Genetic mechanisms of critical illness in COVID-19

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Genesi del progetto

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- Epidemiologia dei primi mesi di pandemia
  - Ampia variabilità di impatto clinico dell'infezione
  - Distribuzioni diverse nelle diverse etnie
  - Confounding con altri fattori, non genetici

- Raccolta dati molto frammentaria

- Varianti a geni candidati
  - ACE1/ACE2 Genes
  - *ACE2* rs2285666 polymorphism
    - Effetti sull'ipertensione
  - X chromosome

- Coordinamento ospedali lombardi non IRCCS

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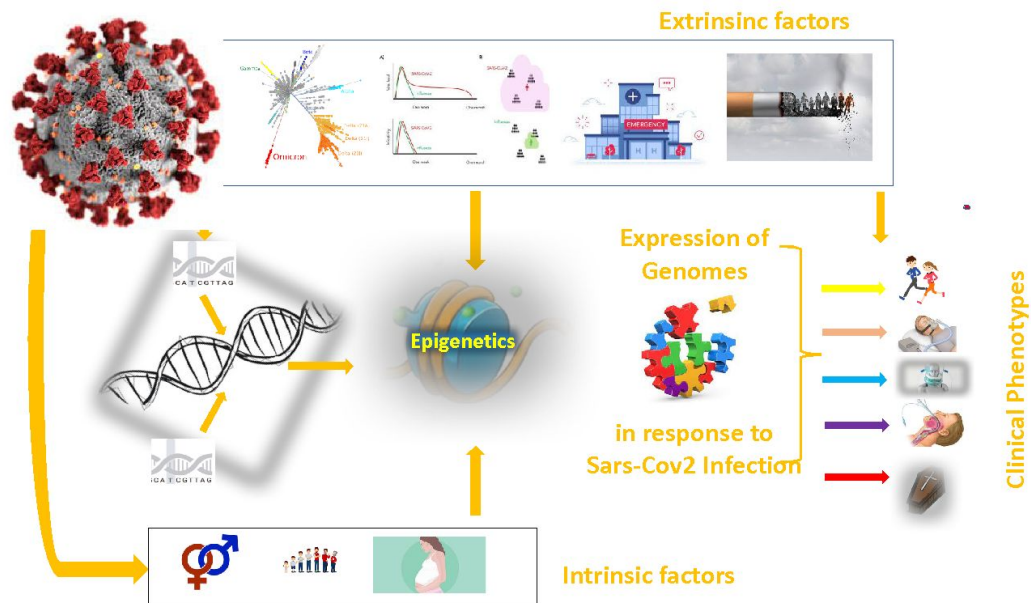
Project Gen-Covid

Coordinator: Università degli Studi di Siena (Prof. Alessandra Renieri: https://sites.google.com/dbm.unisi.it/gen-covid)

Linked to the "Host Genetics Initiative" (HGI, https://www.covid19hg.org)

GWAS

- Complessità genetica del carattere
- Effetti allelici
- Linkage disequilibrium
- Fenotipo
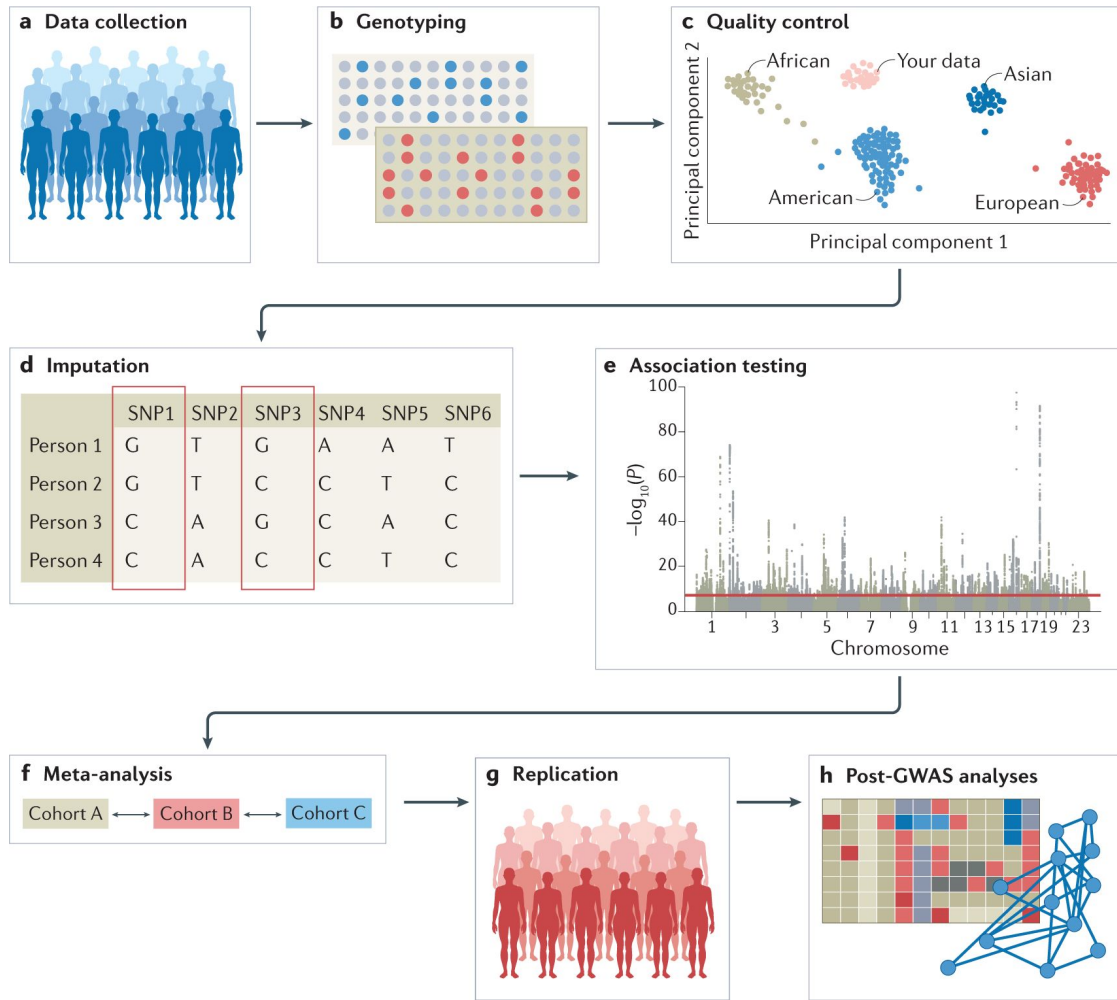
GEN-COVID biobank

- **Biological samples** (blood, leukocytes, DNA etc.) → GC-B

- **Clinical data** → GC-PR (patient registry)

- **Exome-sequencing, SNP genotyping** → GC-GDR (genetic data registry)

Employing a systematic approach to biobanking and analyzing clinical and genetic data for advancing COVID-19 research

Sergio Daga[1,2] · Chiara Fallerini[1,2] · Margherita Baldassarri[1,2] · Francesca Fava[1,2,3] · Floriana Valentino[1,2] · Gabriella Doddato[1,2] · Elisa Benetti[2] · Simone Furini[2] · Annarita Giliberti[1,2] · Rossella Tita[3] · Sara Amitrano[3] · Mirella Bruttini[1,2,3] · Ilaria Meloni[1,2] · Anna Maria Pinto[3] · Francesco Raimondi[4] · Alessandra Stella[5] · Filippo Biscarini[5,13] · Nicola Picchiotti[6,7] · Marco Gori[6,8] · Pietro Pinoli[9] · Stefano Ceri[9] · Maurizio Sanarico[10] · Francis P. Crawley[11,13] · Giovanni Birolo[12] · GEN-COVID Multicenter Study · Alessandra Renieri[1,2,3] · Francesca Mari[1,2,3] · Elisa Frullanti[1,2]

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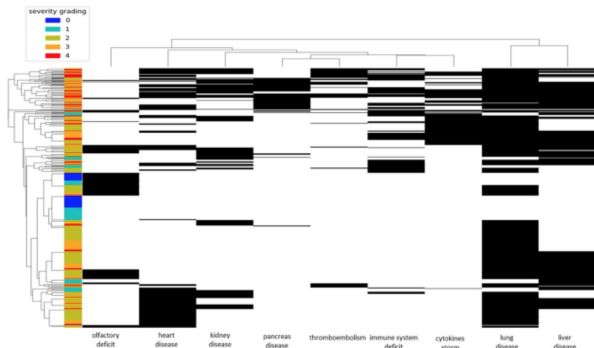
Does COVID-19 severity have a genetic component?

Covid-19 <u>mortality risk</u>:
- **susceptibility** to viral infection
- propensity to develop harmful **inflammation**

Susceptibility to infections and immune-mediated diseases are both known to be heritable → **host genetic variants** (e.g. influenza, RSV, coronaviruses)

Covid-19 critical illness
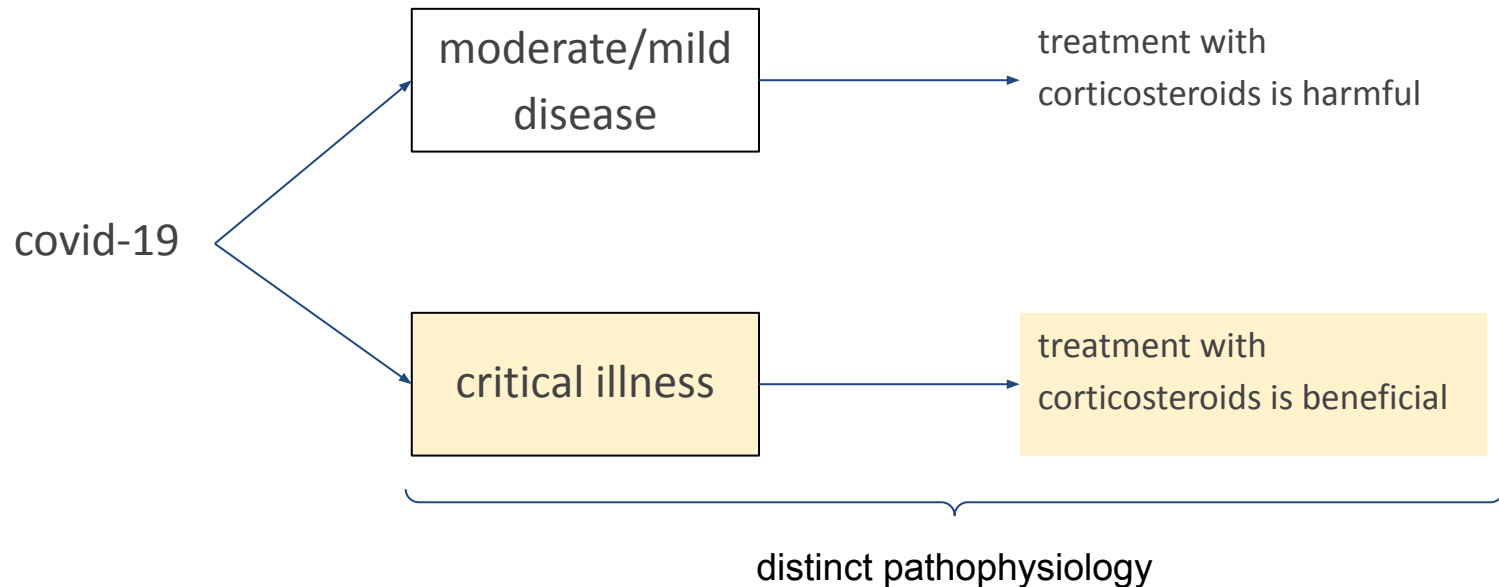
GWAS for covid-19 critical illness

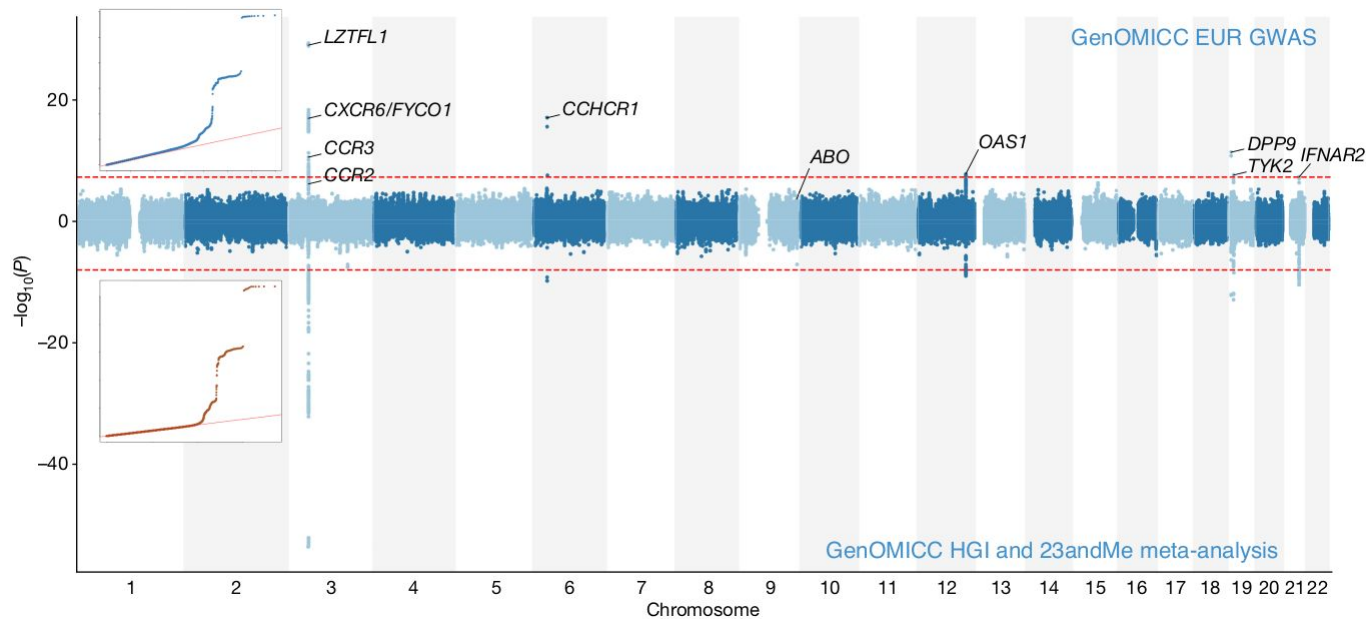| Critically-ill patients	vs	Healthy controls
~ 2,500 (UK ICU)		~ 500k (UK Biobank, 100k genomes project) (no positive Sars-cov2 test)

- ~ **4.5 million SNP** variants
- **logistic regression model** (case/control) accounting for age, sex, deprivation decile, first 10 principal components

GWAS for covid-19 critical illness

- (top): GWAS results
- (bottom): meta-analysis (replication)

- Chr3: *LZTFL1*
- Chr6: *HLA-G, CCHCR1*
- Chr12: *OAS1-OAS3*
- Chr19: *DPP9, TYK2*
- Chr21: *IFNAR2*

- **h^2 = 0.065**

GWAS for covid-19 critical illness

- *IFNAR2, OAS1-3* →**innate antiviral defenses**
    - (interferon alpha and beta receptor subunit-2)
    - (2'-5'-oligoadenylate synthetases) → antiviral restriction enzyme activators

- *DPP9, TYK2* → **host-driven inflammation** (lung injury)
    - (dipeptidyl peptidase 9) → variants associated with idiopathic pulmonary fibrosis
    - (tyrosine-protein kinase)

TYK2 is a gene target for JAK inhibitors, e.g. baricitinib:

(Janus kinase inhibitors → inflammatory disease, like rheumatoid arthritis)

Next steps

Ongoing activities:

- GWAS for clinical severity and for mortality/survival in cohorts of cases only (no healthy controls)

- Predictive models for:

    - Diagnosis of cases

    - Prognosis of clinical severity

Take-home messages

-   Severe covid-19 ≠ mild/moderate covid-19

-   There is a **heritable component** to susceptibility to
    Sars-Cov2 infection and to development of harmful
    inflammatory response → **host genetic variants matter!**

-   Genomics can help to:

    -   Make diagnosis
    -   Predict prognosis
    -   Understand the pathophysiology of the disease

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