The contribution of sequencing based GWAS in explaining the missing heritability of quantitative traits

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Genome-wide association studies (GWAS) have yielded valuable insights into the genetic architecture of complex quantitative traits, but have often left much of the trait heritability unexplained. To assess the hypothesis that a portion of unexplained heritability can be due to variants not included or poorly tagged in common genotyping arrays and in the HapMap dataset, we analyzed 6,145 individuals from the SardiNIA study, for a set of ~8 million variants, directly genotyped or imputed with a reference panel derived from whole-genome low-pass sequencing of 1,146 Sardinian individuals, focusing on four quantitative traits: hsCPR, IL-6, MCP-1 and ESR. When considering only loci previously identified by us in the same cohort, for the first two traits we observed no improvement in the heritability, the top variants resulting from this analysis being in strong linkage disequilibrium (LD) with those already described. By contrast, for MCP-1 and ESR, we observed different leading variants not in LD with those found previously, as well as additional independent signals, which led to an increase in the heritability explained from 9.4% to 11.6%, and from 2.7% to 3.9%, respectively. The imputation of variants detected by sequencing also contributed to the identification of two novel loci for both MCP-1 and hsCRP. The inclusion of these markers further increased the heritability explained to 12.5% for MCP1, and from 5.0% to 6.7% for hsCRP. Our results thus indicate that the forthcoming sequencing based GWAS will contribute to better account for the heritability at previously described loci, and will further help to explain the missing heritability with the identification of novel associations.