From LD-based mapping to GWAS

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Journal Club

COMPLEX TRAITS

FROM LD-BASED MAPPING TO GWAS

> the first empirical proof that LD could be used to map a human disease gene by genome-wide screening

Back in 1986, Lander and Botstein proposed that mapping based on linkage disequilibrium (LD) — the non-random association of alleles at different loci — could be used to screen the entire human genome for disease loci. Until then, the classical approach had been to apply parametric linkage analysis in families with clear disease inheritance. However, it was a landmark paper by Houwen et al., published in 1994, that provided the first empirical proof that LD could be used to map a human disease gene by genome-wide screening.

The team used a set of only 256 so-called microsatellite markers but were able to identify chromosomal segments that were shared between three seemingly unrelated patients with autosomal recessive benign recurrent intrahepatic cholestasis (BRIC). Given the rarity of the disease and the fact that the patients with BRIC were all from an isolated fishing community in the Netherlands, the authors hypothesized that the affected individuals were distant relatives descended from a common ancestor 10–12 generations ago (based on the population increase in their community around the year 1800). The authors were fortunate to identify the roughly 20 cM chromosome 18q21–22 haplotype that was shared identity-by-descent (IBD) with such a sparse set of markers and an average spacing of 10–20 cM.

Lodewijk Sandkuijl, the statistical geneticist on the Houwen et al. article, had conceived of the possibility of mapping complex traits in population isolates using LD, and he used the BRIC study as a proof of principle to show the power of this approach. The paper elegantly showed the inverse relation between the median length of a shared IBD segment around a disease gene and the number of meiotic steps that separate two patients from a common ancestor.

Genome-wide association studies (GWAS) for complex diseases and traits are based on this concept. The common variants associated to common diseases are often shared IBD, and unrelated patients are presumed to be descended from a much more distant ancestor (10s to 100s of generations ago). Consequently, the LD between a tested DNA marker and disease-associated alleles is very small, and the ability to map such alleles has only become possible with the advent of high-resolution maps of single-nucleotide polymorphisms (SNPs) and DNA chip technology. Nowadays, genotyping large numbers of these SNPs on 1,000s to 10,000s of disease cases and controls is quick and relatively cheap.

In 2005, the first GWAS was conducted on a complex disease by genotyping 116,204 SNPs in 96 cases of age-related macular degeneration and in 50 controls. Lodewijk Sandkuijl passed away suddenly in 2002 at the age of only 49 years. He has not been able to witness his conceptual legacy working its magic in the widespread use of GWAS, nor its success in mapping genes for complex diseases and traits. Nevertheless, it was his forward thinking that inspired me in 1996, when setting up my own research group, to move into complex disease genetics. My major research focus was on coeliac disease, for which we conducted the first successful GWAS in 2007.

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ORIGINAL ARTICLE Houwen, R. H. J. et al. Genome screening by searching for shared segments: mapping a gene for benign recurrent intrahepatic cholestasis. *Nat. Genet.* **8**, 380–386 (1994)