Whole-Exome sequencing in patients with familial hypercholesterolemia without functional mutation in candidate genes

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Introduction

Familial hypercholesterolemia (FH) is a common autosomal-dominant disorder caused by mutations in four known genes (LDLR, APOB, PCSK9 and APOE). However, about 20-40% of patients with the clinical diagnosis of FH are mutation negative, indicating that there are new genes still to be discovered.

Objective

Whole exome sequencing could allow us to discover new genes involved in the FH

Methods

Sequencing analysis

1. Checked all loss-function and missense variants predicted as damaging in *LDLR* and all rare variants annotated as pathogenic in ClinVar in *PCSK9*, *LDLR* and *APOB*.
2. We analysed the binding between LDLc-LDLr in all FH subjects by ELISA
3. Family analysis: pathogenic rare variants present in all affected family members and not present in non-affected family members
4. We ran single variant association using firth logistic regression to compare our cases with controls from two European cohort studies with LDLc ≤ 150 mg/dL.

Results

Family segregation p.Cys216Arg in *LDLR*

Family analysis p.Glu277Ter in *BRD7* gene

Table 1. Mutations in candidate genes

Gene	Variant	Patients carried	Frequency in general population	Bioinformatic analysis	Clin Var	Previously described in FH
<i>LDLR</i>	p.(Asp175Gly)	1 patient	0%	Pathogenic	-	No
<i>LDLR</i>	p.(Cys216Arg)	4 related patients	0%	Pathogenic	Pathogenic	Yes
<i>LDLR</i>	p.(Val827Ile)	1 patient	0%	Pathogenic	Uncertain	No
<i>LDLR</i>	p.(Glu277Lys)	2 unrelated patient	0%	Pathogenic	Likely Bening	No
<i>APOB</i>	p.(Lys3344Glu)*	2 unrelated and 2 related patient	0%	Pathogenic	Uncertain	No
<i>APOB</i>	p.(Ala3396Val)*	1 patient	0%	Pathogenic	-	No
<i>APOB</i>	p.(Ser3294Pro)	1 patient	0.019%	Probably damaging	Bening/ Uncertain	No
<i>APOB</i>	p.(Ser3279Gly)	2 unrelated patient	0.30%	Probably damaging	Bening/ Uncertain	No
<i>APOB</i>	p.(Asn3106Ser)	1 patient	0%	Probably damaging	-	No
<i>APOB</i>	p.(Gly3054Arg)*	1 patient	0%	Probably damaging	-	No

*These patients present affected binding between LDLr-LDL particle

- BRD7 is a bromodomain-containing protein 7, which has been involved in atherosclerosis.
- Inhibition of Brd7 accelerates atherosclerosis lesion formation in ApoE^{-/-} mice.

CONCLUSIONS

- We found new missense variants in *LDLR* and *APOB* and a new gene (BRD7) which could be involved in FH.