Genetic and Environmental Contributions to Cardiovascular Risk

Lessons From North Karelia and FINRISK

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ABSTRACT

Systematic collection of DNA samples started in FINRISK during the 1992 survey and has continued in all surveys since then. At the moment, FINRISK has DNA, careful phenotyping at baseline, and prospective follow-up for incident disease for about 34,000 participants. These data have been used for genome-wide association studies by contributing to numerous large international consortia, mainly focused on cardiovascular diseases and their risk factors. In parallel, genomic data from FINRISK have been used for cardiovascular risk estimation, and our constantly improving knowledge of cardiovascular disease risk variants generates promising prospects in this field. The isolated nature of the Finnish population and recent bottlenecks in our population history, particularly in eastern Finland, provide certain advantages for sequencing studies. The power to detect low-frequency variants is stronger in isolated populations, like those in eastern Finland, than in more admixed populations. Together with country-wide and reliable electronic health records, this provides a resource that is currently widely utilized in whole exome and whole genome sequencing studies.

FINRISK is a national risk factor monitoring system in Finland, based on surveys of random population samples and carried out every 5 years. Its history goes back to the population surveys implemented in 1972 and 1977 in eastern Finland to evaluate the North Karelia Project. The surveys continued in the framework of the WHO Monica Project and under the name FinMonica in 1982 and 1987 and then developed to more national FINRISK surveys, starting in 1992, to monitor the national development.

Early prospective analyses of FINRISK/North Karelia Project data demonstrated that parental history of coronary heart disease (CHD) was independently associated with elevated risk of an incident CHD event among FINRISK participants [1]. The hazard ratios (HR), adjusted for conventional cardiovascular risk factors, were 1.61 in men and 1.85 in women. Likewise, parental history of cardiovascular disease (CVD) was independently associated with the risk of stroke [2]. The HRs for stroke, adjusted for conventional risk factors, were 1.89 in men and 1.80 in women. These initial studies, together with the technical developments in genotyping and visionary investigators, stimulated the collection of DNA in the 1992 FINRISK survey and every survey after that. This has led to a unique collection of about 34,000 individuals with DNA, careful phenotyping at baseline, and prospective follow-up for incident disease.

GENOME-WIDE ASSOCIATION STUDIES

After the first DNA collection for 6,000 participants in 1992, it took more than 10 years before the investment started to bear fruit. Genome-wide association studies (GWAS) enabled analyses of common, genetic variation, which was envisioned to provide a better understanding of the biology of common complex diseases. The effect sizes of common genetic variants are usually small, however, and their detection in GWAS analyses with a stringent correction for the large amount of statistical tests required very large numbers. This was accomplished with international collaboration leading to large multinational consortia, which discovered several single-nucleotide polymorphisms (SNP) associated with common, complex diseases and their quantitative risk factor traits. FINRISK has made important contributions to many of these consortia: for example, the Genetic Investigation of Anthropometric Traits (GIANT), International Consortium for Blood Pressure Genome-Wide Association Studies (ICBP), Global Lipids Genetics Consortium (GLGC), Diabetes Genetics Replication and Meta-Analysis Consortium (DIAGRAM), the Coronary Artery Disease Genome-Wide Replication and Meta-Analysis Consortium (CARDIoGRAM), and the Coronary Artery Disease Genetics (C4D) consortium. These large consortia have helped to gain important insights into the genetic underpinnings of CVDs and their risk factors. On the other hand, the proportion of variance in the phenotypic traits explained by the discovered SNPs has remained small, usually well below 10%, and translation of these findings into clinical prevention and treatment is still pending.

CARDIOVASCULAR RISK ESTIMATION

A strength of FINRISK is that the setting has enabled prospective studies on genotypes as risk factors for

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incident cardiovascular events, which have been relatively rare among the GWAS so far. We have utilized this opportunity in cardiovascular risk estimation by constructing a genetic risk score (GRS) for cardiovascular events and testing whether it improves cardiovascular risk estimation over and above the existing, currently used risk functions [3]. A CHD GRS consisting of 13 SNPs was associated with incident CHD events, after adjusting for conventional risk factors, with an HR of 1.66 comparing the highest quintile with the lowest quintile (Table 1). Further adjustment for family history did not change this estimate. More recent studies have revealed additional SNPs associated with the CHD risk, and it is likely that with additional novel SNPs and with more sophisticated analysis techniques, the performance of the GRS can be improved further.

We have also constructed a blood pressure (BP) GRSs from 32 common SNPs, known to associate with either systolic or diastolic BP, and tested its association with incident CVD events [4]. As expected, the BP GRSs were highly significantly associated with systolic and diastolic BP and hypertension. Importantly, the GRS quintiles were associated in a dose-dependent manner with the risk of incident CVD events (Fig. 1). The discrimination and reclassification improvements due to GRS remained modest, however.

FINNISH POPULATION HISTORY AND ELECTRONIC HEALTH RECORDS IMPROVE POWER

In general, the effects of common genetic variants on the phenotype are small and the effects of low-frequency and rare variants are larger. It has been hypothesized accordingly that low-frequency SNPs might help to increase the proportion of variance explained in the phenotypic traits and add more explanatory power to cardiovascular risk estimation. Consistent with this line of thinking, lipid analyses of the European Network of Genomic and Genetic Epidemiology (ENGAGE) project revealed that low-frequency variants increased the proportion of variance explained, particularly for low-density lipoprotein cholesterol and total cholesterol [5]. Due to the isolated nature of the Finnish population and recent bottlenecks in our population history, low-frequency (prevalence 0.5% to 5%) variants are enriched in Finland, particularly in eastern Finland, compared with non-Finnish Europeans (Fig. 2) [6,7]. Therefore, the Finnish population provides better statistical power for detecting low-frequency variants than more admixed populations.

TABLE 1. Association between genetic risk score and incident coronary heart disease, cardiovascular disease, and myocardial infarction*

	Genetic Risk Score Quintile					
	1 (reference)	2	3	4	5	p Value for Trend
HR (95% CI) for CHD (total n = 25,243)						
FR 1992	1.00	0.97 (0.65–1.45)	1.07 (0.71–1.60)	1.60 (1.10–2.34)	1.54 (1.06–2.25)	0.001
FR 1997	1.00	1.02 (0.72–1.44)	1.17 (0.84–1.62)	1.32 (0.95–1.83)	1.76 (1.28–2.41)	1.1×10^{-5}
FR 2002	1.00	1.06 (0.56–1.99)	1.18 (0.65–2.15)	1.43 (0.79–2.58)	1.82 (1.03–3.22)	0.019
Health 2000	1.00	0.93 (0.51–1.68)	1.41 (0.81–2.45)	1.13 (0.62–2.06)	1.51 (0.87–2.62)	0.087
Pooled†	1.00	1.00 (0.80–1.25)	1.17 (0.94–1.46)	1.39 (1.12–1.72)	1.66 (1.35–2.04)	7.3×10^{-10}
HR (95% CI) for CVD (total n = 29,318)						
FR 1992	1.00	1.03 (0.74–1.43)	1.10 (0.79–1.54)	1.35 (0.98–1.87)	1.55 (1.14–2.12)	0.001
FR 1997	1.00	0.88 (0.66–1.18)	1.12 (0.86–1.46)	1.20 (0.92–1.58)	1.54 (1.18–1.99)	1.1×10^{-5}
FR 2002	1.00	1.18 (0.70–2.00)	1.43 (0.87–2.36)	1.33 (0.79–2.23)	2.01 (1.24–3.25)	0.004
Health 2000	1.00	1.03 (0.63–1.69)	1.31 (0.81–2.12)	1.30 (0.80–2.12)	1.70 (1.08–2.68)	0.009
MDC-CC	1.00	0.83 (0.57–1.19)	0.82 (0.57–1.18)	0.75 (0.51–1.10)	1.13 (0.80–1.58)	0.511
Pooled†	1.00	0.95 (0.80–1.12)	1.10 (0.93–1.29)	1.16 (0.99–1.36)	1.50 (1.29–1.75)	1.9×10^{-10}
HR (95% CI) for MI (total n = 29,318)						
FR 1992	1.00	1.00 (0.57–1.73)	1.00 (0.57–1.77)	1.60 (0.95–2.69)	1.45 (0.86–2.44)	0.039
FR 1997	1.00	1.02 (0.63–1.65)	1.36 (0.87–2.11)	1.32 (0.84–2.08)	1.87 (1.21–2.87)	0.002
FR 2002	1.00	1.22 (0.50–2.95)	0.89 (0.35–2.26)	1.16 (0.48–2.81)	2.05 (0.92–4.60)	0.095
Health 2000	1.00	0.89 (0.44–1.81)	1.68 (0.89–3.17)	1.00 (0.48–2.05)	1.35 (0.70–2.62)	0.320
MDC-CC	1.00	0.93 (0.58–1.51)	0.78 (0.47–1.28)	0.89 (0.55–1.46)	1.03 (0.65–1.64)	0.891
Pooled†	1.00	0.99 (0.76–1.27)	1.11 (0.87–1.43)	1.19 (0.93–1.53)	1.46 (1.15–1.86)	2.8×10^{-5}

CHD, coronary heart disease; CVD, cardiovascular disease; FR, FINRISK; HR, hazard ratio; MDC-CC, Malmö Diet and Cardiovascular cohort; MI, myocardial infarction.

*Association tested with Wald test with a Cox proportional hazards model adjusted for sex, low- density lipoprotein and high-density lipoprotein cholesterol, smoking, body mass index, systolic and diastolic blood pressure, blood pressure treatment and diabetes; age was used as the time scale.

†Results were combined with fixed effects meta-analysis.

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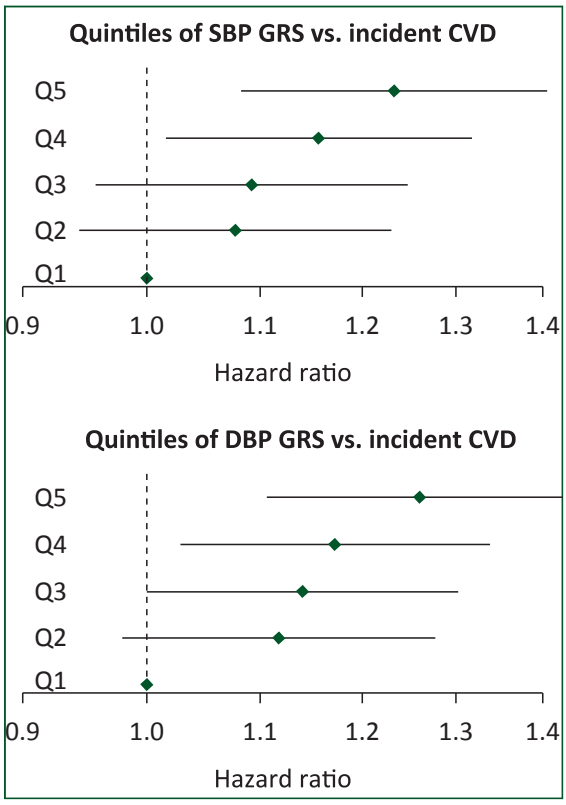

FIGURE 1. Association of the systolic blood pressure and diastolic blood pressure genetic risk score quintiles with incident cardiovascular disease events. Cox proportional hazards regression analysis adjusted for sex and study area; age was used as the time scale. Redraw reproduced with permission from Havulinna et al. [4].

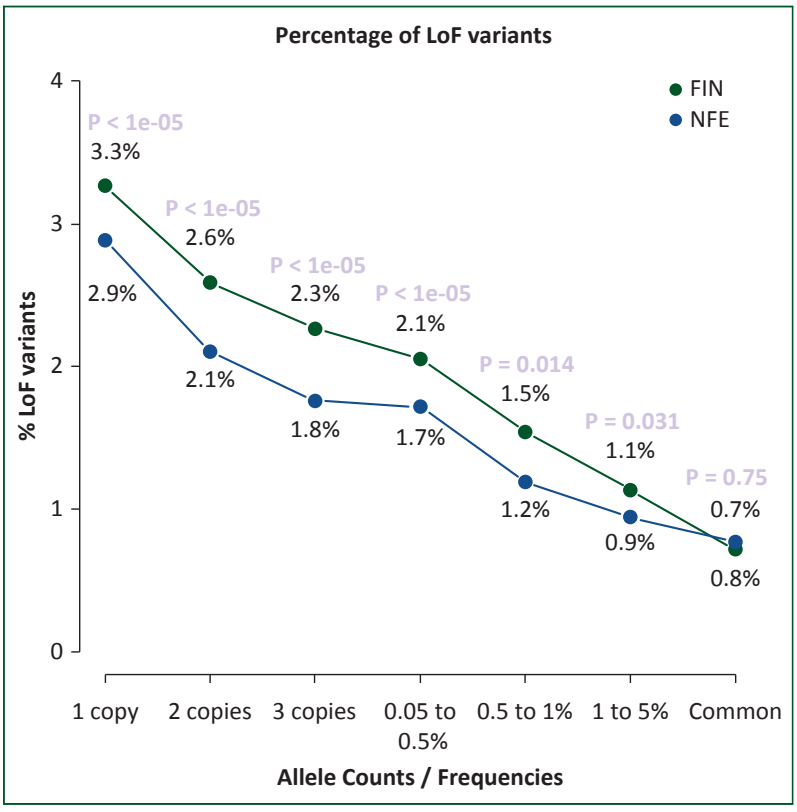

FIGURE 2. Proportion of low-frequency loss-of-function (LoF) variants in Finns (FIN) versus non-Finnish Europeans (NFE). Redraw reproduced with permission from Lim et al. [6] (http://creativecommons.org/licenses/by/4.0/legalcode).

We recently took advantage of the special features of the Finnish population by genotyping 83 low-frequency loss-of-function variants in 36,262 Finns and in a group of non-Finnish Europeans and examined their associations with 60 phenotypes [6]. The project produced several interesting observations, showing, for example, that the splice variants in the LPA gene, which strongly lower plasma lipoprotein(a) levels, confer protection from CVD and do not seem to lead to any adverse health consequences (Fig. 3). This suggests that LPA might be a potential therapeutic target. The isolated nature of the Finnish population is also utilized in whole exome sequencing and whole genome sequencing studies, which are extensively ongoing in the Finnish population.

Study	Ncases n/N	Ncontrols n/N	Odds Ratio (95% CrI)	Odds Ratio (95% CrI)
FINRISK (CHD)	1076/25020	23944/25020		0.79 (0.72 to 0.86)
Estonian ExomeChip (IHD+HF)	768/4600	3832/4600		0.69 (0.31 to 1.50)
Estonian Imputed (IHD+HF)	853/7953	7100/7953		0.83 (0.51 to 1.36)
MIGEN ExA (MI)	8890/18176	9286/18176		0.88 (0.78 to 0.99)
Total	**11587/55749**	**44162/55749**		**0.84 (0.80 to 0.88)**

FIGURE 3. Association of LPA splice variants with cardiovascular disease events. CHD, coronary heart disease; CrI, credible interval; HF, heart failure; IHD, ischemic heart disease; LPA, apolipoprotein (a); MI, myocardial infarction. Redraw reproduced with permission from Lim et al. [6] (http://creativecommons.org/licenses/by/4.0/legalcode).

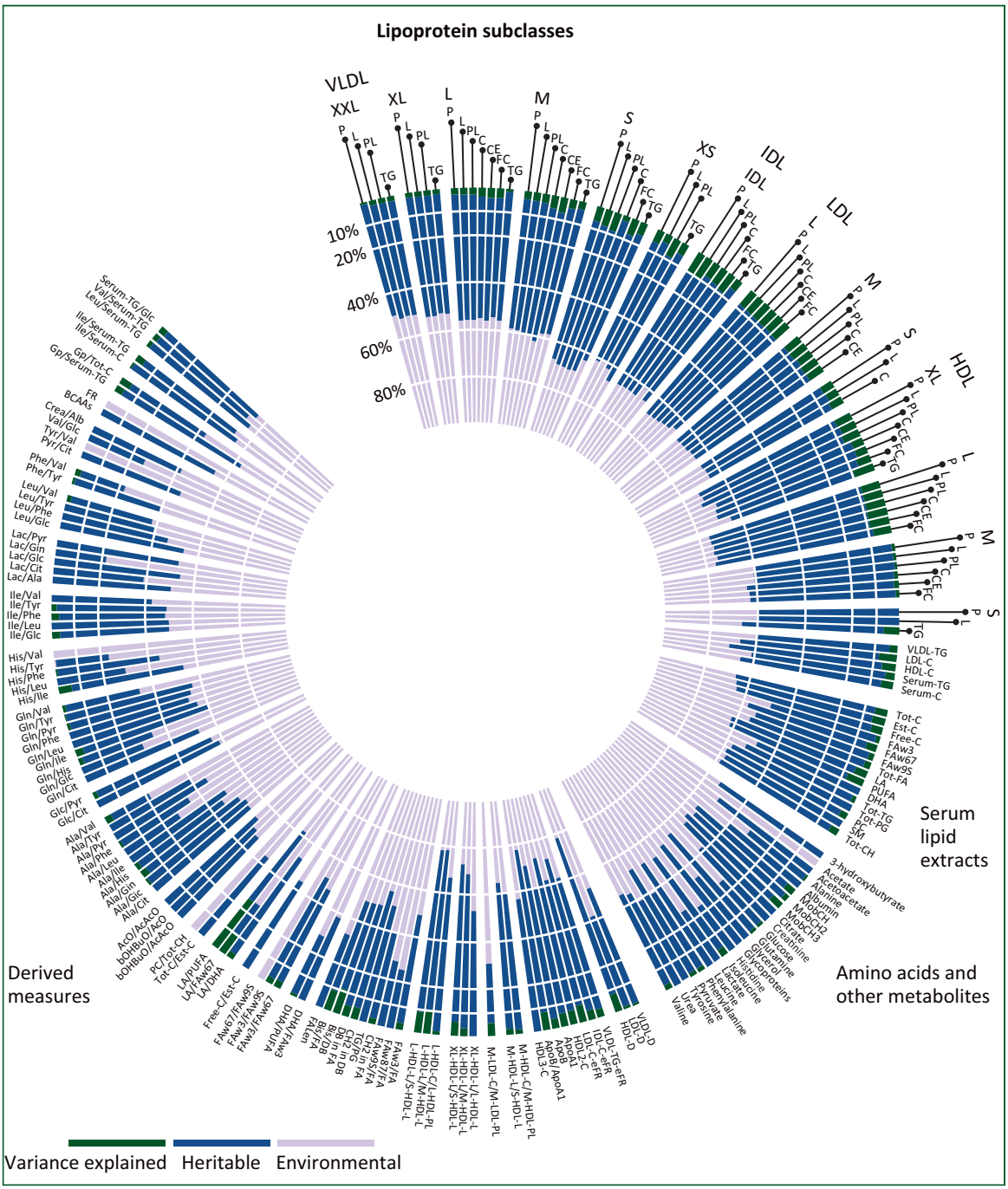

FIGURE 4. The heritability estimates and proportion of variance explained for serum metabolites determined using nuclear magnetic resonance metabolomics. C, total cholesterol; CE, cholesterol esters; FC, free cholesterol; L, total lipids; P, concentration of particles; PL, phospholipids; TG, triglycerides. Redraw reproduced with permission from Kettunen et al. [8].

OTHER "OMICS"

It is often useful to examine genomics together with other "omics" to learn more about the biology underlying the genotype-phenotype associations. FINRISK has carried out transcriptomics and epigenomics on subsamples of participants, and metabolomics has been applied quite extensively. Nuclear magnetic resonance-based metabolomics profiling has been performed for the FINRISK

1997 and 2007/DILGOM cohorts, and mass spectrometry-based targeted metabolomics determinations have been done for sizable subsamples of the FINRISK cohorts, and these determinations are quickly expanding. Our analyses have shown that precise phenotyping with metabolomics produced stronger genetic associations than the conventional phenotyping [8]. SNPs at the 31 loci associated with individual metabolites in our study accounted for up to 40% of the genetic component of trait variance, which is clearly more than usually observed in GWAS (Fig. 4).

GENETIC VERSUS ENVIRONMENTAL DETERMINANTS OF CVD

The post-war increase in CHD mortality and its subsequent decline in Finland have been large and rapid [9]. It is clear that our genetic background does not change in 50 years. Yet, the heritability of CHD has been estimated to be high, about 50% to 60% [10,11]. It is important to note that CHD is a multifactorial disease and the genetic basis for common, complex disease is not deterministic. Rather, the genetic background sets the level of susceptibility, which then forms the basis for the influence of risk factors. The high level of CHD mortality and morbidity in eastern Finland, which has continued over the years [12], suggests that the genetic susceptibility to CHD is high in this population. It is well known that the population of eastern Finland differs genetically from the population of southern and western Finland [13], but the consequences of those differences in terms of cardiovascular risk have not been reported using the tools of modern genomics. For the first time, we are now in a position to address the question regarding genetic versus environmental contributions to the differences in CHD mortality and morbidity between eastern and western Finland.

COLLABORATION AND DATA SHARING

The achievements of GWAS, and those of the sequencing studies, have been based on wide international and national collaboration and data sharing. The recently enacted law on biobanking in Finland has created the background for sharing the FINRISK genetic data with the scientific community. The National Institute for Health and Welfare (THL) has established a biobank, and the FINRISK data have been made available to the scientific community based on a written application to the THL biobank (https://www.thl.fi/fi/web/thlfi-en/topics/information-packages/thl-biobank). Likewise, the whole genome sequencing and the whole exome sequencing data from FINRISK, as well as from other Finnish cohorts, have been collected into the database of the Sequencing Initiative Suomi (SISu) project (http://www.sisuproject.fi/), which provides opportunities for searching the database for autosomal SNPs and indels, as well as applying for the data in collaboration with the THL biobank.

SUMMARY

Modern genomics has identified several genetic variants associated with cardiovascular risk, and this development is likely to accelerate. FINRISK has helped to accomplish this and has tested the effects of the identified variants in the Finnish population. The technology is proceeding with a rapid pace, and it will soon be feasible to include all variants relevant in the Finnish population in a single genotyping chip and use these genotyping results for building a new layer of precise prevention and treatment measures on top of the continuing population-wide prevention efforts.

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