APPLICATIONS OF GENOMICS AND COMPUTATIONAL BIOLOGY TO THE UNDERSTANDING OF ELITE HUMAN PERFORMANCE

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PURPOSE: To search for novel genetic variants of elite human performance, we conducted an imputation-driven meta-analysis of three genome-wide association studies (GWASs) in elite Jamaican (Jam), African-American (A-A) and Japanese (Jpn) sprint athletes and their matched controls. **METHODS:** 95 Jam athletes and 102 Jam controls, 108 A-A athletes and 397 A-A controls, and 54 Jpn athletes and 118 Jpn controls were analysed on Illumina BeadChips (~1 million markers). Following the standard GWAS quality control (QC) procedures, each GWAS cohort was subjected to two imputation pipelines (i.e., IMPUTE2 on the 1000G Phase 3 reference panels and Sanger Imputation Sever on the African Genome Resources, respectively). Post imputation QC was set for imputation quality measure>0.3 and minor allele frequency, MAF≥0.05. Genetic associations were tested using SNPTEST Frequentist additive model, conditioning on population structure and genotyping centres where appropriate. Meta-analysis was performed in METAL using the inverse variance-weighted fixed-effect model with genomic control (GC) correction. **RESULTS:** The meta-analyses resulted in a list of ~10 million genetic markers following the IMPUTE2 or Sanger imputation. The genomic inflation factor values were close to 1. The imputed marker at chr2:154837893 (GRCh37; MAF: 0.06-0.35; tightly linked with the top genotyped signal at chr2:154826491, r^2=0.97, D' =1) in the intron of *GALNT13* exhibited the strongest evidence for association with a combined odds ratio of 2.52 ($P_{combined}$=2.75x10^{-7} GC corrected, I^2=0%, P_{het}=0.63, IMPUTE2; and $P_{combined}$=3.16x10^{-7} GC corrected, I^2=0%, P_{het}=0.64, Sanger). This finding was independently replicated in two European cohorts (234 athletes vs. 1525 controls from Belarus, Lithuania and Russia and 171 athletes vs. 595 controls from Australia, Belgium, Greece and Poland). In addition, among 98 genetic markers located in 32 genes exceeding a suggestive P<1x10^{-5} (Sanger), enrichment clustering analysis (in Metascape) revealed genes associated with the neuronal system, steroid biosynthetic process and a variety of transporter activities (prior to Benjamini-Hochberg P-value correction). **CONCLUSIONS:** These data highlight potential genetic loci for elite sprint performance. Research challenges lie in deeper understanding of the gene functions/networks and the underlying complete genetic architecture of elite human performance, requiring a concerted research effort and diverse expertise in systems biology.