**Supplementary method: Rare variants burden analysis**

Controls were from the gnomAD East Asian population (https://gnomad. broadinstitute.org/). Rare variants were defined by minor allele frequency (MAF) lower than 0.1% in the public database as mentioned above. Combined Annotation Dependent Depletion (﻿CADD) integrates predictions from numerous bioinformatic algorithms into a single ‘C-score’ and ranks all possible nucleotide changes in the genome based on potential to disrupt gene/protein function(Uitterlinden *et al.*, 2017). In accordance with the previous study, we defined a stringent CADD C-score≥12.37 as likely damaging variants, representing the top 2% most damaging of all possible nucleotide changes in the genome—this subset is enriched for known pathogenic alleles(Uitterlinden *et al.*, 2018). All the rare and rare deleterious variants annotated as “missense”, “splice donor”, “splice acceptor”, “splice region”, “stop-gained” or “in-frame deletion” were included. Five different algorithms method were used for burden analysis with AssotesteR Package in the rare variants level and rare deleterious variants level(Lee *et al.*, 2014), including Comprehensive Approach to Analyzing Rare Genetic Variants (CARV), Sum of Squared Score (SSU), Sum Test (SUM), Cumulative Minor Allele Test (CMAT), and Bayesian Score Test (BST).

**Reference:**

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