GENETIC STUDY OF HYPERTROPHIC CARDIOMYOPATHY

PARTIAL REPORT

Patient Name: NA	**Patient Birth Date**: NA
Medical reference: NA	**Patient Gender**: NA

Consultancy Referral Number: NA
Specimen Type: NA
Requisition Date: NA
Fulfillment Date: NA

Referring physician: NA,
Harvesting facility: NA
Referring facility: NA
Purpose: NA

Referral reason: NA
Sample Reference: NA

1 – Results

This genetic study shows 4 genetic variants in the genes *MYBPC3, MYH7, PLN, and TNNT2* that can be associated with hypertrophic cardiomyopathy.

1 – Genetic Information

The results, described according to HGVS nomenclature (http://www.hgvs.org), are presented in the following table.

Gene	Genetic variant references		Nucleotidic change	Aminoacidic change	Observation
	HGMD	Ensembl			
MYBPC3	–	–	c.3188-21A>G	–	Genetic intronic variant in heterozygozity that may cause changes in splicing. Not described in the literature and of unknown clinical significance.
MYH7	CM050712	rs3729823	c.4472C>G	p.Ser1491Cys	Mutation in heterozygosity.
PLN	CR111409	–	c.*-30G>T	–	Mutation in heterozygosity.
TNNT2	CD044989	rs45533739	c.53-11_53-7delCTTCT	–	Polymorphism in heterozygosity.

Hypertrophic cardiomyopathy is mainly caused by genetic alterations that deregulate the cardiac contraction mechanism comprising the dysfunction of the mechanical, biochemical and cell bioenergetics.

- ***MYBPC3*, c.3188-21A>G**: The *MYBPC3* gene encodes for the cardiac myosin binding protein C, a sarcomeric motor protein important for cardiac muscle contraction. This intronic variant was found in a Portuguese cohort of 300 patients with clinical diagnosis of HCM. As so it is considered as an HCM-related polymorphism and may contribute to HCM severity when associated with other genetic variants.
- ***MYH7*, CM050712 / rs3729823**: The *MYH7* gene encodes for the beta heavy chain subunit of the cardiac isoform of myosin, a sarcomeric motor protein with ATPase activity and hence important in cardiac contraction. This mutation is considered to be a risk factor or a disease modifier and not an HCM-causative variant [1, 2].
- ***PLN*, CR111409**: The *PLN* gene encodes the phospholamban protein, whose unphosphorylated form acts as an inhibitor of sarcoplasmatic reticulum calcium ATPase in cardiac muscle cells. This genetic variant is potentially associated with the development of hypertrophic cardiomyopathy (HCM) and it was described in a North American cohort of over 1000 HCM-patients [3, 4]. This genetic variant is located in the promotor region of *PLN* gene. *In vitro* functional studies demonstrated that mutations in this region decrease promotor activity, affecting protein expression [5]. Both inhibition and overexpression of phospholamban have been associated with the development of primary

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cardiomyopathies [6, 7].

- ***TNNT2*, CD044989 / rs45533739**: The *TNNT2* gene encodes for the troponin T, the alpha-tropomyosin-binding subunit of the sarcomeric troponin complex that regulates muscle contraction in response to the intracellular calcium concentration. This polymorphism is associated with left ventricular hypertrophy and increased interventricular septal wall thickness. HCM patients who are homozygous carriers of this variant present a larger left ventricular mass/height ratio [8].

This information is supported by peer reviewed scientific papers indexed on PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and also by The Human Gene Mutation Database (HGMD Professional ® version 2013.4) [4], accessed on 4^{th} November 2014.

Hypertrophic cardiomyopathy has a 50% chance of being transmitted to family relatives; therefore, we recommend a carrier testing for these genetic variants to direct members of the patient.

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2 – Technical Information

2 – Methodology

1. A commercial kit was used to perform DNA extraction and purification from na. DNA concentration and quality were evaluated with MultiskanGo spectrophotometer (Thermo Scientific).
2. Genotyping was performed through molecular analysis of 963 genetic variants in 57 genes associated with hypertrophic cardiomyopathy.
3. Genotyping was achieved using a high-throughput DNA Microchip platform, the iPlex MassArray system from Agena. This array platform allows an optimal genetic analysis by combining the benefits of accurate primer extension chemistry with MALDI-TOF mass spectrometry. The different masses of each generated PCR product are then converted into genotype information.

2 – Test Accuracy

The technical accuracy of this test is estimated to be 99%.
HeartGenetics applies a rigorous quality control which may not exclude the possibility of error that might influence the test results. The results presented in this report are limited to the available scientific knowledge at the time this test was developed.

2 – HeartGenetics Panel

OBSCN (NM_ 052843), ***MYOM1*** (NM_ 003803.3), ***ACTA1*** (NM_ 001100), ***ACTC1*** (NM_ 005159), ***DES*** (NM_ 001927), ***CRYAB*** (NM_ 001885), ***JPH2*** (NM_ 020433), ***MAP2K2*** (ENST00000262948), ***MAP2K1*** (ENST00000307102), ***MYL2*** (NM_ 000432), ***MYL3*** (NM_ 000258), ***RAF1*** (NM_ 002880), ***CAV3*** (NM_ 033337), ***NDUFV2*** (NM_ 021074.4), ***KLF10*** (NC_ 000008.11), ***MYH6*** (NM_ 002471), ***CALM3*** (NM_ 005184.2), ***CASQ2*** (NM_ 001232), ***TPM1*** (NM_ 000366), ***SLC25A3*** (NM_ 005880.3), ***FHL1*** (NG_ 015895.1), ***MYPN*** (NC_ 000010.11), ***NEXN*** (ENST00000334785), ***GLA*** (NM_ 000169), ***TNNI3*** (NM_ 000363), ***TTN*** (NM_ 133378), ***PRKAG2*** (NM_ 016203), ***SRI*** (NC_ 000007.14), ***MYH7*** (NM_ 000257), ***PDLIM3*** (NM_ 014476), ***COA5*** (NG_ 031918.1), ***VCL*** (NM_ 003373), ***MTO1*** (ENST00000498286), ***MYLK2*** (NM_ 033118), ***SLC25A4*** (NM_ 001151), ***LDB3*** (NM_ 001080116), ***FXN*** (NM_ 000144), ***MRPL3*** (NC_ 000003.12), ***LAMP2*** (NM_ 002294), ***PLN*** (NM_ 002667), ***TRIM63*** (NC_ 000001.11), ***ANKRD1*** (NG_ 023227.1), ***TCAP*** (NM_ 003673), ***ACTN2*** (NM_ 001103), ***FHOD3*** (NC_ 000018.10), ***TNNT2*** (NM_ 000364), ***SOS1*** (NM_ 005633), ***MYO6*** (NM_ 004999), ***MYBPC3*** (NM_ 000256), ***BRAF*** (NM_ 004333), ***MYOZ2*** (NM_ 016599), ***NDUFAF1*** (NC_ 000015.10), ***CSRP3*** (NM_ 003476), ***FLNC*** (NM_ 001458), ***CALR3*** (NC_ 000019.10), ***COX15*** (NM_ 004376), and ***TNNC1*** (NM_ 003280).

Cantanhede, NA

Technical Direction

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3 – REFERENCES

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