# HCM variant c.1458-1G>A in MYBPC3 and BrS association

Dr. Andrés R. Pérez Riera

This variant c.1458-1G>A in MYBPC3 **below to** Familial hypertrophic cardiomyopathy 4 OMIM # 115197. Familial hypertrophic cardiomyopathy is largely due to mutations in genes encoding sarcomere proteins. However, there are phenocopies that are due to mutations in protein kinases. These genes include the prkag2 gene which encodes a regulatory subunit of AMPK. The mutation appears to lead to constitutive activation of AMPK and results in a glycogen storage hypertrophic myopathy and tachyarrhythmias (as seen in Wolfe–Parkinson–White syndrome) (Gramlich M, Pane LS, Zhou Q et al. Antisense-mediated exon skipping: a therapeutic strategy for titin-based dilated cardiomyopathy. EMBO Mol Med 2015:7(5):562-576.).

This disorder is extremely difficult to treat and early mortality is common. Given the potent off-target inhibition of AMPK by sunitinib (Haas J, Frese KS, Peil B et al. Atlas of the clinical genetics of human dilated cardiomyopathy. Eur Heart J 2015:36(18):1123-1135a.), pre-clinical studies could be undertaken that would examine whether sunitinib can prevent, delay, or even reverse the disease phenotype.

Another group of HCM phenocopies is the Noonan, Costello, and cranio-facio-cutaneous syndromes which are due to mutations involving the Ras/Raf pathway and the phosphatase regulating it (PTPN11), leading to constitutive activation of the pathway (Akinrinade O, Alastalo TP, Koskenvuo JW. Relevance of truncating titin mutations in dilated cardiomyopathy. Clin Genet 2016:90(1):49-54. 40) (Zhou Q, Kesteven S, Wu J et al. Pressure Overload by Transverse Aortic Constriction Induces Maladaptive Hypertrophy in a Titin-Truncated Mouse Model. Biomed Res Int 2015:2015:163564.) (Semsarian C, Ingles J. Expanding the genetic spectrum of hypertrophic cardiomyopathy: X marks the spot. Circ Cardiovasc Genet 2013:6(6):528-530.). These disorders are also very difficult to treat and lead to early mortality. It is conceivable that Raf pathway inhibitors, including sorafenib, could be used in the treatment of these patients, in whom there are very limited treatment options.

**Phenocopies of HCM**

There are some recognized HCM phenocopies, which can masquerade HCM, caused by mutations in

**1)** LAMP2 (Danon disease),

**2)** PRKAG2 (Wolff-Parkinson-White syndrome),

**3)** GLA (Anderson-Fabry disease),

**4)** RAF1 and PTPN11 (LEOPARD syndrome and Noonan's syndrome),

**5)** GAA (Pompe's disease),

**6)** TTR (amyloidosis) and FXN (Friederich's ataxia) ( . Semsarian C, Ingles J. Expanding the genetic spectrum of hypertrophic cardiomyopathy: X marks the spot. Circ Cardiovasc Genet 2013:6(6):528-530.)(Rapezzi C, Arbustini E, Caforio AL et al. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013:34(19):1448-1458.). From those syndromic or metabolic cases, Fabry disease is particularly common in a 1-3% of adult HCM male series (Yousef Z, Elliott PM, Cecchi F et al. Left ventricular hypertrophy in Fabry disease: a practical approach to diagnosis. Eur Heart J 2013:34(11): 802-808.).

Age at diagnosis is a key point to know the etiology of cardiomyopathies. Inborn errors of metabolism are more commonly diagnosed in infants than in adults. HCM is also prevalent in patients with cardio-facio-cutaneous syndrome, which is a genetic disorder characterized by mutations in genes involved in the RAS/MAPK pathway. RASopathies (Noonan, Costello and LEOPARD syndromes) are also a cause of HCM in children that could justify some cases of adults that could pass unnoticed (part of morphotype may be lost with development). (Kaski JP, Syrris P, Shaw A, et al. Prevalence of sequence variants in the RASmitogen activated protein kinase signaling pathway in pre-adolescent children with hypertrophic cardiomyopathy. Circ Cardiovasc Genet 2012:5(3):317-326.) (Arad M, Maron BJ, Gorham JM et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. N Engl J Med 2005:352(4):362-372.).

**Ruggiero Mango, MD, PhD; Andrea Luchetti, BSc; Raffaele Sangiuolo, MD; Valentina Ferradini, BSc; Nicola Briglia, MD; Emiliano Giardina, BSc; Fabrizio Ferrè, BSc; Manuela Helmer Citterich, BSc; Francesco Romeo, MD; Giuseppe Novelli, BSc; Federica Sangiuolo, BSc.** **Next Generation Sequencing and Linkage Analysis for the Molecular Diagnosis of a Novel Overlapping**

**Syndrome Characterized by Hypertrophic Cardiomyopathy and Typical Electrical Instability of Brugada Syndrome**

**Circ J 2016;(4) 80: 938–949.** doi: 10.1253/circj.CJ-15-0685.

Free article.

Background: Familial hypertrophic cardiomyopathy (HCM) is an autosomal dominant inherited disorder; mutations in at least 20 genes have been associated. Brugada syndrome (BrS) is an autosomal dominant inherited disorder caused by mutations mainly in the SCN5A gene. A new clinical entity that consists of HCM, typical electrical instability of BrS and sudden death (SD), is described. Methods and Results: The family was constituted by 7 members, 4 of who presented clinical features of HCM and electrical instability of BrS. The clinical presentation of proband was ventricular fibrillation. All members were clinically evaluated by physical examination, 12-lead electrocardiography, 2-dimensional echocardiography, stress test, electrocardiogram Holter, flecainide test, and electrophysiological study. An integrated linkage analysis and next generation sequencing (NGS) approach was used to identify the causative mutation. Linkage with the α-tropomyosin (TPM1) gene on chromosome 15q22 was identified. The NGS study identified a missense mutation within the TPM1 gene (c.574G>A; p.E192K), exactly located in a binding domain with polycystin-2 protein. No other pathogenic mutations were identified. Conclusions: This is the first report of an association between HCM and BrS, and the first to use a combined approach of linkage and NGS to identify a causative mutation in SD. The present study expands the clinical spectrum of disorders associated with the TPM1 gene and may be useful to report novel mechanisms of electrical instability in HCM and BrS. (Circ J 2016; 80: 938–949)

Key Words: Brugada syndrome; Hypertrophic cardiomyopathy; Next generation sequencing; Sudden death

| Disease | Rhythm Abnormality | Inheritance | Chromosome Location | Gene |
|---|---|---|---|---|
| Ventricular arrhythmias | | | | |

| | | | | |
|---|---|---|---|---|
| Hypertrophic cardiomyopathy | VT, VF | AD | 1q3, 2q31, 3p21.2, 7q3, 11p11.2, 11p15.1, 12q23, 14q11, 15q14, 15q2, 19p12 | Cardiac troponin T (1q3), titin, myosin essential light chain, myosin regulatory light chain, β-myosin heavy chain, α-actin, MLP, α-tropomyosin, cardiac troponin I |
| ARVD/ cardiomyopathy | VT, VF | AD | 1q42–43, 2q32, 3p23, 6p24, 10p12-14, 10p22, 12p11, 14q12-22, 14q24.3 | RyR2, desmoplakin, plakophilin-2 |
| ARVD/ cardiomyopathy with myofibrillar myopathy | VT, VF | AD | 10q22.3 | ? |
| Familial palmoplantar keratosis | VT, IVCD | AR | 17q21 | Plakoglobin with ARVD (Naxos syndrome) |

| | | | | |
|---|---|---|---|---|
| Familial palmoplantar keratosis | VT, IVCD | AR | 6p24 | Desmoplakin with ALVD (Carvajal syndrome) |
| Dilated cardiomyopathy | VT | AD | 1q32, 1q42, 2q31, 2q35, 5q33, 6q12, 6q22.1, 9q13, 9q22, 10q21, 10q22.3, 11p11, 11p15.1, 14q12, 15q14, 15q22 titin (2q31) | Desmin, δ-sarcoglycan, α-actin, titin, β-myosin heavy chain, α-tropomyosin, MLP, α-actinin-2, ZASP, Phospholamban |
| Dilated cardiomyopathy | VT | X-linked | Xp21 | Dystrophin |
| Mitral valve prolapse | AF, ? SD | AD | 16p11.2-12.1 | ? |
| Barth syndrome | VT | X-linked | Xq28 | G4.5 (tafazzin) |
| Left ventricular noncompaction | VT | X-linked | Xq28 | G4.5 (tafazzin) |
| Left ventricular noncompaction | VT | AD | 10q22.3, 11p15, 18q12 | ZASP; α-dystrobrevin |
| Supraventricular arrhythmias | | | | |

| | | | | |
|---|---|---|---|---|
| Familial amyloidosis | Atrial standstill, AF | AD | TTR locus | Prealbumin (transthyretin) |
| Conduction abnormalities | | | | |
| Idiopathic restrictive | AVB, VT | AD,AR | 2q31,[a] TTR locus; 19p12.2 | Desmin (2q31), prealbumin cardiomyopathy (transthyretin), troponin I |
| Familial amyloidosis | AVB | AD | TTR locus | Prealbumin (transthyretin) |
| Dilated cardiomyopathy with | AVB | AD | 1p1–1q1, 3p22, 6q23 | Lamin A/C, SCN5A conduction disease |
| Holt–Oram syndrome | AVB, AT | AD, X-linked | 12q24.1 | TBX-5 |
| Familial atrial septal defect | AVB, AF, SD | AD, ? | 5q35, 5 p | Nkx2-5 |
| Noonan syndrome | AVB, BBB, IVCD | AD | 12q24 | PTPN11 |
| LEOPARD syndrome | AVB, BBB, IVCD | AD | 17, 12q24 | Neurofibromin; PTPN11 |
| Heterotaxy | AVB, SVT, AF | X-linked | Xp26 | Zic3 |

| | | | | |
|---|---|---|---|---|
| Heterotaxy | AVB, SVT, AF | AD | — | NODAL, LEFTY A, LEFTY B, activin type IIB |
| Neurologic disorders | | | | |
| Muscular dystrophies | | | | |
| Duchenne | ST, AT, IVCD, VT | X-linked | Xp21 | Dystrophin |
| Becker | AVB SVT, AF | X-linked | Xp21 | Dystrophin |
| Limb-girdle | AVB | AR | 2p13, 4q12, 5q33-34, 13q12, 15q15, 17q11-12, 17q21[a] | Dysferlin, β-sarcoglycan, δ-sarcoglycan, γ-sarcoglycan, calpain-3, telethonin, α-sarcoglycan |
| Limb-girdle | AVB, VT | AD | 1q11–21, 3p25, 5q31, 6q23 | Lamin A/C, caveolin-3 (3p25), myotilin |
| Facioscapulohumeral | Atrial standstill, AF | AD | 4q35, 10q | D4Z4 |
| Emery–Dreifuss | Atrial standstill, AF | X-linked | Xq28 | Emerin |
| Emery–Dreifuss | Atrial standstill, AF | AD | 1p1–1q1 | Lamin A/C |

| | | | | |
|---|---|---|---|---|
| Myotonic dystrophy | AVB, VT | AD | 19q13.3 | Myotonin protein kinase |
| Other neurologic disorders | | | | |
| Freiderich ataxia | Variable | AR | 9q13–31.3 | Frataxin |
| Kearns–Sayre syndrome | AVB | Mitochondrial | mtDNA | tRNAleu(UUR)-3243 |
| MELAS syndrome | AVB, VT | Mitochondrial | mtDNA | |
| MERRF syndrome | AVB, VT | Mitochondrial | mtDNA | |
| McArdle syndrome | SD, AVB | AR, AD | ? | ? |
| Kugelberg–Welander syndrome | Atrial standstill, AF, AVB | AR | ? | ? |