GENETIC STUDY OF FAMILIAL HYPERCHOLESTEROLEMIA

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

Genotyping was performed through molecular analysis of 165 genetic mutations in the *LDLR*, *APOB*, *PCSK9*, *STAP1* and *LDLRAP1* genes associated to familial hypercholesterolemia and by the study of 2 *APOE* genetic variants related to premature cardiovascular disease.

1.1 – Associated genetic mutations

This genetic study shows 1 genetic mutation (out of 165) in the *LDLR* gene associated with familial hypercholesterolemia.

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	*Legacy*(1)	Mutation class(2)	Observation
	HGMD	Ensembl					
LDLR	CM920457	rs144614838	c.1432G>A	p.Gly478Arg		2	Mutation in htz

(1) RefSeq aminoacid numbering update.
(2) Familial hypercholesterolemia is mainly caused by mutations in the *LDLR* gene, organized in 5 classes according to their effect on the synthesized protein. Mutations of classes 1 and 3 are considered to be more severe when compared with mutations from classes 2, 4 or 5 [1, 2].

- ***LDLR*, CM920457 / rs144614838**: Mutations in the LDL receptor gene (*LDLR*) promote an increase in the circulating levels of LDL-cholesterol (LDL-C). The CM920457 mutation is considered pathogenic and associated with familial hypercholesterolemia phenotype since it modifies the precursor region of epidermal growth factor (EGF), reducing or inhibiting the LDLR protein maturation [3, 1].

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® version 2013.4), last accessed on 4th November 2014 [4].
Familial hypercholesterolemia is an hereditary disease that can be transmitted to family relatives. Therefore, it is recommended a carrier testing for this mutation, the lipid profile and personalized therapeutic measures.

It should be noted that a negative result does not exclude the presence of the pathology since other causal factors are not included in this evaluation.

1.2 – Associated genetic risk factor

The *APOE* gene is not a direct cause of familial hypercholesterolemia but it can aggravate a premature cardiovascular disease associated to familial hypercholesterolemia.

Gene	Genetic variant references		Nucleotidic change	Aminoacidic change	Combined genotype
	HGMD	Ensembl			
APOE	CM900020	rs429358	c.388T>C	p.Cys130Arg	**gs246 (T,T) (C,C) (Apo-$\varepsilon_3/\varepsilon_3$)**
APOE	CM860003	rs7412	c.526C>T	p.Arg176Cys	Not associated with cardiovascular risk

- ***APOE*, CM900020 / rs429358 + *APOE*, CM860003 / rs7412**: Apolipoprotein E (APOE) is a ligand of the LDL receptor (LDLR) and mediates LDL and VLDL clearance. Polymorphisms in the *APOE* gene encoding the isoforms ε_2, ε_3 and ε_4 promote changes in total cholesterol, triglycerides and circulating VLDL cholesterol levels. Combined genotypes of ε_3 and ε_4 contribute to increased risk of atherosclerosis, coronary heart disease, stroke and peripheral artery disease [5, 6, 7, 8, 9, 10, 11]. The wildtype and most frequent haplotype is the APOE ε_3.

2 – Technical Information

2.1 – 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 165 genetic mutations in the *LDLR*, *APOB*, *PCSK9*, *STAP1* and *LDLRAP1* genes associated to familial hypercholesterolemia and by the study of 2 *APOE* genetic variants related to premature cardiovascular disease.
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.

2.2 – 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.

2.3 – HeartGenetics Panel

PCSK9 (ENSG00000169174), ***APOB*** (ENSG00000084674), ***STAP1*** (ENSG00000035720), ***LDLR*** (ENSG00000130164), ***APOE*** (ENSG00000130203), e ***LDLRAP1*** (ENSG00000157978).

Cantanhede, NA

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