High Polygenic SNP scores do not exclude monogenic Familial Hypercholesterolaemia

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Introduction

Mutations in three different genes (*LDLR*, *APOB* and *PCSK9*) affecting the LDL-receptor pathway are known to cause autosomal dominant Familial Hypercholesterolaemia (FH). In approximately 20% of probands with a definite clinical diagnosis of FH no mutations are detected suggesting that there may be FH causing mutations located in other genes. However it is proposed that polygenic SNP scores above the median in mutation negative patients infer a low likelihood of monogenic FH. LDL-C SNP scores in the 6th-10th decile of the distribution reported by Talmud *et al* ., (2013)¹ are considered to have high likelihood of polygenic aetiology.

Methods

DNA samples from probands with a Dutch Lipid Clinic Network (DLCN) score of 6 or greater were tested using a bespoke MALDI-TOF Sequenom mass spectrometry assay incorporating the low-density lipoprotein cholesterol gene score reported by Talmud et al., to distinguish patients with polygenic and monogenic hypercholesterolaemia^{1,2}. Samples in which no FH causing mutations were identified underwent further analysis by Next Generation Sequencing (NGS, MiSeq/Multiplicom). Captured regions included the entire coding region and untranslated regions of *LDLR*, *PCSK9* and *APOE* genes as well as a selected region of the *APOB* gene (Exon 26 p.3395 to p.3701). We compared the frequency of pathogenic mutations among FH probands in relation to deciles of polygenic SNP scores.

Results

Of the 478 FH probands tested, 48 (10.0%) had LDL-C SNP scores in the 1st-3rd decile indicating low likelihood of polygenic aetiology, 79 (16.5%) had LDL-C SNP scores in the 4th-5th decile indicating borderline likelihood of polygenic aetiology and the vast majority 363 (73.5%) had LDL-C SNP scores in the 6th-10th decile indicating high likelihood of polygenic aetiology (Figure 1). Of the probands with high likelihood of polygenic aetiology 68 (19.2%) were mutation positive. Of the 121 mutation positive probands 68 (56.2%) had a polygenic score in the 6th-10th decile suggesting high likelihood of polygenic aetiology and 49 (40.5%) of mutation positive FH patients had polygenic SNP scores in the top 3 deciles (Figures 2/3). Four unrelated probands with the pathogenic *APOE* mutation (*APOE* c.500_502delTCC p.(Leu167del) had LDL-C SNP scores in the 6th-10th decile that would be considered compatible with polygenic hypercholesterolaemia (Table 1).

Figure 1: FH probands by likelihood of polygenic aetiology

Figures 2/3: Percentage of mutation + & mutation – probands by decile

Proband	APOE pathogenic variant	Gender	Age	LDL-C SNP score	LDL-C SNP decile
NUT 157	APOE c.500_502delTCC p.(Leu16Tdel)	F	43	1.010	8th
SUN 092	APOE c.500_502delTCC p.(Leu16Tdel)	F	45	1.007	7th
DUR 111	APOE c.500_502delTCC p.(Leu16Tdel)	F	32	1.020	7th
SUN 155	APOE c.500_502delTCC p.(Leu16Tdel)	F	51	1.026	8th

Table 1: LDL-C SNP scores of probands with APOE pathogenic variant

Conclusion

In our population, the probability of finding monogenic disease was two times higher among probands with LDL-C SNP scores in the 1st-5th decile compared with those in the 6th-10th decile (mutation yield 41.7% cf. 19.2%). However SNP scores in the top 3 deciles are prevalent among patients with monogenic FH and were observed in 40.5% of this group. Mutations in the *APOE* gene can cause autosomal dominant Familial Hypercholesterolaemia but this gene is not routinely screened in some genetic laboratories. The four probands we identified had LDL-C SNP scores that would be considered compatible with polygenic aetiology. Genetic laboratories which do not routinely sequence the *APOE* gene may miss such patients and misclassify them as polygenic hypercholesterolaemia. Screening of the *APOE* gene is warranted in the setting of molecular diagnosis of FH along with the *LDLR*, *APOB* and *PCSK9* genes. Low-density lipoprotein cholesterol gene scores do not reliably distinguish patients with monogenic familial hypercholesterolaemia from those with polygenic hypercholesterolaemia. LDL-C SNP scores should be interpreted in relation to the severity of the lipid phenotype such as age and gender specific LDL-C centiles.

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References

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