

R E V I E W

Monogenic hyperlipidemias

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Summary. Monogenic hyperlipidemias are a group of inherited disorders characterized by elevated plasma concentrations of lipids and lipoproteins. High plasma concentrations of lipids are the most frequent risk factor for cardiovascular disease. Monogenic hyperlipidemias are a minor cause with respect to multifactorial hyperlipidemias. Diagnosis is based on clinical findings and lipid panel measurements. Genetic testing is useful for confirming diagnosis and for differential diagnosis, recurrence risk calculation and prenatal diagnosis in families with a known mutation. Monogenic hyperlipidemias can have either autosomal dominant or recessive inheritance. (www.actabiomedica.it)

Key words: hyperlipidemia, cholesterol, triglycerides, LDL, HDL

Monogenic hyperlipidemias are a group of inherited disorders characterized by elevated plasma concentrations of lipids, such as cholesterol and triglycerides (TG), and lipoproteins, such as chylomicron, very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) (1). High plasma concentrations of lipids, especially low density lipoprotein cholesterol (LDL-C), lead to early onset atherosclerosis and are the most frequent risk factor for cardiovascular disease (2), whereas high plasma levels of HDL-C are associated with a lower risk of cardiovascular disease (2). Monogenic hyperlipidemias are a minor cause with respect to multifactorial hyperlipidemias (3).

Monogenic hyperlipidemias are classified on the basis of the primary lipid or lipoprotein anomaly, such as elevated concentrations of LDL-C, low concentrations of HDL-C, or elevated TG. Primary disorders with elevated plasma concentrations of LDL-C include familial hypercholesterolemia (FH), autosomal

dominant hypercholesterolemia types 2, 3, 4 and 5, and autosomal recessive hypercholesterolemia. The most frequent condition is FH, characterized by very high LDL-C and xanthomas (patches of yellowish cholesterol build-up) around the eyelids and in the tendons of the elbows, hands, knees and feet. Heterozygous FH has a prevalence of 1:200-250, while homozygous FH (including true homozygosity and compound heterozygosity) is much rarer with a prevalence of 1:160000-250000 (4).

Since plasma levels of HDL-C are inversely related to cardiovascular risk, hereditary disorders that decrease HDL levels are of clinical importance, though rare. They include Tangier disease and homozygous deficiencies in apolipoprotein A-1 or lecithin-cholesterol acyltransferase (2).

Primary hypertriglyceridemias result from genetic defects in metabolism or synthesis of TG. Their prevalence is estimated at less than 0.2%. Except for lipoprotein lipase deficiency, which manifests in child-

hood, they usually manifest in adulthood (5). Disorders in this category include familial chylomicronemia (associated with deficiencies in LPL or APOC2), severe hypertriglyceridemia (associated with deficiencies in APOA5, LMF1 or GPIHBP1), infantile hypertri-

glyceridemia and hyperlipoproteinemia type 3. Clinical findings may include eruptive or palmar xanthomas and very high TG levels which are associated with increased risk of recurrent pancreatitis and premature cardiovascular disease.

Table 1. Genes associated with various forms of monogenic hyperlipidemia

<i>Gene</i>	OMIM gene	Disease	OMIM disease	Inheritance	Function
<i>APOB</i>	107730	Hypercholesterolemia, B	144010	AD	Major protein constituent of chylomicrons, LDL, VLDL
<i>LDLR</i>	606945	FH	143890	AD	Endocytosis of LDL
<i>PCSK9</i>	607786	FH3	603776	AD	Crucial regulator of plasma cholesterol homeostasis
<i>LDLRAP1</i>	605747	ARH	603813	AR	Endocytosis of LDLR in hepatocytes and lymphocytes
<i>APOE</i>	107741	Hyperlipoproteinemia, type III	617347	AD	Lipoprotein-mediated lipid transport between organs via plasma and interstitial fluids
<i>USF1</i>	191523	Combined hyperlipidemia 1	602491	AD	bHLH transcription factor that binds pyrimidine-rich initiator elements, E-box motifs
<i>ABCA1</i>	600046	Primary hypoalphalipoproteinemia	604091	AR	Cholesterol efflux pump for lipid removal from cells
<i>APOA1</i>	107680	Primary hypoalphalipoproteinemia	604091	AR	Promotion of cholesterol efflux from tissues to liver
<i>LCAT</i>	606967	FED	136120	AR	Esterifying enzyme required for cholesterol transport
<i>LPL</i>	609708	Hyperlipoproteinemia type I	238600	AR	Hydrolysis of triglycerides of circulating chylomicrons, VLDL
<i>APOC2</i>	608083	Apolipoprotein C-II deficiency	207750	AR	Activator of lipoprotein lipase
<i>GPIHBP1</i>	612757	Hyperlipoproteinemia type ID	615947	AR	Lipolytic processing of chylomicrons
<i>GPD1</i>	138420	HTGTI	614480	AR	Synthesis of glycerol-3-phosphate, NAD ⁺
<i>LMF1</i>	611761	Combined lipase deficiency	246650	AR	Maturation and transport of lipoprotein lipase
<i>APOA5</i>	606368	Familial hypertriglyceridemia	145750	AD	Regulator of plasma triglyceride levels

FH=familial hypercholesterolemia; ARH=autosomal recessive hypercholesterolemia; FED=Fish-eye disease; HTGTI=transient infantile hypertriglyceridemia; AD=autosomal dominant; AR=autosomal recessive.

Diagnosis is based on clinical findings and lipid panel measurements, including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides. Genetic testing is useful for confirming diagnosis and for differential diagnosis, recurrence risk calculation and prenatal diagnosis in families with a known mutation. Differential diagnosis should consider secondary causes of hypercholesterolemia and hypertriglyceridemia, such as diabetes mellitus (types I and II), obesity, metabolic syndrome, hyperthyroidism, medications, nephrotic syndrome, acute hepatitis, alcohol abuse and pregnancy. Primary causes of hyperlipidemia also require differential diagnosis among themselves.

Monogenic hyperlipidemias can have autosomal dominant or autosomal recessive inheritance (Table 1). Pathogenic variants may be missense, nonsense, splicing or small indels. Large deletions/duplications have been reported in *APOB*, *LDLR*, *LDLRAP1*, *APOE*, *ABCA1*, *APOA1*, *LCAT*, *LPL*, *APOC2*, *GPIHBP1* and *APOA5*.

We use a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes, and MLPA to detect duplications and deletions in *APOB*, *LDLR*, *LDLRAP1*, *APOE*, *ABCA1*, *APOA1*, *LCAT*, *LPL*, *APOC2*, *GPIHBP1* and *APOA5*. Worldwide, 30 accredited medical genetic laboratories in the EU and 8 in the US, listed in the Orphanet (6) and GTR (7) databases, respectively, offer genetic tests for monogenic hyperlipidemias. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (8).

Conclusions

We created a NGS panel to detect nucleotide variations in coding exons and flanking regions of all

the genes associated with cardiac disorders. When a suspect of hyperlipidemia is present, we perform the analysis of all the genes present in this short article.

In order to have a high diagnostic yield, we developed a NGS test that reaches an analytical sensitivity (proportion of true positives) and an analytical specificity (proportion of true negatives) of $\geq 99\%$ (coverage depth $\geq 10x$).

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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