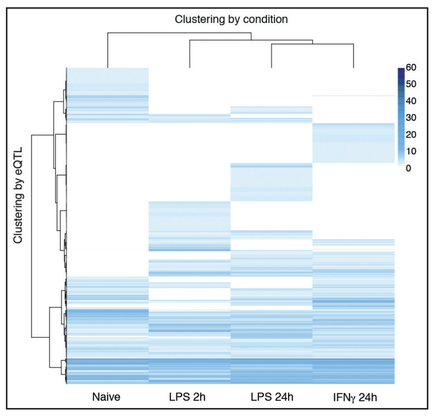
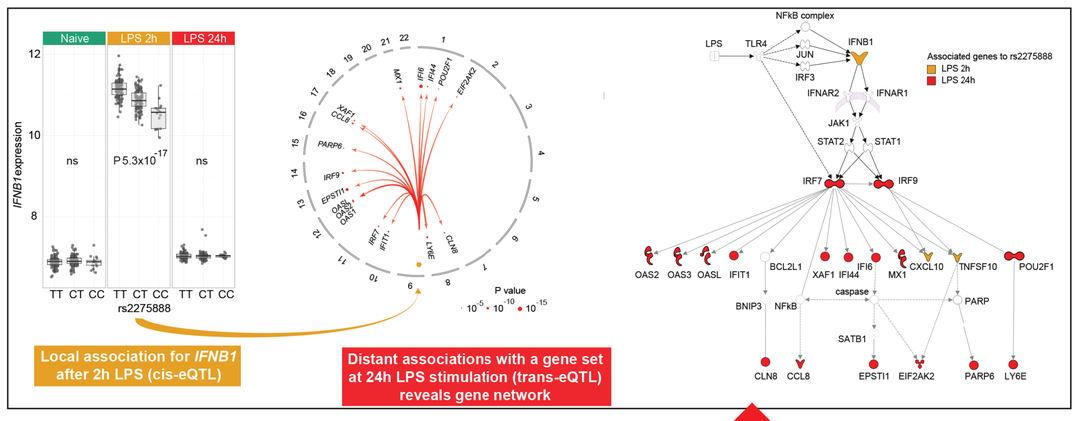
The Wellcome Trust Centre for
Human Genetics

UNIVERSITY OF OXFORD

Towards deciphering the genetic variation of human immune responses



Genotype modulates the gene expression response to innate different immune stimuli in monocytes (shown hierarchically in this cluster plot of genes with significant eQTL (FDR < 0.05) arranged by condition)

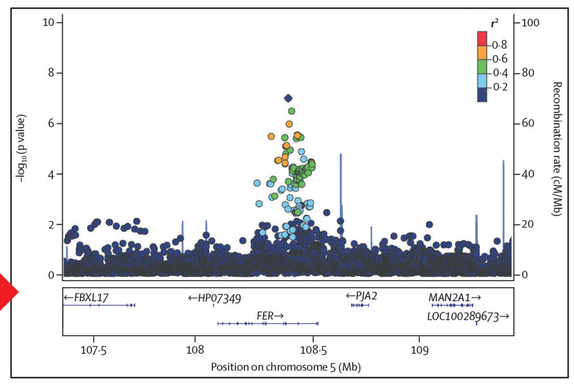


Local association for *IFNB1* after 2h LPS (cis-eQTL)

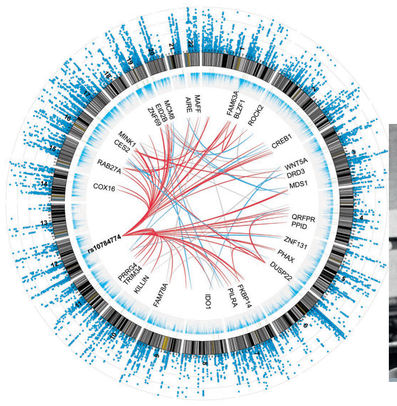
Distant associations with a gene set at 24h LPS stimulation (trans-eQTL) reveals gene network

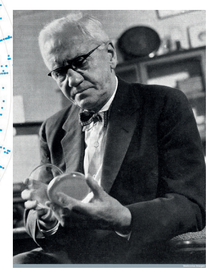
Genetic variants modulate expression of a key inflammatory cytokine (IFNB) only after activation of cells with endotoxin (LPS) for 2 hours with a downstream network of genes showing association after 24 hours

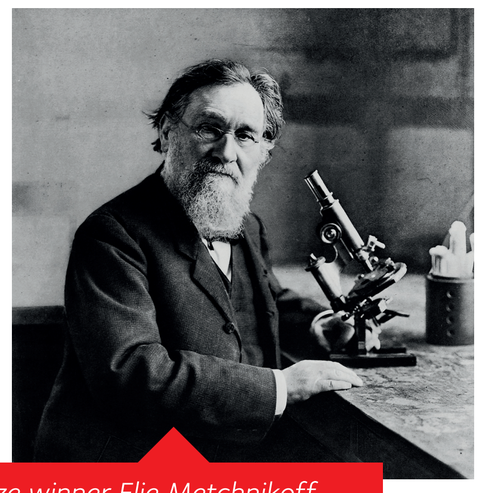
Genetic association involving variants in the FER gene with 28-day survival in patients with sepsis due to pneumonia



A polymorphism on chromosome 12 affecting expression of the lysozyme gene in monocytes was associated with expression of 62 other genes across the genome (shown in this Circos plot). Sir Alexander Fleming discovered lysozyme







Nobel prize winner Elie Metchnikoff was the first to observe bacteria being taken up (phagocytosed) into macrophages and microphages

WHAT WAS KNOWN

- Very rare genetic variants may result in uncommon primary immunodeficiency syndromes
- Genome-wide association studies (GWAS) similarly implicated common genetic variants to influence the immune system across several autoimmune and inflammatory diseases
- Understanding the functional impact of these common variants was limited
- Given their location in non-coding DNA, the majority of variants were thought to regulate the amount of a gene expressed. However in which cells and under which circumstances was unknown
- Common genetic variants unequivocally associated with severe infection (sepsis) were unknown

WHAT WE DID

- We explored the effect of genetic variation on gene expression (eQTL mapping) in different subsets of white blood cells, representing different arms of the immune system – initially monocytes and B-cells
- Monocytes are key to the early response to infection. We asked how the activity of a monocyte influences the effect of genetic variation and how this variation feeds back into monocyte activity!
- We established functional evidence for how certain key regulatory genetic variants act across the whole genome
- We took these results and integrated them with GWAS disease associated variants, helping shed light on the cell types and activity of importance
- We explored how genetic variation makes individuals susceptible to sepsis

WHAT THIS ADDS

- Genetic variants modulating gene expression are common and frequently act in a specific cell type or context
- Many disease associated variants demonstrate this specific cell type and activity-dependent effect
- By understanding which genes are modulated by such variants we can gain new insights into biologically important pathways and gene networks, and inform drug target discovery and prioritisation
- Disease relevance of eQTL involving response to endotoxin includes sepsis, for which the first GWAS was completed

REFERENCES

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