Genome-wide association defines more than thirty distinct susceptibility loci for Crohn's disease

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Genome-wide association studies (GWAS) in Crohn's disease (CD) published as of June 2007 have defined unequivocal evidence of 9 novel, replicating loci, increasing the total number of confirmed risk factors from 2 to 11. It is clear from the published data, however, that the loci identified to date constitute only a minority of the overall heritability, and that power in the individual studies was quite low to identify even loci that were later confirmed. Thus, to further gene discovery from these efforts, we have embarked on a joint analysis and coordinated replication study of top results.

The combined study begins with a meta-analysis of the three published scans: 1748 cases/2938 controls (Wellcome Trust Case Control Consortium, UK) - Affymetrix 500K, 946 cases/977 controls (NIDDK IBD Genetics Consortium, North America) - Illumina HumanHap 300K, 547 CD cases/928 controls (Belgium/France) - Illumina HumanHap 300K. We have combined the existing genotype data with "imputed" genotypes predicted via statistical models of known haplotypes from the HapMap project to enable a joint analysis of roughly 3200 cases and 4800 controls on the superset of 650,000 SNPs contained on one or both genotyping platforms. This combined data set offers substantially increased power to detect genes of modest effect: a 20% risk allele with an OR of 1.2 has only a 6% chance of achieving a $p < 0.0001$ in a "typical" 1000 case/1000 control GWAS, but a 78% chance of doing so in the combined study.

The initial meta-analysis convincingly confirms all replicated published loci (including established older associations at NOD2 and IBD5 and all recently reported hits such as IL23R, ATG16L1, IRGM, and NKX2-3), 9 of which have $p < 10^{-8}$. Importantly, the meta-analysis has revealed more than 30 additional loci with $p < 10^{-5}$. Very few such results are expected by chance and, as the bulk of the distribution indicates no systematic inflation ($\lambda_{GC} < 1.1$), the majority of these likely constitute novel risk factors. The results of a coordinated replication effort in independent samples will be reported, providing a dramatically augmented picture of the genetic architecture of Crohn's disease.