ALLERGY, GENETICS

IL4 AND ASTHMA

10.09.2020

A new Cell paper on “The Polygenic and Monogenic Basis of Blood Traits and Diseases” now highlights the association of IL4 and asthma.

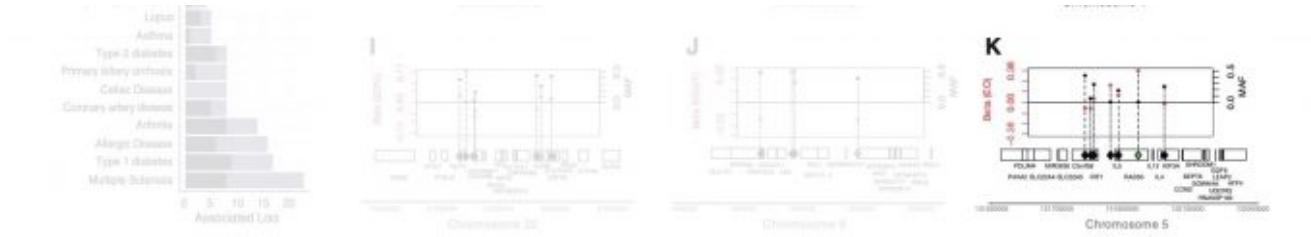

Figure 5. Polygenic Prediction of Blood Traits and Contribution to Common Diseases

(A) Portability of the PGS across populations with European ancestry for 15 available traits. The red bar represents the Pearson's correlation (R) between the score and the trait in the validation cohort (INTERVAL). Blue bars show the same in a French Canadian cohort called CARTAgENE.

(B and C) Saturation analysis showing the number of discovered variants (B) and the proportion of heritability explained (C) as a function of GWAS sample size for mean platelet volume. The black dotted line is a linear projection of the first 3 points, the red dotted line is a linear interpolation of all points, and the red solid curve is the best model fitting the 4 points.

(D) Number of loci with multiple sentinel variants, stratified by trait group.

(E) Number of disease loci colocalizing (posterior probability > 99%) with at least one blood count locus, colored by known vs. new loci.

(F–K) Examples of loci with multiple sentinels associated with blood cell counts, and with at least one disease-colocalization (red diamond) or PheWAS association (green diamond) for the following genes and diseases: *ITGA4* and Inflammatory Bowel Disease (IBD) (F), *RUNX1* and Rheumatoid Arthritis (G), *NFKB1* and IBD (H), *C1QTNF6* and Type-1 Diabetes (I), *JAK2* and IBD (J), *IL4* and asthma (K). In each panel, black dots show MAF (right y axis) and red dots show the effect size (in SD for the phenotype between brackets, left y axis) of each variant as a function of the variant's position in the genomic interval.

trial for this therapeutic application (Todd et al., 2018) (ClinicalTrials.gov ID: NCT01862120). There were 3 colocalizing loci between asthma and eosinophil count and/or percentage and a further three novel PheWAS associations of rare non-coding variants near known asthma genes (*GATA3*, *RAD50*, and *IL33*). One of the rare variants is part of a 270-kb set of sentinels on chromosome 5 associated with eosinophil count, including another rare variant and 5 common signals (Figure 5K). The genes implicated are *C5orf56* (*IRF1-AS1* or *IRF1* antisense RNA 1), *IRF1*, *IL5*, *RAD50*, *IL13*, *KIF3A*, and *IL4*. Interestingly, both IL5 and IL4 are current therapeutic targets for treating a number of allergic diseases (Ortega et al., 2014; Chang and Nadeau, 2017). Overall, this large set of

The Influence of Polygenic Variation on Blood Disorders

Mendelian blood disorders display considerable heterogeneity in penetrance and expressivity. Furthermore, estimates of effect size and penetrance of pathogenic variants tend to be inflated when ascertained from patient populations (Wright et al., 2019). While the PGSs defined by the common variants discovered in this study explain a substantial proportion of variance of respective phenotypes, the extent to which polygenic variation contributes to the manifestation of rare diseases remains to be determined. To address this question, we first explored the genetic landscape of classical blood disorders in UK Biobank. We annotated each protein-coding sentinel variant using (1) ClinVar (Landrum et al., 2014), (2) Human Gene Muta-

Unfortunately we know that already for 27 years. Is genomic science suffering already from amnesia?