Presentation title: Detection and replication of epistasis influencing transcription in humans

Abstract:
Epistasis is the phenomenon whereby one polymorphism's effect on a trait depends on other polymorphisms present in the genome. The extent to which epistasis influences complex traits and contributes to their variation is a fundamental question in evolution and human genetics. Although often demonstrated in artificial gene manipulation studies in model organisms, and some examples have been reported in other species, few examples exist for epistasis among natural polymorphisms in human traits. Its absence from empirical findings may simply be due to low incidence in the genetic control of complex traits, but an alternative view is that it has previously been too technically challenging to detect owing to statistical and computational issues. Here we show, using advanced computation and a gene expression study design, that many instances of epistasis are found between common single nucleotide polymorphisms (SNPs). In a cohort of 846 individuals with 7,339 gene expression levels measured in peripheral blood, we found 501 significant pairwise interactions between common SNPs influencing the expression of 238 genes ($P < 2.91 \times 10{-}16$). Replication of these interactions in two independent data sets showed both concordance of direction of epistatic effects ($P = 5.56 \times 10{-}31$) and enrichment of interaction P values, with 30 being significant at a conservative threshold of $P < 9.98 \times 10{-}5$. Forty-four of the genetic interactions are located within 5 megabases of regions of known physical chromosome interactions ($P = 1.8 \times 10{-}10$). Epistatic networks of three SNPs or more influence the expression levels of 129 genes, whereby one cis-acting SNP is modulated by several trans-acting SNPs. For example, MBNL1 is influenced by an additive effect at rs13069559, which itself is masked by trans-SNPs on 14 different chromosomes, with nearly identical genotype–phenotype maps for each cis–trans interaction. This study presents the first evidence, to our knowledge, for many instances of segregating common polymorphisms interacting to influence human traits.