also a Noonan Syndrome.

Gene	Mutation
MyBPC3	2 x R502Q/g10952G>A
	R470W/g10770C>T
	R502W/g10951C>T
	IVS22-1/g14970G>A
MYH7	H251N/g6648C>A
	R453H/g9124G>A
	T1759M/g22083C>T
MYL3	A57D/g2629C>A
TNNT2	R278C/g18433C>T
ACTC	L106V/g2278C>G

Conclusions:
Mutations in cardiac sarcomere proteins are a common cause of pediatric HCM, also in the group of infants and children. Therefore, systematic screening of relatives of HCM patients, even in those aged younger than 13 years, is needed. The description of novel mutations will expand the range of reported sarcomeric mutations, improving the knowledge and management of pediatric HCM.