Extended Abstract
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The genetics of common diseases

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Abstract

At deCODE genetics in Iceland we have sequenced the whole genomes of 50.000 Icelanders or 12.5% of the nation and genotyped 180.000 or 60% of the nation. In addition we have the genealogy of the entire nation going centuries back in time on a computer database. This allows us to impute sequence variants with allelic frequency down to about 0.01% into all genotyped individuals and their first and second degree relatives. We are in the privileged position of being able to phase the entire genomes of all Icelanders. This has allowed us to determine whether there is a difference in the impact of sequence variants depending on the parent it is inherited from. Taking advantage of this we have found sequence variants that increase the risk of disease when it is inherited from one sex and protect against the same when it is inherited from the other sex. Furthermore, we have discovered a number of sequence variants where there is a difference in the size of the effect depending on the parent of origin. Hence, a parent of origin analysis of associations between variants in the sequence and diversity in phenotypes is a part of our daily routine. Furthermore, we have combined whole genome oxidative bisulfite sequencing of 285 individuals and allele specific RNA sequencing of 11,617 blood samples with parnet-of-orgin phased haplotyes, to produce a new map of imprinted methylation and gene expression pattern across the human genome. Through this we have, for example, gained new insights into parent of origin specific effects on phenotypes

Inherited genetic variation contributes to individual risk for many complex diseases and is increasingly being used for predictive patient stratification. Previous work has shown that genetic factors are not equally relevant to human traits across age and other contexts, though the reasons for such variation are not clear. Here, we introduce methods to infer the form of the longitudinal relationship between genetic relative risk for disease and age and to test whether all genetic risk factors behave similarly. We use a proportional hazards model within an interval-based censoring methodology to estimate age-varying individual variant contributions to genetic relative risk for 24 common diseases within the British ancestry subset of UK Biobank, applying a Bayesian clustering approach to group variants by their relative risk profile over age and permutation tests for age dependency and multiplicity of profiles. We find evidence for age-varying relative risk profiles in nine diseases, including hypertension, skin cancer, atherosclerotic heart disease, hypothyroidism and calculus of gallbladder, several of which show evidence, albeit weak, for multiple distinct profiles of genetic relative risk. The predominant pattern shows genetic risk factors having the greatest relative impact on risk of early disease, with a monotonic decrease over time, at least for the majority of variants, although the magnitude and form of the decrease varies among diseases. As a consequence, for diseases where genetic relative risk decreases over age, genetic risk factors have stronger explanatory power among younger populations, compared to older ones. We show that these patterns cannot be explained by a simple model involving the presence of unobserved covariates such as environmental factors. We discuss possible models that can explain our observations and the implications for genetic risk prediction.

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