



## RESEARCH TOPIC DASMEN4

### IDENTIFICATION OF GENETIC DETERMINANTS OF COVID-19 SUSCEPTIBILITY, SEVERITY AND SEX-SPECIFIC MANIFESTATIONS BY LARGE GENOME-WIDE GENETIC ASSOCIATION ANALYSIS AND EXOME SEQUENCING. DATASCIENCE UNIT NAME AND ADDRESS

#### Datascience Unit name and address

Medical Genetics and RNA Biology  
Humanitas University, Pieve Emanuele

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#### Abstract

As the outbreak of coronavirus disease 2019 (COVID-19) progresses, prognostic markers for early identification of high-risk individuals and more effective therapeutic approaches are urgent medical needs. Worldwide, a more severe course of COVID-19 is associated with older age, comorbidities and male sex. At all ages, the male fatality rate is higher, with an overall male:female ratio, in Italy, of 2.04. Variations in virus characteristics and in patient immunology, as well as in specific genes related to viral infection and disease pathogenesis are likely to be involved.

Here, we plan to investigate whether genetic factors play a role in modulating susceptibility to SARS-CoV-2 infection and severity of clinical manifestations. Importantly, we will explore the contribution of variants in the X chromosome in protecting women towards more severe outcomes.

We will perform a genome-wide association study (GWAS) on a cohort of patients collected in one of the most affected area in Italy (Milano, Monza, Bergamo). We plan to adopt a GWAS study design, which is a robust, easy-to-perform, industry-standardized tool for deciphering genetic predisposition, and allows, using imputation, to capture the great majority of genetic variability. In addition, on patients showing “extreme” phenotypes (e.g. young patients with severe outcomes), we plan to perform exome sequencing.

We plan to stratify patients based on severity of symptoms, age, and/or sex. Importantly, clinical and genetic data will be analyzed together using an unbiased approach (based on machine learning) to identify combinations of variables able to predict different outcomes (eg, severe vs milder symptoms).



Our study has the potential to identify genetic variants: 1) predisposing to increased susceptibility to infection; 2) explaining different outcomes in affected; and 3) protecting women against more severe outcomes.

### **Main technical approaches**

- Usage of DNA databases (Genome Browser, 1000Genomes, HapMap, dbSNP, GnomAD)
- Bioinformatic analyses of nucleotide sequences (exome, genome) (alignment, filtering, annotation, and variant calling using specific pipelines and software, such as BWA, Samtools, Annovar, FastQC, Galaxy)
- In-silico analysis of the effect of mutations (using programs such as Polyphen, Sift, Mutation taster, Condel, NNSPLICE, Human Splicing Variation, NetGene2)
- GWAS data QC, imputation, association analyses
- Haplotype analysis
- XWAS analysis
- Integration of genetic and clinical data by machine learning

### **Scientific references**

Considering the topic, the project has just started. Nonetheless, 3 articles have already been sent (two under review, one submitted):

1) Asselta R, Paraboschi EM, Mantovani A, Duga S. ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy.

<https://doi.org/10.1101/2020.03.30.20047878>.

2) Lazzeri M, Duga S, Azzolini E, Fasulo V, Buffi N, Saita A, The Humanitas COVID-19 Task Force, The Humanitas Gavazzeni COVID-19 Task Force, Hurle R, Nobili A, Cecconi M, Casale P, Asselta R. Impact of anti-androgen therapies on COVID-19 susceptibility: a case-control study in male population from two COVID-19 regional centers of Lombardy (Italy)

3) Benetti E, Tita R, Spiga O, Ciolfi A, Birolo G, Bruxelles A, Doddato G, Giliberti A, Marconi C, Musacchia F, Pippucci T, Torella A, Trezza A, Valentino F, Baldassarri M, Brusco A, Asselta R, Bruttini M, Furini S, Seri M, Nigro V, Matullo G, Tartaglia M, Mari F, Renieri A, Pinto AM. ACE2 variants and inter-individual variability and susceptibility to COVID-19 in Italian population.

### **Type of contract**

PhD scholarship of € 18.000 gross per year or equivalent contract.

Borsa di dottorato di € 18.000 annui lordi o forme di sostegno finanziario equivalenti.