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Incorporating family disease history in risk prediction models with large-scale genetic data substantially dissolves unexplained variability

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Motivation: Despite the many successes of genome-wide association studies (GWAS), the known susceptibility variants identified by GWAS have modest effect sizes, leading to notable scepticism about the effectiveness of building a risk prediction model from large-scale genetic data. However, in contrast to genetic variants, the family history of diseases has been largely accepted as an important risk factor in clinical diagnosis and risk prediction. Nevertheless, the complicated structures of the family history of diseases have limited their application in clinical practice.

Results: Here, we developed a new method that enables incorporation of the general family history of diseases with a liability threshold model, and propose a new analysis strategy for risk prediction with penalized regression analysis that incorporates both large numbers of genetic variants and clinical risk factors. Application of our model to type 2 diabetes (T2D) patients in the Korean population (1846 cases and 1846 controls) demonstrated that single nucleotide polymorphisms accounted for 32.5% of the variability of risk in T2D cases, and incorporation of family history led to an additional 6.3% improvement in prediction. Our results illustrate that the family medical history is valuable information on the variability of complex diseases and improves prediction performance.