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Research Article

New cases of rare dyslipidemias in clinical practice

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Abstract

Lipid metabolism can experience different disorders resulting in changes in the function and concentrations of plasma lipoproteins. These changes affect alone or interact with other cardiovascular risk factors involved in the development of atherosclerosis. Therefore, dyslipidemias cover a wide spectrum of disorders lipids. Some of them have a genetic origin and very low prevalence. The main objective of this article is to report new cases of rare dislipemias of genetic origin in our population.

Genetic analysis was performed by Next Generation Sequencing (NGS) using a customized panel of 436 genes in DNA samples of four patients. The results confirmed the genetic origin of the following dyslipidemias: fish-eye disease, primary hypoalphalipoproteinemia-2, familial hypercholesterolemia by a variant in *STAP1* and Sitosterolemia.

This approach allows us to confirm the genetic diagnosis of four patients with alterations in lipid metabolism, this will help to improve patient management, achieving early diagnosis in the study of family members

Introduction

Dyslipidemias are alterations in lipid metabolism that occur with variations in lipid concentrations. Different studies have shown that modifications in levels of plasma lipoproteins are associated with the development of cardiovascular disease [1-3].

In some cases, alterations in lipid levels can be deter mined by genetic factors. So far, different monogenic lipid disorders with low prevalence had been identified [4], such are Fish-eye disease (FED; MIM# 136120), Primary hypoalphalipoproteinemia-2 (MIM#618463), Sitosterolemia (STSL1; MIM #210250) and Familial Hypercholesterolemia (FH; MIM#143890) caused by variants in *STAP1* among others.

Fish-eye disease is a rare disease; approximately 30 cases have been reported in the medical literature, with an inheritance pattern autosomal recessive caused by partial Lecithin Cholesterol Acyltransferase deficiency (LCAT) [5]. The LCAT enzyme plays a central role in removing cholesterol from the blood and tissues. This soluble enzyme converts cholesterol and phosphatidylcholines lecithins to cholesteryl esters and lysophosphatidylcholines on the surface of High-Density Lipoproteins (HDL). Two activities are related to LCAT, the main is alpha LCAT activity in HDL, furthermore has beta LCAT activity in Very Low-Density Lipoproteins (VLDL) and Low-Density Lipoproteins (LDL). Pathogenic variants at the *LCAT* gene can cause fish-eye disease impairing alpha LCAT activity, therefore, reducing the enzyme's ability to attach cholesterol to HDL. This disorder is characterized by increasing cloudiness

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of the corneas in the patients due to small grayish dots of cholesterol in them that can lead to severely impaired vision and very low levels of HDL-cholesterol (HDL-c). Other typical findings are raised levels of total cholesterol, and triglycerides and decreased levels of Apolipoprotein A-I (apoA-I) and Apolipoprotein B (apo B) in serum.

Primary hypoalphalipoproteinemia-2 is generally an autosomal recessive disorder associated with extremely low levels of apoA-I and HDL-c in serum, xanthomas, corneal opacities and in most patients, premature atherosclerotic cardiovascular disease [6]. Currently, 30 families have been described. This disease is caused by pathogenic variants in the *APOA1* gene (MIM 107680) that code for the apoA-I, the major structural component of HDL. It is also needed to activate LCAT and to mediate the interaction of HDL with cell surface receptors, such as scavenger receptor B1, or plasma membrane transporters such as ABCA1 [6].

Autosomal-dominant hypercholesterolemia is a common genetic disorder (1:250-1:500) [7], associated with extremely high levels of LDL-cholesterol (LDL-c). Molecular diagnosis can be confirmed by the presence of pathogenic variants in *LDLR* (low-density lipoprotein receptor, OMIM#606945), *APOB* (Apolipoprotein B, OMIM#107730), and *PCSK9* (proprotein convertase subtilisin/Kexin type 9, OMIM#607786). Recent studies suggested the *STAP1* (signal transducing adaptor family member 1, OMIM#604298) as the fourth FH gene [8].

Sitosterolemia is a rare autosomal recessive hereditary lipid storage disorder characterized by increased plant sterol levels, xanthomas and accelerated atherosclerosis [9]. It is caused by homozygous or compounds heterozygous mutations in one of the two *ABCG5* (STSL2; MIM# 618666) and *ABCG8* (STSL1; MIM #210250) genes encoding the sterol efflux transporter ABCG5 and ABCG8. Recent studies have shown that the prevalence of subjects with deleterious variants in *ABCG5* and/or *ABCG8* genes could be more than 1 in ~200,000 individuals among the general population [10].

The main objective of this article is to report new cases of rare dyslipidemias of genetic origin in our population.

Materials and methods

Patients

The patients were referred to our Laboratory of Genetics of Metabolic diseases. These patients came from the Departments of Endocrinology & Nutrition and Internal Medicine. All patients were informed of the genetic tests performed and signed the informed consent. Clinical characteristics of patients are described individually in each of the cases presented throughout this work.

Genetic analysis

The genomic DNA (gDNA) from probands was extracted from EDTA-treated whole blood samples using Chemagen (Chemagic DNA extraction special, Perkin Elmer Inc, Baesweiler, Germany). DNA quantification was performed using a fluorimeter Invitrogen Qubit 2.0. Genetic analysis was performed by Next Generation Sequencing (NGS) using a customized panel of 500 genes. Library preparation and exome enrichment steps were performed according to the manufacturer´s workflow (Nimblegen, Roche) and it was sequenced using HiSeq4000 system Sequencing, Illumina. NGS data was suitable for analysis after passing the quality parameters established in our laboratory: a number of reads more than 30× in the 99% of the target bases. Sanger sequencing was used to confirm the presence of the new variants.

In silico analysis

Bioinformatic analysis was performed using algorithms developed by our bioinformatics unit. Briefly, sequences were mapped to the *CRCh37/hg19* human reference sequence and databases used for analysis were Human Gene Mutation Database (HGMD®) (http://www.hgmd.cf.ac.uk/ac/index.php) from BIOBASE Corporation; Online Mendelian Inheritance in Man (www.omim.org); Gene Tests (www.genetests.org). Variant annotation was carried out with Ensembl´s variant Effect Predictor Tool and was based on the transcripts ENST00000264005.5-*LCAT*,ENST00000236850.4-*APOA1*,ENST00000558518-*LDLR*, ENST0000023324-*APOB*, ENST00000302118-*PCSK9* and ENST00000374338-*LDLRAP1*, ENST00000265404.2-*STAP1*, ENST00000260645.1-*ABCG5*, ENST00000272286.2-*ABCG8 In silico* predictors of pathogenicity used were CADD (Combined Annotation Dependent Depletion; Damaging|s>=14), Polyphen (Polymorphism Phenotyping; Benign|s<0.03), MutAssesor (Benign|s<1.12), Fasthmm (Damaging|s<=-1) and Vest (Benign|s<0.17). Scores of conservation used: Gerp2 (Conserved|s>2.45), PhasCons, Phylop in relation to thirteen species. MaxEntScan, NNSplice, GeneSplicer and Human Splicing Finder were used as splicing predictors. The factors taken into consideration were Damaging or Possibly Damaging to three or more pathogenicity predictors and conservation for Gerp2. The interpretation of sequence variants was carried out according to the recommendations of The American College of Medical Genetics and Genomics (ACMG) [11]. The files were uploaded in BAM format for analysis using Alamut Visual V.2.8.0 (Interactive Biosoftware; France).

Results

Case 1

A 27-years-old male with mixed dyslipidemia showed "white halo" in eye. He had familial antecedent of corneal opacity (father and grandfather), without loss of seeing. The patient was diagnosed of corneal lipoid dystrophy in fish-eye with prominent gerontoxon in the ophthalmology unit.

Complete biochemical analysis was performed, highlighting a very low level of HDL-c and raised levels of triglycerides, liver enzymes and homocysteine levels in serum (Table 1).

Hematologic and coagulation tests were normal. Serology about HCV, CMV, HIV, EBV and toxoplasmosis were negatives. Splenomegaly with normal liver without anemia or kidney disease was observed.

A suspicion of fish-eye disease was supposed due to clinical

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and biochemical findings. Differential diagnosis included Schnyder corneal dystrophy, familial *LCAT* deficiency and Tangier disease.

A missense variant in *LCAT* *NM_000229.2:c.491G>A* p.(Arg164His) was found an homozygous and confirmed by Sanger sequencing (Figure 1). In silico analysis showed a very low allelic frequency, high conservation and the bioinformatics prediction tools classified the variant as damaging (Table 2). No pathogenic variants were found in *ABCA1*. It was also found a common polymorphism in *MTHFR*, *NM_005957.4:c.665C>T*; (p.Ala222Val), that is related with hyperhomocysteinemia.

Table 1: Highlights of biochemical analysis of patient with *LCAT* variant.

Analyte, Units	Male 27 - year - old	Reference values
Glucose, mg/dL	98	(70 - 110)
Creatinine, mg/dL	1.01	(0.6 - 1.3)
Urea, mg/dL	22	(15 - 45)
Urate, mg/dL	8.5	(3.5 - 7.2)
Creatine kinase (CK), U/L	174	(38 - 174)
Protein, g/dL	8.8	(6.4 - 8.3)
Bilirubin total, mg/dL	1.96	(0.2 - 1.2)
(AST), U/L	29	(4 - 50)
(ALT), U/L	47	(5 - 40)
γ - glutamyltransferase (GGT), U/L	290	(10 - 50)
Alkaline phosphatase, U/L	119	(53 - 128)
Cholesterol, mg/dL	212	< 200
LDL colesterol, mg/dL	182	< 130
HDL colesterol, mg/dL	< 5	>40
Triglyceride, mg/dL	747	(25 - 200)
Homocysteine, uM/L	> 50.0	(5 - 12)

Case 2

A 58-year-old woman with xanthomas, corneal clouding and paternal and maternal antecedents of isquemic cardiopathy was remitted to our service for genetic testing. The patient had extremely low levels of apoA-I (<16 mg/dL) and HDL-c (6 mg/dL) in serum (Table 3). We also tested the patient's daughter, a 21-year-old woman with xanthomas, low levels of apoA-I (99 mg/dL) and normal levels of HDL-c (42 mg/dL) in serum. Sanger sequencing was used to confirm the familiar variant in *APOA1* Figure 2.

The genetic analysis of the patient showed a frameshift variation in homozygosity in *APOA1*, *NM_000039.2:c.85dupC*;p.(Gln29Profs*29) (Figure 3). This variant was confirmed by Sanger sequencing. The analysis of the patient's daughter showed the variant in *APOA1*, *NM_000039.2:c.85dupC*;p.(Gln29Profs*29) in heterozygous (Figure 4).

Case 3

Three patients remitted to our unit with suspicious of familiar hypercholesterolemia (FH) showed no pathogenic variants at the *LDLR*, *APOB*, *PCSK9* and *LDLRAP1*. Characteristics of patients are shown in Table 4. In the extended analysis to genes related with lipid metabolism, we found variants in heterozygous at the *STAP1* gene in each patient. Three variants have been previously reported.

Figure 1: Snapshot of the Alamut window for the *LCAT*, NM_000229.2: c.491G>A p.(Arg164His).

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Table 2: Bioinformatic analysis of variants found in the cases 1, 2, 3 and 4.

ID patient	Variant cDNA, gDNA (hg19)	GENE	GnoMAD	CADD	Sift	Polyphen2	MutAssesor	Fathmm	VEST	Gerp2	ACMG
Case 1	NM_000229.2: c.491G>A; p.(Arg164His) Chr16:g. 67976606G>A	LCAT	0.000008	27	Damaging	Damaging	Damaging	Damaging	Damaging	Conserved	*p*
Case 3-1	NM_012108.2:c.35G>A p.(Arg12His) Chr4:g. 68424562G>A	STAP1	0.000255	Damaging	Damaging	Damaging	Damaging	Possibly Damaging	Possibly Damaging	Conserved	VUS
Case 3-2	NM_012108.2:c.120+6T>C p.(?) Chr4:g. 68424653T>A	STAP1	0.004479	*	*	*	*	*	*	*	LB
Case 3-3	NM_012108.2:c.526C>T p.(Pro176Ser) Chr4:g. 68447185C>T	STAP1	0.000308	Damaging	Damaging	Damaging	Damaging	Possibly Damaging	Damaging	Conserved	VUS
Case 4	NM_022437.2:c.788G>A p.(Arg263Gln) Chr2:g.44079831G>A	ABCG8	0.000141	Damaging	Damaging	Damaging	Possibly Damaging	Benign	Damaging	Conserved	VUS
	NM_022437.2:c.1083G>A p.(Trp361Ter) Chr2:g. 44099233G>A	ABCG8	0.000937	Damaging	Damaging	Benign	Benign	Possibly_Damaging	Benign	Conserved	*p*

Table 3: Highlights of biochemical analysis of patient with *APOA1* variant.

Analyte, Units	Mother, 58 - year - old	Daughter, 21 - year - old	Reference values
Apolipoprotein A - I, mg/dL	<16	99	(101 - 223)
Apolipoprotein B, mg/dL	90	50	(53 - 182)
Ratio apoA - I/apoB		1.98	
Ratio apoB /apoA - I		0.5	
Lp (a), mg/dL	6.3		(< 30)
Plasma homocysteine, uM/L	6.6	8.9	(5 - 12)
Cholesterol, mg/dL	159	111	(< 200)
HDL cholesterol, mg/dL	6	42	(> 35)
LDL cholesterol, mg/dL	137	61	(< 130)
Triglyceride, mg/dL	78	39	(25 - 200)

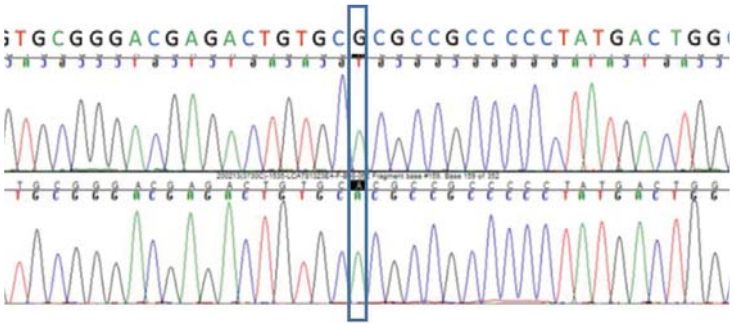

Figure 2: Confirmation by Sanger sequentiation of *LCAT*, NM_000229.2: c.491G>A p.(Arg164His).

Patient 3.1 carried the variant *STAP1:NM_012108.3:c.35G>A*:p.(Arg12His) and patient 3.2 carried the *STAP1:NM_012108.3:c.526C>T*:p.(Pro176Ser), these variants showed frequencies less than 0.03%, were conserved and the *in silico* predictors showed damage. Patient 3.3 carried the variant *STAP1:NM_012108.3:c.120+6T>C*, this variant did not show impact according to splicing predictors (Table 2). The variant c.35G>A was found in the sister of patient 3.1presenting LDL-c>155 mg/dL (Figure 5). In the rest of the patients we were unable to carry out segregation studies because we did not get a sample.

Case 4

A 55-year-old woman with hypercholesterolemia total cholesterol 282 mg/dl, LDL-c 194 mg/dl and HDL-c 76 mg/dl, normal triglycerides 56 mg/dl , lp(a) 10.2 mg/dl and homocysteinemia 10.5 mg/dl Table 5. The patient have familial antecedent of vascular disease, mother with ischemic heart disease. The patients were being treated with statin and poor control, being referred for genetic study. The result of the genetic study of FH including the standard analysis of genes *LDLR*, *APOB*, *PCSK9* and *LDLRAP1* showed no pathogenic variants. In the extended analysis to other genes involved in lipid metabolism we found two variants in heterozygous in *ABCG8_NM_022437.2*: *c.788G>A*;p.(Arg263Gln) and *c.1083G>A*;p.(Trp361*), both showed impact according to bioinformatic tools (Table 2). The variant p. (Arg263Gln) is a missense-type variant and the second variant, p. (Trp361 *) is a stop variant

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Figure 3: Snapshot of the Alamut window for the *APOA1* mutation in homozygosis.

(null allele), both of them have been described in the literature associated with sitosterolemia [12-14].

Discussion

In this work, we have reported four cases of rare dyslipidemias. The genetic analysis help in final confirmation of the diagnosis. The variant found in *LCAT c.491G>A*;p.(Arg164His) had been previously reported in three siblings with typical triad of Familial Deficiency of LCAT: corneal opacity, hemolytic anemia and kidney dysfunction. Functional study showed complete deficiency of the LCAT enzyme [15].

Table 4: Characteristics of the patients with *STAP1* variant.

ID patient	Age	Sex	LDL-c mg/dL	Reference values	Family History
Case 3-1	76	Male	190-249	(< 130)	No
Case 3-2	56	Female	190-249	(< 130)	Yes
Case 3-3	41	Male	250-329	(< 130)	Yes

Table 5: Biochemical analysis of patient with sitosterolemia.

Analyte, Units	Female 54 - year - old	Reference values
Red blood cell count, 10^6mL	3,45	(4.00 - 5,50)
Hematocrit, %	31,7	(36 - 47)
Hemoglobin, g/L	11,1	(12.0 - 17.5)
Mean Corpuscular Volume, fL	92	(82.0 - 98.0)
White blood cell count, 10^3mL	4,1	(4.00 - 11.00)
Platelet count 10^3mL	144	(140 - 400)
Mean Platelet Volume (fL)	13	(7,50 - 11,00)
Cholesterol, mg/dL	282	< 200
LDL cholesterol, mg/dL	194	< 130
HDL cholesterol, mg/dL	76	> 40
Triglyceride, mg/dL	56	(25 - 200)
Glucose, mg/dL	84	(70 - 110)
Protein, g/dL	7,3	(6.4 - 8.3)
Creatinine, mg/dL	0,65	(0.6 - 1.3)
Urate, mg/dL	2,5	(3.5 - 7.2)
(AST), U/L	17	(4 - 50)
(ALT), U/L	14	(5 - 40)

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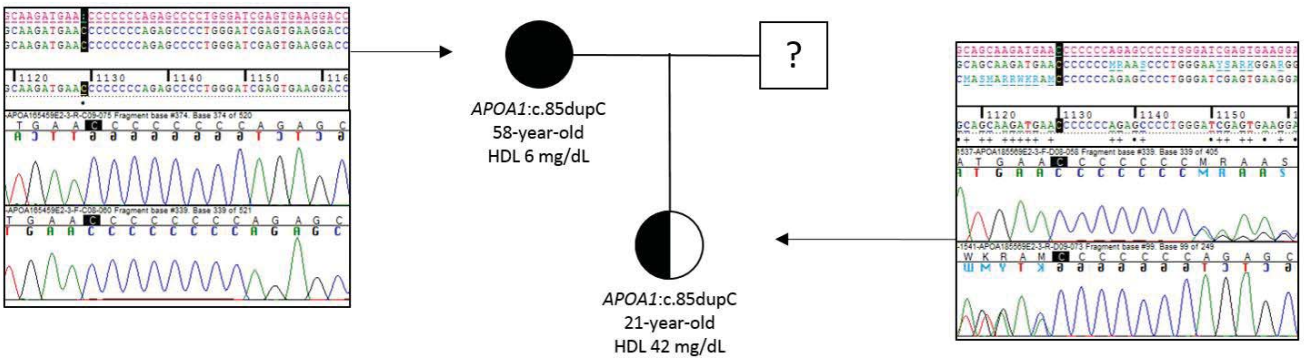

Figure 4: Confirmation by Sanger sequencing of *APOA1*, NM_000039.2:c.85dupC;p.(Gln29Profs*29).

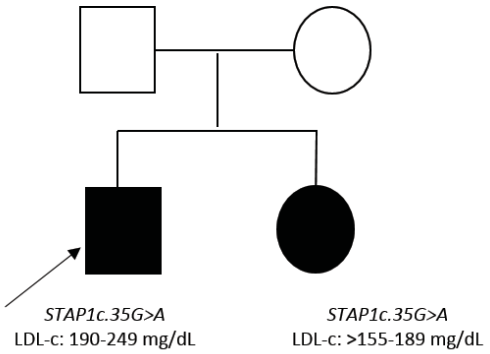

Figure 5: Pedigree of family carrier of *STAP1*:c.35G>A.
The index case is indicated with an arrow; circle and square symbols represent women and men respectively; shadow filled symbol indicates the affected members with *STAP1*.

However, our patient exhibited a mild phenotype despite of display of same variant. In other variants of *LCAT*, different clinical and biochemical pictures have been found among family members and suggesting the existence of others factors as environmental factors or other minor genes that may be involved in the clinical presentation of each patient.

The variant *APOA1: c.85dupC*;p.(Gln29Profs*29) had been previously described as an autosomal dominant cause of apoA-I deficiency [16]. ApoA-I deficiency is generally associated with markedly increased risk of atherosclerotic cardiovascular disease. However, in this study we identified a frameshift mutation of the *APOA1* gene as the molecular basis of apoA-I deficiency in a 58-year-old woman without isquemic cardiopathy. Patient's daughter showed the variant in heterozygous without alteration neither the lipid profile or in clinical signs confirming cosegregation in this variant.

There is controversy about the role of STAP1 in FH [17]. Some studies have showed lack of cosegregation in some variants found in *STAP1* in FH patients [18]. In this study we found three variants previously described in patients with hypercholesterolemia. The variant *c.120+6T>C* did not show impact; the variant *c.526C>T*:p.(Pro176Ser) was found in a patient but we could not analyze relatives and the variant *c.35G>A*:p.(Arg12His) was in a patient and his daughter. Further studies of cosegregation and functional studies should be performed in order to confirm the role of *STAP1* in FH.

To date an estimated 30 variants have been described in each of the genes *ABCG5* and *ABCG8* associated with sitosterolemia (The Human Gene Mutation Database) [19]. According to The Exome Aggregation Consortium (ExAC) exome browser, 1 in ~220 individuals show loss of function (LOF) mutations in *ABCG5* or *ABCG8* genes [10]. Nevertheless, the prevalence of Sitosterolemia is under 1/1.000.000 indicating that could be underdiagnosed. Quantification of phytosteroles in our patients could be useful but we have not this possibility, however we were able to analyze the genes responsible for sitosterolemia and thus to contribute to the diagnosis of this disease.

There is no doubt that the genetic analysis using customized panels of genes related with metabolism of lipids is a useful tool to confirm or even to detect low frequency dislipidemias. In this work, we have reported four dyslipidemias of genetic origin due to variants of low frequency confirming the genetic diagnosis in these patients. The importance of reporting these cases has an impact on appropriate patient's management as they allow an early diagnosis.

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