Clinical management and genetic architecture of severe hypercholesterolemia in Finland

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Aim

To characterize the prevalence, clinical management, and underlying genetic architecture of severe hypercholesterolemia, we studied individuals with LDL cholesterol ≥ 5 mmol/l in the prospective GeneRISK study.

Study population

The GeneRISK study

- Randomly ascertained participants from Southern Finland
- 7349 subjects, aged 45-65 years, 36,1% males
- Clinical checkup, blood lipids, questionnaire at baseline, follow-up after 1,5 years

Prevalence of severe hypercholesterolemia:

- Mean LDL-C: 3,4 mmol/l
- 5,0% (N = 366) with LDL-C ≥ 5 mmol/l

Hypercholesterolemia and 10-year risk for cardiovascular diseases (CVD)

CVD risk among cases with LDL-C ≥ 5 mmol/l (N = 366)

11,1% of subjects at high CVD risk (risk >10%) had LDL-C ≥ 5 mmol/l

All GeneRISK participants received information of their personal 10-year CVD risk, which is based on age, smoking, blood pressure, lipids and a polygenic risk score (49 000 SNPs) (3).

Hypercholesterolemia mutations

Mutation screening:

Genotyping and whole-exome sequencing (N=206, LDL-C ≥ 5 mmol/l)

Results:

- > No carriers of the 7 Finnish *LDLR* founder mutations
- > A novel, likely pathogenic mutation *LDLR* R574L identified:
  - Once previously associated with familial hypercholesterolemia (4)
  - Frequencies in gnomAD database: Finnish: 0,0002 other populations: 0
  - Pathogenic *in silico* predictions in all 8 tested programs

Birth places of *LDLR* R574L carriers (N=7)

Management of hypercholesterolemia

At baseline

	CVD risk >10%, LDL ≥ 5	CVD risk <10%, LDL ≥ 5
N (male %)	188 (45,2%)	178 (33,1%)
Age (years)	57,6 $\pm$ 5,1	55,3 $\pm$ 5,2***
BMI (kg/m ²)	28,3 $\pm$ 4,1	27,5 $\pm$ 4,5*
Systolic BP (mmHg)	134,8 $\pm$ 16,7	127,7 $\pm$ 17,0***
Diastolic BP (mmHg)	89,7 $\pm$ 10,3	85,1 $\pm$ 10,3***
Total cholesterol (mmol/l)	8,1 $\pm$ 0,9	7,4 $\pm$ 0,3***
HDL-C (mmol/l)	1,6 $\pm$ 0,5	1,5 $\pm$ 0,3
LDL-C (mmol/l)	5,8 $\pm$ 0,8	5,3 $\pm$ 0,2***
Triglycerides (mmol/l)	1,7 $\pm$ 0,6	1,4 $\pm$ 0,5***
Smoking (yes)	25,0%	14,0%*
BP lowering medication (yes)	20,7%	13,5%
Lipid lowering medication (yes)	4,3%	3,9%
Previous hypercholesterolemia (yes)	86,7%	84,3%

BP: blood pressure; * p<0,05; ** p<0,01; *** p<0,001

At follow-up

	CVD risk >10%, LDL ≥ 5	CVD risk <10%, LDL ≥ 5
N (male %)	127 (44,9%)	114 (34,3%)
My results were surprising	48,8%	21,9%***
My results were concerning	58,3%	35,1%**
My results were useful	88,2%	90,4%
Seen a doctor during follow-up	37,8%	14,9%***
Lipid lowering medication	33,9%	17,9%*
Changes in:		
BMI (kg/m ²)	0 $\pm$ 1,4	0,2 $\pm$ 1,3*
Total cholesterol (mmol/l)	-1,6 $\pm$ 1,6	-0,8 $\pm$ 1,1***
HDL-C (mmol/l)	0 $\pm$ 0,3	0 $\pm$ 0,2
LDL-C (mmol/l)	-1,6 $\pm$ 1,5	-0,8 $\pm$ 1,1***
Triglycerides (mmol/l)	0 $\pm$ 0,6	0,1 $\pm$ 0,5*

* p<0,05; ** p<0,01; *** p<0,001

Conclusions

- Severe hypercholesterolemia is poorly treated in Southern Finland
- A significant proportion of patients are unaware of their CVD risk
- The contribution of known hypercholesterolemia-associated mutations in Southern Finland appears smaller than previously anticipated
- There is an unmet need to further characterize causal variants and to raise awareness among caretakers to adequately treat patients.

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