# Genetic findings in a cohort of over 1,000 patients with suspected monogenic lipid disorders

P13

**Julie Hathaway**[1], Johanna Huusko[1], Saija Ahonen[1], Johanna Tommiska[1], Kimberly Gall[1], Alicia Scocchia[1], Khalida Liaquat[1], Victoria Howell[1], Allison Sluyters[1], Janica Djupsjöbacka[1], Mikko Muona[1], Inka Saarinen[1], Eija Seppälä[1], Tiia Kangas-Kontio[1], Lotta Koskinen[1], Pertteli Salmenperä[1], Samuel Myllykangas[1], Juha Koskenvuo[1]

1. Blueprint Genetics, Espoo, Finland

## Introduction

Genetic testing for monogenic lipid disorders, such as familial hypercholesterolemia (FH), has demonstrated clinical utility[1] but is often underutilized. While the yield of genetic testing has been described in FH, it is not as well defined in other suspected monogenic lipid disorders. We describe the yield of genetic testing in a heterogeneous cohort of patients with suspected monogenic lipid disorders.

## Methods

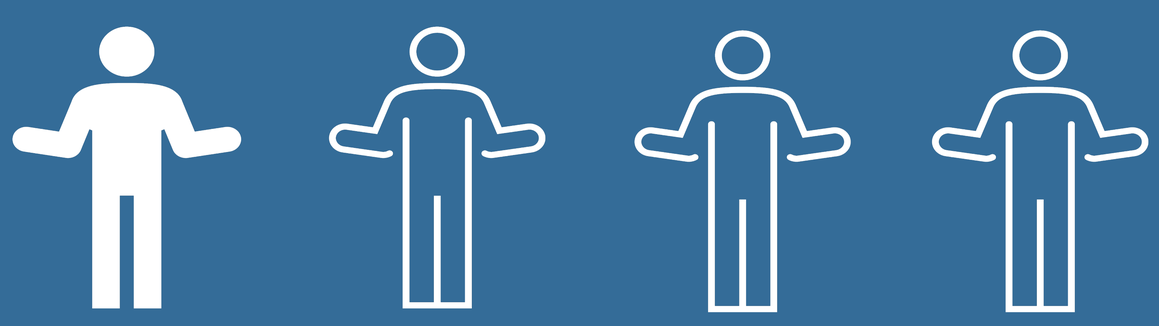
We retrospectively reviewed genetic test results from 1,041 consecutive patients with suspected monogenic lipid disorders. Sequencing and high-resolution copy number variant (CNV) analysis was performed by next-generation sequencing (NGS) as an FH core (4 genes: *LDLR*, *APOB*, *PCSK9* and *LDLRAP1*) or broad dyslipidemia (≤20 genes) panel. The broad dyslipidemia panel includes the 4 FH core genes plus up to 16 genes associated with other monogenic lipid disorders. Detection of a pathogenic (P), likely pathogenic (LP) variant(s) (using a modified ACMG/AMP classification scheme) or risk factor(s) was considered an informative result if consistent with disease inheritance. Chi-square analyses determined statistical significance (α=.05).

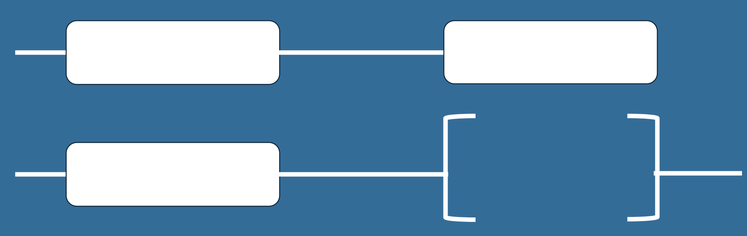
## Results

A total of 1,041 patients underwent testing; 87.3% (909/1,041) were adults (≥18 years of age at the time of testing). Half of patients were reportedly male (50.0% [520/1,041], sex not known for 1 individual). The median age at the time of testing was 41 years (range: birth to 85 years). Over three-quarters of patients (77.7% [809/1,041]) were tested with a broad panel. Overall, 28.0% (292/1,041) of patients had an informative result. The yield was higher for pediatric patients (<18 years old at testing) than adult patients (43.9% [58/132] vs 25.7% [234/909], $P<.05$, $\chi^2=18.91$) and for the core panel than the broad panel (42.7% [99/232] vs 23.9% [193/809], $P<.05$, $\chi^2=31.63$) (Table 1). LP/P variants in genes included only on the broad panel accounted for 14.0% (27/193) of all broad panel informative results. The most common informative results overall were explained by a heterozygous LP/P variant in *LDLR* (77.1% [225/292]), followed by heterozygous LP/P variants in *APOB* (9.6% [28/292]).

In adult patients, heterozygous LP/P variants in *LDLR* made up 78.2% (183/234) of informative results and heterozygous variants in *APOB* made up 9.0% (21/234) all informative results (Figure 1). In pediatric patients, heterozygous variants in *LDLR* made up 72.4% (42/58) of all informative results and heterozygous variants in *APOB* accounted for 12.1% (7/58) (Figure 2). In total, 313 LP/P or risk factor variants were identified in 11 different genes.

LP/P CNVs accounted for 12.8% (40/313) of all informative variants; 97.5% (39/40) were intragenic in the *LDLR* gene (Table 2). Of these, 37.5% (15/40) were 1 exon in size. Single exon deletions therefore accounted for 4.8% (15/313) of all LP/P variants.





More than 1 in 4 patients undergoing NGS panel testing for a monogenic lipid disorder received an informative result.

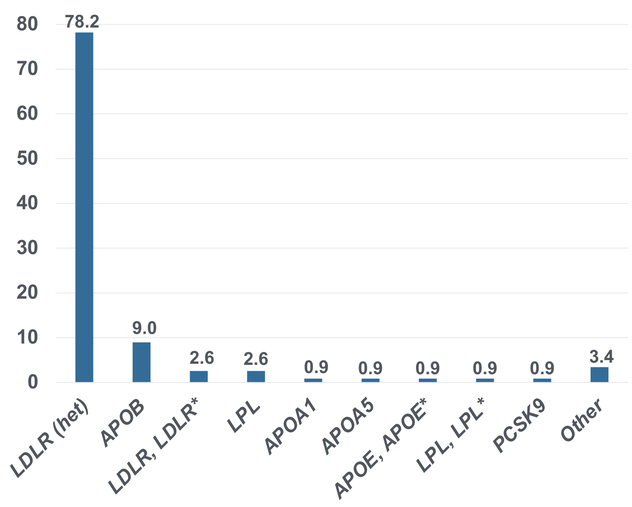
Single exon CNVs accounted for ~5% of all LP/P variants in the cohort.

**Table 1. Patient demographics**

| Demographic | % of cohort (n) | % with informative result (n) |
|---|---|---|
| Male[a] | 50.0% (520) | 27.9% (145) |
| Female[a] | 50.0% (520) | 28.3% (147) |
| Adult (≥18 yrs) | 87.3% (909) | 25.7% (234)[b] |
| Pediatric (<18 yrs) | 12.7% (132) | 43.9% (58)[b] |
| All patients core panel | 22.3% (232) | 42.7% (99)[c] |
| All patients broad panel | 77.7% (809) | 23.9% (193)[c] |

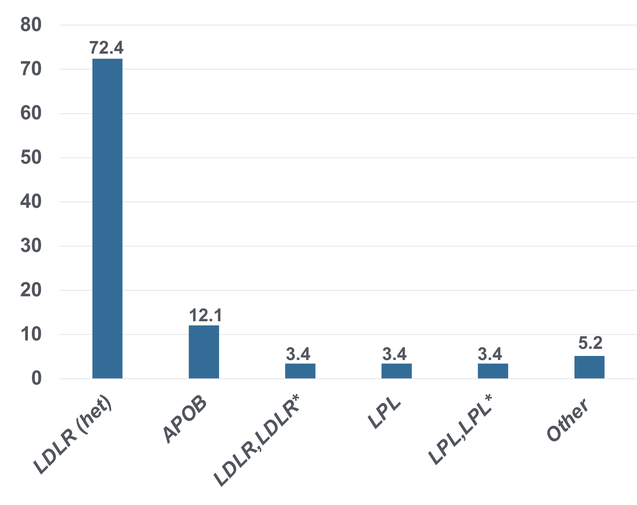
[a]sex not known n=1; [b]compared for statistical significance, significant at $P<.05$, $\chi2=[18.91]$; [c]compared for statistical significance, significant at $P<.05$, $\chi^2=[31.63]$.

**Figure 1. Informative results by gene (%), adult patients**




"Other" includes genes with <2 cases.*denotes patients who are homozygous or compound heterozygous.

**Figure 2. Informative results by gene (%), pediatric patients**




"Other" includes genes with <2 cases. *denotes patients who are homozygous or compound heterozygous.

**Table 2. LP/P CNVs identified in the cohort**

| Gene | Event | Size (bp) | Count |
|---|---|---|---|
| *LDLR* | Duplication | >1,000 | 3 |
| *LDLR* | Deletion | >600 | 21 |
| *LDLR* | Deletion | <600 (1 exon) | 15 |

bp, base pairs; CNV, copy number variant; LP/P, likely pathogenic/pathogenic. One LP/P CNV has been removed from the table due to small numbers and the potential for patient identification.

## Conclusions

- **In this cohort, ~28% of patients received an informative result; the yield of testing was significantly higher in pediatric patients and in patients who were tested with a smaller core panel of genes.**
- **LP/P CNVs accounted for 12.8% of all informative variants; single exon deletions accounted for ~5% of all informative variants.**
- **These findings demonstrate the importance of genetic testing with high-resolution CNV analysis for monogenic lipid disorders.**

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**Conflict of interest statement: All authors are employed by Blueprint Genetics.**

### References

1.Sturm AC, Knowles JW, Gidding SS, Ahmad ZS, Ahmen CD et al. Clinical genetic testing for familial hypercholesterolemia: JACC scientific expert panel. *J Am Coll Cardiol*. 2018. Aug 7;72(6):662-680. doi:10.106/j.jacc.2018.05.044