ALLERGY

NOTHING NEW UNDER THE SUN THAN STRONG SHADOWS

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There is a new NEJM paper on asthma genetics.

I am not really sure if I am really an author of this paper (I am listed as collaborator whatever that means). At least, the study relies heavily on thousands of samples and a big data set that I sent to the study management board) while it its certainly a paper that summarizes the efforts of many years of research.

Unfortunately it shares all problems of current GWAs studies. As I did not have any chance to comment on it during the preparation, here are some thoughts (and it is funny to see that my blog is ranked higher in Google search than the original paper- a curiousity showing a changing world where scientists have already lost their power on public opinion). But lets work along the abstract.

Susceptibility to asthma is influenced by genes and environment; implicated genes may indicate pathways for therapeutic intervention.

The first sentence is a bit trivial. I usually delete such sentences from manuscripts. The second sentence is a mantra repeated over and over again, never proven, origininating from application prose than from any scientific study.

We carried out a genomewide association study by genotyping 10,365 persons with physician-diagnosed asthma and 16,110 unaffected persons, all of whom were matched for ancestry. We used random-effects pooled analysis to test for association in the overall study population and in subgroups of subjects with childhood-onset asthma (defined as asthma developing before 16 years of age), later-onset asthma, severe asthma, and occupational asthma.

I wonder why we need now >25,000 DNAs as Coookson already reported in his book that “he found the asthma gene” (ref)? Are effects are so small (or is the design of genotyping chips so poor) that we need so many samples? The introduction says that current GWAS technology is the method of choice for identifying genes that influence complex disease.

I do not agree – we need better defined phenotypes than just some self reported disease (separating all kind of "asthmatic" obstruction). We need SNP alleles of the whole frequency range (not just the tagging SNPs), simply speaking *better* and not just *larger* studies.

We observed associations of genomewide significance between asthma and the following single-nucleotide polymorphisms: rs3771166 on chromosome 2, implicating IL1RL1/IL18R1 (P=3×10(?9)); rs9273349 on chromosome 6, implicating HLA-DQ (P=7×10(?14)); rs1342326 on chromosome 9, flanking IL33 (P=9×10(?10)); rs744910 on chromosome 15 in SMAD3 (P=4×10(?9)); and rs2284033 on chromosome 22 in IL2RB (P=1.1×10(?8)). Association with the ORMDL3/GSDMB locus on chromosome 17q21 was specific to childhood-onset disease (rs2305480, P=6×10(?23)). Only HLA-DR showed a significant genomewide association with the total serum IgE concentration, and loci strongly associated with IgE levels were not associated with asthma.

Although not referenced in the paper, we described an association with the IL1 cluster already in 1994 that I further refined in 2008 to IL18R1 which was also published in our NG paper 2009.

IL13, IL33, HLA-DQ, IL2RB: nothing new under the sun. Also the "ORMLD3" story has been fully published (see some earlier comments), while ORMLD3 doesn't even appear in table 2 (reported are only results for GSDMA and GSDMB). For any unknown reason ORMDL3 makes it into the last sentence of the paper and the abstract. I have no idea how in such highly correlated number space, a forward stepwise regression can establish an independent association. Ordering results by p value, does that make any sense?

What worries me: There was non interaction between SNP variants, which would indicate that a single gene alone could lead to asthma – something extremely unlikely from all previous studies where we could never find a monogenic asthma form.

CONCLUSIONS: Asthma is genetically heterogeneous. A few common alleles are associated with disease risk at all ages. Implicated genes suggest a role for communication of epithelial damage to the adaptive immune system and activation of airway inflammation. Variants at the ORMDL3/GSDMB locus are associated only with childhood-onset disease. Elevation of total serum IgE levels has a minor role in the development of asthma.

Where is the longstanding claim of Cookson of IgE and FCER1B? Gone? The current NEJM article even refutes the January NEJM issue of DENND1B (largely by the same authors: "none of these associations were significant after correction for multiple comparisons"). What will be the content of the next paper in 2020 with 100K asthmatics?

The little overlap between "IgE loci" and "asthma loci" is not an argument that "elevation

of IgE level is an inconstant secondary effect of asthma" as also this new paper is just a cross-sectional study and these are just some association, nothing else.