**TITLE PAGE**

**Prevalence of familial hypercholesterolaemia (FH)-causing variants and impact on LDL-C concentration in European, South Asian, and African ancestry groups of the UK Biobank**

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**ABSTRACT**

**Background**: Familial Hypercholesterolaemia (FH) is a monogenic disease which causes high low-density lipoprotein cholesterol (LDL-C) and higher risk of premature coronary heart disease (CHD). The prevalence of FH-causing variants and their association with LDL-C in non-European populations remains largely unknown. Using DNA diagnosis in a population-based cohort, we aimed to estimate the prevalence of FH across three major ancestry groups in the UK.

**Methods**: Principal component analysis (PCA) was used to distinguish genetic ancestry in UK Biobank participants. Whole exome sequencing (WES) data were analysed to provide a genetic diagnosis of FH. LDL-C concentrations were adjusted for statin use.

**Results**: PCA distinguished 140,439 European (Eur), 4,067 South Asian (SA), and 3,906 African (Afr) participants with lipid and WES data. There were significant differences between the three groups, including total and LDL-C concentrations, and prevalence and incidence of CHD. We identified 488, 18, and 15 participants of Eur, SA, and Afr ancestry carrying a likely pathogenic or pathogenic FH-variant. No statistical difference in the prevalence of an FH-causing variant was observed: 1/288 (95%CI: 1/316;1/264) in Eur, 1/260 (95%CI: 1/526;1/173) in Afr, and 1/226 (95% CI: 1/419;1/155) in SA. Carriers of an FH-causing variant had significantly higher LDL-C concentration than non-carriers in every ancestry groups. There was no difference in mean (statin-use adjusted) LDL-C concentration in FH-variant carriers depending on their ancestry background. Self-reported statin use was non-significantly highest in FH-variant carriers of SA ancestry (55.6%), followed by Afr (40.0%) and Eur (33.8%) (p=0.15).

**Conclusions**: The prevalence of FH-causing variants in the UK Biobank is similar across the ancestry groups analysed. Despite overall differences in lipid concentrations, FH-variant carriers across the three ancestry groups had similar LDL-C levels. In all ancestry groups, the proportion of FH-variant carriers treated with lipid-lowering therapy should be improved to reduce future risk of premature CHD.

**KEY WORDS:** FH, variant frequency, LDL-C, ancestry, UK Biobank

**NONSTANDARD ABBREVIATIONS AND ACRONYMS:**

|  |  |
| --- | --- |
| NONSTANDARD ABBREVIATIONS AND ACRONYMS | |
| Afr | African |
| *APOB* | Apolipoprotein B gene |
| *APOE* | Apolipoprotein E gene |
| CHD | Coronary heart disease |
| Eur | European |
| FH | Familial Hypercholesterolaemia |
| IQR | Interquartile range |
| LDL-C | Low density lipoprotein cholesterol |
| *LDLR* | Low density lipoprotein receptor gene |
| Lp(a) | Lipoprotein (a) |
| PCA | Principal component analysis |
| *PCSK9* | Proprotein convertase subtilisin/kexin 9 gene |
| SA | South Asian |
| T2D | Type 2 diabetes |
| TC | Total cholesterol |
| TG | Triglyceride |
| VUS | Variant of unknown significance |

**INTRODUCTION**

Familial Hypercholesterolaemia (FH) is a monogenic disease of high low-density lipoprotein cholesterol (LDL-C) concentrations, caused by rare variants in the *LDLR* (low-density lipoprotein receptor), *APOB* (apolipoprotein B), or *PCSK9* (proprotein convertase subtilisin/kexin 9) gene.[1] Carriers of an FH-causing variant are predisposed to a high risk of premature coronary heart disease (CHD), because they are exposed to increased LDL-C concentrations from birth.[2] Likely pathogenic and pathogenic variants in *LDLR*, *APOB* or *PCSK9* can be found in 1 in 250 individuals (95% CI: 1:345; 1:192), as demonstrated in a recent meta-analysis.[3] Despite FH being one of the most common Mendelian diseases, it remains highly underdiagnosed worldwide,[1] and even when diagnosed, it is often inadequately treated.[4] The majority of available data on the prevalence of FH come from studies conducted on individuals of European ancestry, therefore significant gaps in the understanding of the disease burden in non-European ancestry groups remain.[5] A previous study using the predominately male Million Veteran Program data observed differences in FH variant frequency between individuals of European and African background,[6] however the authors employed a genotyping array for FH variant identification, which is likely to miss some rare pathogenic variants, especially those unique to non-European populations. A recent systematic review observed differences in FH prevalence between different ethnicities, however FH diagnosis was mainly based on a mixture of clinical criteria with a limited number being confirmed by genetic testing.[7] One of the research needs highlighted in the Scientific Statement from the American Heart Association is to determine the prevalence of FH-variants in non-European populations.[8] Potential differences in FH-variant frequency between ancestry groups are important to consider when evaluating national screening strategies.

In this study, we assessed the prevalence of FH-causing variants in the UK Biobank and compared it between the three major ancestry groups available: European (Eur), South Asian (SA), and African (Afr). We analysed differences in LDL-C concentration between FH variant carriers across these three groups, and compared them to non-FH participants.

**METHODS**

Because of the sensitive nature of the data generated for this study, requests to access the raw dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the UK Biobank at https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access.

**UK Biobank cohort**

The UK Biobank longitudinal study recruited half a million participants (aged 40-75) from 2006 to 2010.[9] Various biological (e.g. biomarker measures) and non-biological (e.g. lifestyle, family history of disease) measures were recorded, including whole-exome sequencing of participants.[10] The current study was conducted under the approved UK Biobank application 40721.

**PCA analysis**

The genetic ancestry of participants was determined using principal component analysis (PCA) of the genotyping data as previously described in more detail in the supplemental content of the manuscript by Giannakopoulu *et al*.[11] In PCA, participants were confirmed to belong to an ancestry group based on whether they clustered around a known reference group using the PC-Air method.[12]

**Whole exome sequencing analysis**

The *LDLR*, *APOB* and *PCSK9* gene regions +/-100kb (genomic positions shown in **Supplementary Table S1**) were extracted from the whole exome sequencing data for available participants at the time of study completion (~200,000). Variants were first filtered based on a minimum read depth of 10, genotype quality of 20, and a minor allele frequency of 0.0006 or less (i.e. the frequency of the most common FH variant p.Arg3527Gln in *APOB*).

**Variant interpretation**

Variants that passed the initial quality control were interpreted using the American College of Medical Genetics (ACMG) guidelines.[13] Variants classified as likely pathogenic or pathogenic in **Supplementary Table S2** were used to provide a genetic diagnosis of FH. Variants of uncertain significance (VUS) were excluded from the main analysis and presented in **Supplementary Table S3**. FH-causing variants in the *APOB* and *PCSK9* genes were filtered based on a list of variants with functional assay backing.[14] The frequency of the likely pathogenic p.Leu167del variant in *APOE* was also analysed.[15]

**LDL-C concentration data**

Missing LDL-C data was singly imputed using the R package MICE version 3.10.0.[16] The LDL-C concentration of participants who reported using statins was adjusted with the correction coefficient 1.43.[17]

**Statistical methods**

All statistical analyses were performed in R version 4.0.2. The nonparametric Kruskal-Wallis Rank Sum Test was used to compare the median [interquartile range (IQR)] of more than two groups, and the Mann-Whitney-Wilcoxon Test when comparing two groups.

**RESULTS**

**Ancestry groups characteristics**

Using PCA we identified 140,439 White European (Eur), 4,067 South Asian (SA), and 3,906 African (Afr) ancestry individuals with whole exome sequencing data within UK Biobank. Significant differences between the three groups were observed (**Supplementary Table S4**), with the median age being slightly older in Eur (58 vs. 53 years in SA, and 50 years in Afr, p-value <0.001), and having highest total cholesterol (TC) and LDL-C concentrations (median [IQR] TC: 5.68 [4.94, 6.45]mmol/L vs. 5.32 [4.56, 6.03]mmol/L in SA, and 5.24 [4.52, 5.94]mmol/L in Afr, p-value <0.001; LDL-C adjusted for statin use: 3.67 [3.14, 4.25]mmol/L vs. 3.54 [3.02, 4.08]mmol/L in SA, and 3.36 [2.84, 3.95]mmol/L in Afr, p-value <0.001). Median [IQR] triglyceride (TG) concentrations were highest in SA group: 1.67 [1.18, 2.40]mmol/L (vs. 1.49 [1.05, 2.14]mmol/L in Eur, and 1.04 [0.78, 1.46]mmol/L in Afr, p-value <0.001), who also had the highest proportion of prevalent and incident type 2 diabetes (T2D) and CHD, and of prevalent hypertension (**Supplementary Table S4**). Median Lp(a) values were significantly higher in the Afr ancestry group, followed by the SA and Eur groups (overall p-value <0.001) (**Supplementary Table S4**). The lowest proportion of prevalent and incident CHD was observed in the Afr ancestry group (**Supplementary Table S4**).

**Frequency of FH-causing variants**

FH-causing variants, classified as pathogenic or likely pathogenic (**Supplementary Table S2**), were found in 488 Eur, 18 SA, and 15 Afr ancestry participants. These equated to an FH-causing variant prevalence of 1:288 (95% CI 1:315; 1:263), 1:226 (95% CI 1:381; 1:143), and 1:260 (95% CI 1:465; 1:158), respectively, which was not statistically different between the ancestry groups (p-value = 0.57) (**Table 1**). The majority of FH-causing variants were seen in the *LDLR* gene, with *APOB* variants (p.Arg3527Gln and p.Arg3527Trp) accounting for 21%, 20% and 6% FH causes in those of Eur, Afr and SA ancestry, respectively. No pathogenic or likely pathogenic FH-causing variants were seen in *PCSK9* in any of the ancestry groups, while the likely pathogenic variant in *APOE* (p.Leu167del) was found only in those of Eur ancestry. The highest proportion of VUS were found in Eur (n = 661; 1 in 212), followed by Afr (n = 10; 1 in 391) and SA (n = 13; 1 in 313) ancestry groups (**Supplementary Table S3**), with no significant difference in prevalence between groups (p-value = 0.06).

**FH-causing variant and LDL-C concentrations**

Individuals with Afr ancestry and an FH-causing variant had the highest median [IQR] adjusted LDL-C concentration (4.87 [3.49, 5.90]mmol/L), followed by Eur (4.43 [3.67, 5.43]mmol/L), and SA (4.39 [3.80, 5.68]mmol/L) (**Table 1**), however the differences were not statistically significantly (p-value of ancestry group differences for FH-variant carriers only = 0.67480.068) (**Table 1**). Afr ancestry individuals without an FH variant had the lowest LDL-C concentration (3.43 (0.88)mmol/L) (**Table 1**), which differed significantly between the groups (p <2.2x10-16, adjusted for sex and age). Carriers of an FH-causing variant had significantly higher LDL-C concentration than non-carriers in all ancestry groups (**Figure 1**). The mean (SD) LDL-C concentration (adjusted for statin use) in participants with a VUS was intermediate between the FH-positive and FH-negative groups in Eur (4.00 (0.86)mmol/L; p-value <0.001) and Afr (3.79 (1.36)mmol/L; p-value <0.001), and lowest in SA (2.93 (1.09)mmol/L; p-value <0.001).

The proportion of FH-positive individuals with LDL-C concentration above the Simon Broome FH diagnostic threshold of 4.9mmol/L was not statistically different between the ancestries: 46.7% (95% CI: 24.8%; 70.0%) in Afr, 37.7% (95% CI: 33.5%; 42.1%) in Eur, and 33.3% (95% CI: 16.3%; 56.3%) in SA (**Supplementary Table S5**).[18]The highest detection rate (DR) and the lowest false positive rate (FPR) when using the diagnostic LDL-C cut-off of 4.9mmol/L was achieved in Afr ancestry group (DR:46.7% (95% CI: 24.8%; 70.0%); FPR: 5.7% (95% CI: 5.0%; 6.4%)) albeit overlapping confidence intervals between groups (**Supplementary Table S5**).

**Self-reported statin use**

Overall, self-reported statin use was highest in SA (20.3%), with 55.6% of SA FH variant carriers being treated (**Supplementary Table S6**). 13.1% of Eur and 12.5% of Afr ancestry participants reported using statins, with 33.8% and 40.0% of FH variant carriers being treated, respectively. The differences in treatment use between FH variant carriers of these ancestry groups were not statistically significant according to the Kruskal-Wallis (p-value = 0.15) and pairwise Wilcox tests (p-values = 0.17, 0.78, 0.78).

**DISCUSSION**

Although mean LDL-C concentration between European, South Asian, and African ancestry participants of the UK Biobank was significantly different, the frequency of FH-causing variants was not. Minority groups are underrepresented in FH registries and in cardiovascular clinical trials,[5,19] and our results suggest that it is not due to differences in FH-variant frequency in these populations. We observed that FH-variant carriers have significantly higher mean LDL-C concentration than non-carriers, regardless of their ancestry. However, we found that in all three ancestry groups studied, FH-positive individuals were undertreated, therefore not benefiting from lipid-lowering treatment and reduction in CHD risk. In the UK National Health System lipid lowering therapy is affordable and readily available, but in countries where medication is more expensive this gap in treatment may be even greater between ancestry groups. We further found that the incidence and prevalence of T2D and prevalence of hypertension were highest in SA ancestry participants, which probably contribute to the higher rates of incident and prevalent CHD in this group are unclear, but is likely to be a combination of both socioeconomic and lifestyle factors, and genetic background. By contrast, and again as noted previously,[20,22] the prevalence and incidence of CVD was lower in those of Afr origin, although this effect was largely explained by sociodemographic, lifestyle, environmental and clinical factors.[20] However, overall, as more efforts are needed to improve FH diagnosis, our findings suggest that FH-variant carriers in all three ancestry groups have similar mean LDL-C concentration and that the commonly used FH diagnostic threshold of LDL-C >4.9 mmol/L might perform similarly at detecting affected FH individuals.

As expected, in all three ancestry groups, over 77% (80% in Afr, 94% in SA) of the identified pathogenic/likely pathogenic variants were in the *LDLR* gene, with 91 different variants found in the Eur, 11 in the SA, and nine in the Afr ancestry groups (**Supplementary Table S2**). The FH-variant spectrum in SA was quite different, with nine out of the 11 *LDLR* variants being unique to SA (the remaining two also found in Eur individuals). However, in Afr ancestry group only two *LDLR* variants were unique to Afr, with seven also found in Eur. The *APOB* gene two previously reported pathogenic variants were identified,[23,24] while only variants of unknown significance (VUS) were identified in the gene for *PCSK9*, and with the *APOE* likely pathogenic variant seen only the Eur ancestry group. For the Eur and Afr ancestry groups, VUS carriers had intermediate median LDL-C concentration (i.e. higher than non-FH but lower than FH variant carriers), which suggests that some of the VUS are likely to be pathogenic. If this is the case, the prevalence of FH in these ancestry groups would be higher than estimated in this study. These data support the view that that a Next Generation Sequencing approach including all four genes is required to provide a comprehensive genetic diagnostic test for FH.[1,5] A possible limitation to our analyses is that the variant classification, especially VUS, may change in the future as more evidence is gathered and curated by expert panels such as the FH ClinGen consortium.[25] Such changes may have a slight effect on the FH prevalence, DR and FPR values found in our study.

Although the UK Biobank study provides a large dataset for studying FH in different ancestry groups, limitations include the relatively smaller number of non-European ancestry participants. Other study limitations leading to potential inaccuracies of the results are the use of the self-reported statin treatment data field, and the adjustment of LDL-C concentration in these individuals. The adjustment we have adopted might result in an over or underestimation of untreated LDL-C concentration, with greater potential bias in the smaller FH positive Afr and SA groups, as the true effect will be statin type and dose-depended as shown previously.[26] However, this will not influence the FH prevalence estimates obtained using whole-exome sequencing. Regardless of the limitations, this study provides important information on the genetically-confirmed prevalence of FH in individuals of Afr and SA ancestries.

**ACKNOWLEDGMENTS**

This research has been conducted using data from UK Biobank (application number 40721), a major biomedical database. The authors are grateful to UK Biobank participants. UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council, Department of Health, Scottish Government, and the Northwest Regional Development Agency. It has also had funding from the Welsh Assembly Government and the British Heart Foundation.

**SOURCES OF FUNDING**

JG was supported by the BHF studentship FS/17/70/33482. SH and MF received additional support from the National Institute for Health Research University College London Hospitals Biomedical Research Centre. SH and MF were supported by a grant from the British Heart Foundation (BHF grant PG 08/008).

**DISCLOSURES**

No competing interests to declare.

**TABLE AND FIGURE**

**Table 1. FH-variant prevalence and baseline characteristics of European, South Asian, and African ancestry groups stratified by variant status.** CHD = coronary heart disease,HDL-C = high-density lipoprotein cholesterol,LDL-C = low-density lipoprotein cholesterol, SD = standard deviation, T2D = type 2 diabetes.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **White British** | | | **South Asian** | | | **African** | | |
|  | **No** | **Yes** | **p-value of group differences** | **No** | **Yes** | **p-value of group differences** | **No** | **Yes** | **p-value of group differences** |
| n | 139291 | 488 |  | 4036 | 18 |  | 3881 | 15 |  |
| FH-variance prevalence (95% CI) | 1:288 (1:315; 1:263) | | | 1:226 (1:381; 1:143) | | | 1:260 (1:465; 1:158) | | |
| Age (median [IQR]) | 58.00 [51.00, 63.00] | 58.00 [51.00, 63.00] | 0.803 | 53.00 [46.00, 60.00] | 53.50 [45.25, 60.50] | 0.963 | 50.00 [45.00, 58.00] | 53.00 [44.00, 59.50] | 0.509 |
| Sex (male) (%) | 63382 (45.5) | 207 (42.4) | 0.187 | 2123 (52.6) | 7 (38.9) | 0.354 | 1560 (40.2) | 2 (13.3) | 0.064 |
| Statin use (%) | 18139 (13.0) | 165 (33.8) | <0.001 | 813 (20.1) | 10 (55.6) | 0.001 | 478 (12.3) | 6 (40.0) | 0.004 |
| Body mass index, kg/m2 (median [IQR]) | 26.67 [24.10, 29.78] | 27.07 [23.89, 29.75] | 0.689 | 26.58 [24.21, 29.45] | 26.88 [24.21, 29.76] | 0.858 | 28.73 [25.74, 32.42] | 30.14 [28.17, 33.08] | 0.306 |
| **Biomarkers** |  |  |  |  |  |  |  |  |  |
| Total cholesterol, mmol/L (median [IQR]) | 5.68 [4.94, 6.44] | 6.10 [5.20, 7.31] | <0.001 | 5.32 [4.56, 6.03] | 5.49 [4.87, 6.54] | 0.166 | 5.23 [4.52, 5.94] | 5.38 [5.11, 8.42] | 0.032 |
| Imputed LDL-C (unadjusted), mmol/L (median [IQR]) | 3.53 [2.96, 4.13] | 3.90 [3.16, 4.82] | <0.001 | 3.35 [2.78, 3.91] | 3.46 [3.01, 4.38] | 0.155 | 3.23 [2.72, 3.80] | 3.61 [3.21, 5.42] | 0.011 |
| Imputed LDL-C (adjusted for statin users), mmol/L (median [IQR]) | 3.67 [3.14, 4.24] | 4.43 [3.67, 5.43] | <0.001 | 3.54 [3.02, 4.08] | 4.39 [3.80, 5.68] | <0.001 | 3.35 [2.84, 3.94] | 4.87 [3.49, 5.90] | <0.001 |
| HDL-C, mmol/L (median [IQR]) | 1.41 [1.18, 1.69] | 1.38 [1.17, 1.63] | 0.086 | 1.21 [1.03, 1.45] | 1.19 [1.01, 1.38] | 0.577 | 1.39 [1.18, 1.66] | 1.34 [1.25, 1.66] | 0.577 |
| Triglycerides, mmol/L (median [IQR]) | 1.49 [1.05, 2.15] | 1.26 [0.92, 1.91] | <0.001 | 1.67 [1.18, 2.40] | 1.47 [1.06, 2.00] | 0.400 | 1.04 [0.78, 1.47] | 1.22 [0.92, 1.40] | 0.448 |
| Lipoprotein A, nmol/L (median [IQR]) | 20.00 [9.30, 59.81] | 27.60 [10.33, 59.20] | 0.083 | 31.99 [13.60, 64.10] | 54.31 [22.66, 63.20] | 0.235 | 67.15 [38.40, 107.10] | 71.93 [61.10, 90.76] | 0.749 |
| **Disease status** |  |  |  |  |  |  |  |  |  |
| Prevalent T2D (%) | 3593 (2.6) | 11 (2.3) | 0.757 | 378 (9.4) | 1 (5.6) | 0.882 | 180 (4.6) | 0 (0.0) | 0.812 |
| Incident T2D (%) | 4948 (3.6) | 19 (3.9) | 0.776 | 462 (11.4) | 5 (27.8) | 0.073 | 294 (7.6) | 3 (20.0) | 0.186 |
| Incident CHD (%) | 5370 (3.9) | 32 (6.6) | 0.003 | 248 (6.1) | 0 (0.0) | 0.553 | 95 (2.4) | 0 (0.0) | 1.000 |
| Prevalent CHD (%) | 3890 (2.8) | 40 (8.2) | <0.001 | 220 (5.5) | 2 (11.1) | 0.593 | 56 (1.4) | 0 (0.0) | 1.000 |
| Prevalent hypertension (%) | 10747 (7.7) | 48 (9.8) | 0.096 | 460 (11.4) | 2 (11.1) | 1.000 | 461 (11.9) | 2 (13.3) | 1.000 |
| Incident hypertension (%) | 19844 (14.2) | 68 (13.9) | 0.895 | 681 (16.9) | 3 (16.7) | 1.000 | 678 (17.5) | 4 (26.7) | 0.552 |

**Figure 1. LDL-C concentration in FH variant carriers and non-carriers in European, South Asian, and African ancestry groups of the UK Biobank.** LDL-C concentration was adjusted for statin use. FH variant carriers are represented in red, and non-carriers in blue. P-value differences of LDL-C concentration between carriers and non-carriers are indicated for each ancestry group.

**SUPPLEMENTAL MATERIAL LIST**

* **Expanded methods: Disease definition**
* **Supplementary tables: Table S1, Table S2, Table S3, Table S4, Table S5, Table S6**

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Highlights

* Prevalence of FH-causing variants is similar across European, South Asian and African genetic ancestry groups of UK Biobank
* Despite some overall differences in lipid concentrations between the ancestry groups, FH individuals have similar LDL-cholesterol regardless of their ancestry
* Gaps in lipid-lowering treatment exist across all three ancestry groups