Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolemia: a case-control study.

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Background / Objective

Familial hypercholesterolemia (FH) is an autosomal dominant disorder caused by mutations in LDLR, APOB, or PCSK9 in approximately 80% of the cases. It has been shown that mutation negative FH patient may be carrier of the polygenic form of familial hypercholesterolemia (pFH). pFH can be detected based on LDL cholesterol (LDL-C)-associated single nucleotide polymorphisms (SNPs).

Methods

Study subjects and methods.

To address whether polygenic forms may explain hypercholesterolemia in FH mutation negative patients, we gathered data from 125 mutation-negative (FH-) and 295 mutation-positive FH patients (FH+), as well as from 933 controls and genotyped the patients for 6 GLGC SNPs with a RT-PCR method.

	Controls N=933	FH/M- N=125	FH/M+ N=295	Controls vs FH/M-	Controls vs FH/M+	FH/M+ vs FH/M-
Age, years	42.3±11.9	46.9±14.0	41.8±16.3	p<0.001	ns	p=0.004
Sex, % M	73.2 %	48.0 %	48.8 %	p<0.001	p<0.001	ns
BMI, Kg/m ²	25.1±3.8	24.8±3.8	24.7±4.0	ns	ns	ns
CVD, n (%)	43 (4.6%)	5 (4.0%)	32 (10.8%)	p=0.019	p<0.001	p=0.019
TC, mg/dl	193.5±39.9	290.5±45.8	345.1±80.7	p<0.001	p<0.001	p<0.001
TG, mg/dl	100.3±59.4	133.3±74.5	116.6±61.9	p<0.001	p<0.001	p=0.037
HDL-C, mg/dl	56.8±14.8	65.7±31.3	59.5±20.6	p<0.001	ns	p=0.013
LDL-C, mg/dl	117.0±36.3	200.8±48.3	259.2±71.1	p<0.001	p<0.001	p<0.001
DMT-2, n (%)	6 (0.6%)	4 (3.2%)	7 (2.4%)	p=0.005	p=0.008	ns
DLCNS = 3-6, n (%)		103 (82.4%)	103 (34.9%)			
DLCNS = 6-8, n(%)	-	18 (14.3%)	88 (29.8%)			p<0.001
DLCNS >8, n (%)	-	6 (5.0%)	105 (35.6%)			

Table 1. Clinical characteristics of the study population: FH/M-, patients with familial hypercholesterolaemia without a known mutation; FH/M+, patients with familial hypercholesterolaemia with a known mutation. BMI, body mass index; CVD, cardiovascular disease; TC, total cholesterol; TG, triglyceridemia; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol; DMT2, type 2 diabetes mellitus; DLCNS, Dutch lipid criteria network score; ns, not significant.

Genetic risk score computation.

The Genetic Risk Score (GRS) was calculated based on the six selected SNPs. The method used was weighted method (weighted GRS).

	chromosome number	gene	minor allele	common allele	GLGC weigh
rs629301	1	CELSR2	G*	A	0.15
rs1367117	1	APOB	A*	G	0.10
rs4299376	2	ABCG8	G*	T	0.071
rs6511720	19	LDLR	T	G*	0.18
rs429358	19	APOE [§]	C	T	-
rs7412	19	APOE [§]	T	C	-
ε2ε2	19	APOE			-0.9
ε2ε3	19	APOE			-0.4
ε2ε4	19	APOE			0.2
ε3ε3	19	APOE			0
ε3ε4	19	APOE			0.1
ε4ε4	19	APOE			0.2

Table 2. 6-SNP LDL-C gene score calculation. G, guanine; A, adenine; T, thymidine; C, cytosine. * Risk alleles (LDL-C raising).

[§] APOE weights were based on haplotypic effects taken from Bennet Bennet AM et al. (JAMA 2007; 298: 1300-11)

Results

Mutation-negative FH patients had significantly higher 6-SNP (0.69 ± 0.20) score than controls or mutation-positive FH patients (0.62 ± 0.21 and 0.58 ± 0.24, p<0.001 respectively). We observed lower scores in mutation-positive FH patients compared with controls and mutation negative subjects (p=0.037 and p<0.001, respectively).

Figure 1. Comparison of LDL-C weighted gene score between cases (FH/M+ and FH/M-) and controls.

DLCNS	FH/M- N=125	FH/M+ N=295	p
LDL-C mg/dl			
3-6	192,4 ± 42,2	208,2 ± 41,2	0,053
6-8	242,2 ± 41,3	260,6 ± 46,0	0,183
>8	249,6 ± 27,6	318,8 ± 108,6	0,043
6-SNPs score			
3-6	0,69 ± 0,19	0,60 ± 0,24	0,006
6-8	0,70 ± 0,25	0,57 ± 0,23	0,031
>8	0,74 ± 0,06	0,56 ± 0,24	0,079

Table 3. Comparison of LDL-C plasma levels and LDL-C weighted gene score between cases (FH/M+ and FH/M-) and controls in DLCNS groups.

Figure 2. Genetic distribution in clinical FH subjects. pFH, polygenic FH subjects with a LDL-C weighted gene score >0,66.

Figure 3. Distribution of weighted LDL-C gene scores. (A) Controls versus patients with familial hypercholesterolaemia without a known mutation (FH/M-). (B) Controls versus patients with familial hypercholesterolaemia with a known mutation (FH/M+). (C) FH/M- versus FH/M+.

Conclusions

The present study demonstrates the utility of SNP score analysis for identifying polygenic FH in a cohort of clinically diagnosed FH patients by showing that small-effect common SNPs may cumulatively elevate LDL-C levels. In addition, the genetic risk score can be used also as a marker of the severity of hypercholesterolemia in FH patients.