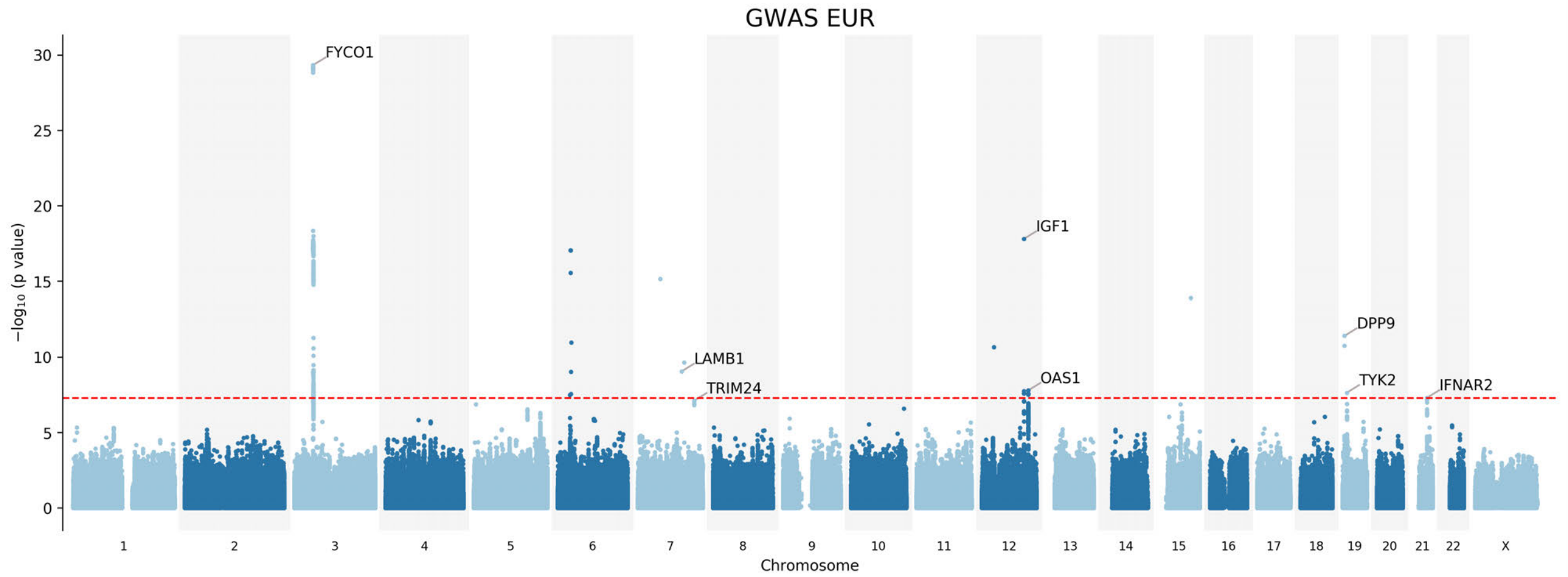
1st October 2020

Human genomics in COVID-19 SAGE

Kenneth Baillie – GenOMICC study, University of Edinburgh

Mark Caulfield – Genomics England


GWAS EUR
FYCO1
IGF1
DPP9
LAMB1
TRIM24
OAS1
TYK2
IFNAR2
−log10 (p value)
30
25
20
15
10
5
0
1
2
3
4
5
6
7
8
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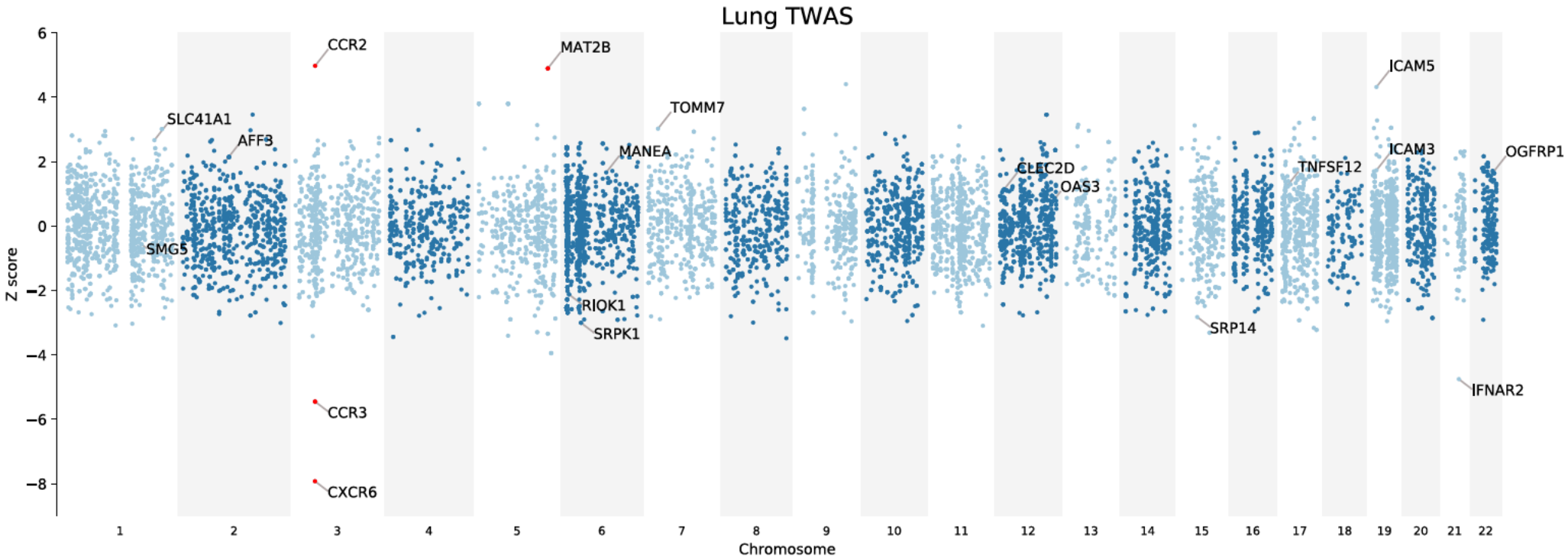
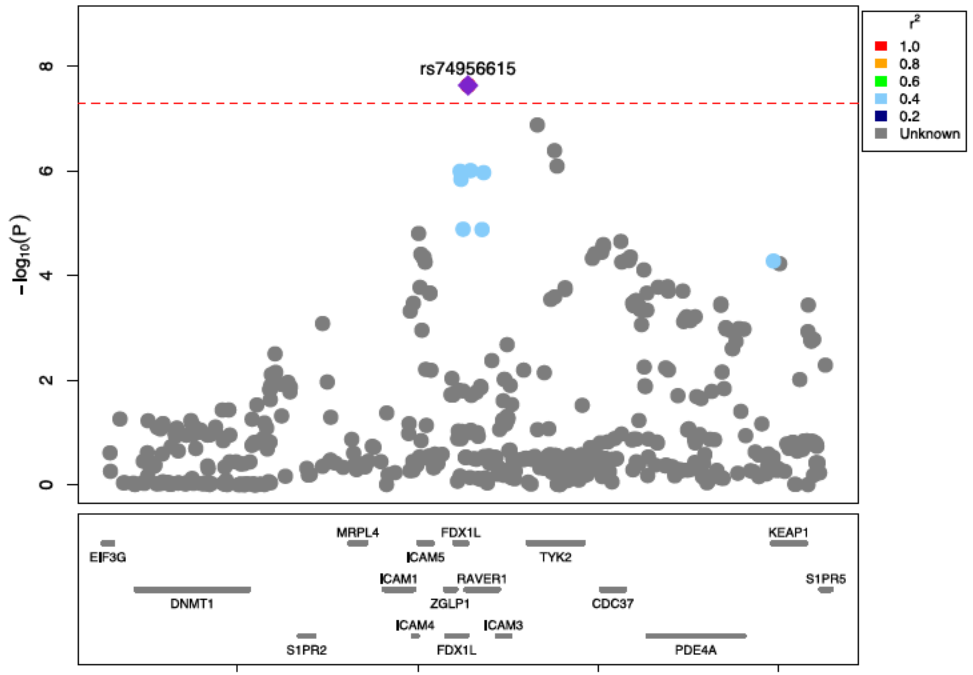
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Chromosome





Therapeutic relevance:

Antiviral effectors *early*

- Interferon and OAS

Anti-inflammatory treatment *late*

- TYK2 and (?) CCR2 (repurposing)

Inborn errors of type 1 interferon in life-threatening Covid

What did they do (Casanova et al – Science 2020)?

- 659 severe Covid patients (men 75%, women 25% and 14% deceased) v 534 COVID +ve mild or asymptomatic controls
- Mix of whole genome and exome sequencing (coding region only)
- Looked for enrichment of variants in 13 genes known to cause inborn errors of immunity (interferon, interferon regulatory factor 7 and toll-like receptor) and susceptibility to viral infection followed by functional testing of variants in Sars-Cov2 infected cells

What did they find?

- 3.5% of severe cases aged 17-77 males and 1 women across many ethnicities had loss of function rare variants in interferon, IRF7 and TLR3 affecting type 1 interferon. ? A role for X chromosome
- Human fibroblasts with these mutations were vulnerable to SARs CoV2

What is the potential clinical implication?

- **Interferon 1 therapy may be of benefit in severe COVID-19**

Auto-antibodies against type I IFNs in patients with life-threatening COVID-19

P. Bastard *et al*., *Science* 10.1126/science.abd4585 (2020).

What did they do:

- Type I IFNs are ubiquitously expressed cytokines contributing to both innate immunity and cell-intrinsic immunity against viral infections. Human inborn errors of type-I IFNs can underlie severe viral diseases, respiratory and otherwise.
- 987 patients hospitalized for life-threatening COVID-19 pneumonia, 663 COVID-19 positive individuals with asymptomatic or mild disease, and 1,227 healthy controls.
- Tested if neutralizing auto-Abs against type-I IFNs might also underlie life-threatening COVID-19 pneumonia.

What did they find:

- 13.7% of patients with life-threatening COVID-19 pneumonia had neutralising IgG auto-Abs against at least one type-I IFN,
- 10.2% having neutralising IgG auto-Abs against IFN-ω, the 13 types of IFN-α**,** or both, at the onset of critical disease.
- Neutralising auto-Abs against type-I IFNs present in patients with life-threatening COVID-19 were not found in asymptomatic/mild COVID-19 (in only 4 of 1,227 healthy individuals).
- The prevalence of auto-Abs against type-I IFNs in the population was 15-fold less than that in life-threatening COVID-19 pneumonia.
- Excess of males (94%) with critical COVID-19 pneumonia and neutralizing auto-Abs against type I IFNs; in critical patients without neutralising auto-Abs, the proportion of men was 75%; and 28% of mild/asymptomatic males, suggesting that the production of auto-Abs against type-I IFNs may be X-linked.
- Patients with auto-Abs were 25-87 years and slightly older than the rest of the cohort

What does it mean for patients

- **B cell auto-immune phenocopy of inborn errors of type-I IFN immunity underlies life-threatening COVID-19 pneumonia in at least 2.6% of women and 12.5% of men.**