

of the effects of novel invasive procedures that aim to decrease lung hyperinflation.

Technical development in this area should continue, with the aim of prolonging the patency of airway stents. In future trials, selection of patients needs to be done carefully so that the chances of producing a persistent therapeutic effect are high. For progress to be made, detailed analysis of the EASE trial will be needed, to identify responding populations and to improve procedural methods. Only then will this type of procedure enrich our therapeutic arsenal for treatment of advanced pulmonary emphysema.

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Successfully mapping novel asthma loci by GWAS

The past several decades have witnessed a revolution in genomic medicine, punctuated in recent years by the explosion of discoveries from genome-wide association studies (GWAS). Shortly after completion of the Human Genome Project in 2003, the technological capacity to rapidly (and cheaply) genotype more than 1 million common (>5%) single nucleotide polymorphisms (SNPs) on thousands of DNA samples from patients phenotyped for various complex clinical traits took the spotlight. Consider the success of GWAS in the span of only 6 years, in which nearly 1000 publications have catalogued up to 5000 SNPs associated with various complex and quantitative traits.¹ But despite its successes, GWAS have come under intense criticism. The debate stems from findings that would have been impossible to obtain before GWAS: most of the common variants associated with complex traits confer very modest effect sizes and can explain only a small fraction of heritability; many of the strongest associations are for loci rather than functional variants—or even known genes—with any obvious biological relevance to disease; and, finally, more common variants worthy of discovery

might not exist because the so-called low hanging fruits have already been picked, and any variants left on the tree would confer only negligible effects.^{2–5} Defence of GWAS design is made more difficult because of a paradigm shift away from the common disease—common variant hypothesis⁶ towards rare variants (unlikely to be identified by GWAS⁷) in non-mendelian diseases.⁸ This trend is driven in part by the upsurge of next-generation sequencing technologies that enable sequencing of all known exons or the entire genome to pick up both rare and common variants controlling disease risk.

Regardless of the shortcomings, GWAS must be given credit as a powerful method for confirmation of suspected pathways and elucidation of new ones. Indeed, in a recent commentary,⁹ GWAS were credited for revealing a greatly expanded list of targets for new drugs, and, additionally, for revealing overlapping molecular pathways across clinical phenotypes⁹ previously believed to be distinct, suggesting there might be greater bang for the buck in both existing and newly developed drugs.



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The compelling evidence for genetic association of two novel loci for asthma presented by Manuel Ferreira and colleagues¹⁰ in *The Lancet* challenges the naysayers, and their results overall are emblematic of the many attributes (and pitfalls) of GWAS. The team took advantage of its own Australian Asthma Genetics Consortium combined with publicly available data from the very large European (GABRIEL) consortium (which published an independent asthma GWAS¹¹), plus replication in four independent and biogeographically diverse cohorts for a total of nearly 58 000 samples. In recent years, the formation of consortia has been an important factor in the optimisation of the likelihood of achieving genome-wide statistical significance, and in the replication of previous results as well as the identification of novel candidates. For example, until the recent US-based EVE consortium's report,¹² there was a lack of overlap of genes from independent asthma GWAS.¹³ The Australian GWAS yielded significant evidence for four loci and suggestive evidence for two additional asthma loci. Two genes (*IL33*, *IL18R1*) fall into the large toll-like receptor/interleukin-1R (TIR) superfamily, a pathway only recently appreciated for its role in production, activation, and recruitment of immune cells contributing to airway inflammation.¹⁴

The loci representing the two strongest novel associations in this report especially underscore the strength of GWAS. The gene encoding the multi-functional, pro-inflammatory cytokine interleukin-6 receptor (*IL6R*), would easily qualify as a candidate gene for asthma, but, with the exception of a single candidate gene study,¹⁵ *IL6R* has not been a serious contender. Ferreira and his team were especially fortunate in finding what could be the causal variant (rs4129267) itself, an unlikely discovery. The other marker, SNP rs7130588 on chromosome 11q13.5, is more characteristic of a GWAS finding: an intergenic variant of unknown function. But in this case, rs7130588 is in strong linkage disequilibrium with rs7927894, for which there is not only a priori association with allergic disease (atopic dermatitis¹⁶), but also with Crohn's disease.

Like most previous GWAS, the two top signals, rs4129267 and rs7130588, are common (minor allele frequency 0.35–0.41) in the European ancestry

discovery and replication cohorts genotyped, and both markers confer only modest risk (OR 1.06–1.13) of asthma. Nevertheless, success in the validation of various candidates (and their pathways) that are already on the asthma shortlist of potential causal genes, and the biological insight to be gained from the novel findings in this report, are grounds for optimism in the continuation of the GWAS approach. Combination of GWAS with next-generation technologies will undoubtedly further help to disentangle the molecular underpinnings of complex traits such as asthma.

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