The power of high-resolution population-specific genetic maps to dissect the genetic architecture of complex diseases: Type 2 Diabetes as an example

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Metric genetic maps in Linkage Disequilibrium Units (LDU) are analogous to Linkage maps in cM but at a much higher marker resolution. LDU blocks represent areas of conserved LD and low haplotype diversity, while steps (increasing LDU distances) define LD breakdown, primarily caused by recombination, since crossover profiles agree precisely with the corresponding LDU steps. However, LDU maps do not only capture recombination events but the detailed linkage disequilibrium information of the population in question. We recently constructed the LDU genetic maps in Europeans and African-Americans and applied these to large T2D case-control samples in order to estimate accurate locations for putative functional variants in both populations. Replicated T2D locations were tested for evidence of being regulatory locations using adipose expression. We identified 111 novel loci associated with T2D-susceptibility locations, 93 of which are cosmopolitan (co-localised on genetic maps for both populations) and 18 are European-specific. We also found that many previously known T2D signals are also risk loci in African-Americans and we obtained more refined causal locations for these signals than the published lead SNPs. Using the same LDU methods, we also showed that the majority of these T2D locations are also regulatory locations (eQTLs) conferring the risk of T2D via the regulation of expression levels for a very large number (266) of cis-regulated genes. We identified a highly significant overlap between T2D and regulatory locations with chromatin marks for different tissues/cells. Sequencing a sample of our locations provided candidate functional variants that precisely co-locate pancreatic islet enhancers, leading to our conclusions that population-specific genetic maps can: (i) provide commensurability when making comparisons between different populations and SNP-arrays; (ii) provide precise location estimates on the genetic map for potential functional variants, since these estimates are more efficient than using physical maps and (iii) effectively integrate disease-associated loci in different populations with gene expression and cell-specific regulatory annotation, by providing precision in co-localisation.