KEYNOTE SPEAKER

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Topic:

Polygenic Risk Scores and prediction of metabolic syndrome: Is more better?

Abstract:

Introduction and Methods: Susceptibility to most common chronic conditions is due to interactions between multiple genetic variants and nongenetic factors. Polygenic scores (PGS) are used to capture the complex genetic effects with the goal of identifying genetically susceptible individuals. PGS are often based on meta-analysis comprised of multiple genome-wide association analyses (GWAS) that emphasize common variants. However, there are many questions about how to best construct a PGS. For example, it is not clear how well PGS based on GWAS from European ancestry (EA) populations will predict disease in non EA populations. We use a multi-ethnic sample of families to: (1) evaluate the association between a common-variant genetic burden PGS and metabolic syndrome (MetS)-related traits; (2) to compare / contrast the prediction of MetS traits from PGS based under different scenarios. In this talk, I will introduce the concept of PGS and will utilize data from a large multi-ethnic family study of type 2 diabetes to illustrate several key points. Briefly, data from the GENNID study consists of 1502 subjects in 259 families from European-American (EA), Mexican-American (MA), African-American (AA), and Japanese-American (JA) families. The Clumping and Thresholding (C + T) method was used to construct PGS based on single ancestry-specific GWAS meta-analysis summaries for body mass index (BMI), summaries based on EA samples only, and from a meta-analysis consisting of multiple populations. We evaluated the association of PGS constructed under these different scenarios and using a linear mixed effects model (with fixed covariate effects and random family effects). P-values were approximated using a normal distribution. For each ethnic group, ROC curves and AUC values (using bootstrapping methods) were used to compare the ability of PGS to predict obesity (BMI>30).
Results and Conclusion: PGS based on a GWAS meta-analysis of multiple populations predicted better (i.e., had higher AUC) than PGS based on either ancestry-specific or EA GWAS. The AUC values ranged from 53% to 71%, but explained less than 6% of the variance in obesity. In general, the proportion of variance explained was low but is consistent with the literature for other common, complex conditions.