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TEMPLATE RICHIESTA ATTIVAZIONE TOPIC AGGIUNTIVI SU FONDI PNRR

D.M. 9 aprile 2022 n. 352

Project title/Titolo del Progetto	Development of clinical polygenic risk scores in common disorders
Principal Investigator	Prof. Rosanna Asselta
Main field of interest/Ambito principale di ricerca	• Medicina rigenerativa, predittiva e personalizzata • Biotecnologie, bioinformatica e sviluppo farmaceutico
Abstract	Genome-wide association studies (GWAS) identified thousands of genetic variants significantly associated with a range of common complex human traits. Given that the risk conferred by an individual common variant is usually small, scientists have aggregated risk alleles across the genome into genetic risk scores to provide a single measure of genetic association for a given disease. Although the earliest genetic scores consisted only of variants meeting genome-wide significance, recently developed computational and methodological approaches have leveraged the summary statistics of all available variants from increasingly larger GWAS to calculate polygenic risk scores (PRS). For some diseases, a PRS in the upper tail of the distribution approximates risks equivalent to those conferred by established clinical risk factors and by genetic variants associated with monogenic disease. These promising results mask the many limitations still existing in this field: - The lack of PRS specifically addressed to take into account ancestry (in the vast majority of cases, they have been developed for North European/US Caucasian populations) - The lack of PRS taking into account the biological sex of individuals (gender medicine) - The lack of pipelines able to integrate common (minor allele frequency, MAF, in the general population >5%) and rare (MAF <1%) variants - The lack of PRS specifically addressed to take into account age groups (it is now established the effect of age on genetic risk for common diseases; however, reasons behind this observation are still unclear) - The lack of scores integrating PRS and data deriving from deep phenotyping. In this frame, in this research project we will - exploit the statistical power of in-house databases to build analysis pipelines capable of integrating phenotypic and PRS data, using both standard statistical methods, or more innovative artificial intelligence (AI) approaches; to this aim, we have huge in-house datasets of Myocardial Infarction (2000 cases and 2000 controls all genome-wide genotyped and exomed), severe COVID-19 (600 cases and 3200 controls, all genome-wide genotyped), primary biliary cholangitis (5000 cases and 10000 controls, all genome-wide genotyped);

	- establish sex-specific and age-related PRS using the above listed datasets; - exploit the statistical power of freely available databases (to be downloaded from public repositories) to establish population-specific PRS. These aims will be pursued in order to feed a future indispensable phase of translation to the bedside. This second phase involves the development of an analytically valid pipeline for calculating, interpreting and reporting PRS results for an individual patient. This phase will be essentially developed thanks to the cooperation with the company involved in this PhD program (GenomSys, see below).
Type of Co-funding	X D.M. 352/2022 - Borse di dottorato cofinanziate dalle imprese
Lab name and address	Medical Genetics and RNA Biology Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20072 Pieve Emanuele, Milan, Italy
Brief description of the coherence of the Project in relation to the PNRR objectives[3]	Our project proposal will be in line with the major objectives of the 2021-2027 National Research Programme, including: **Consequences and challenges of ageing.** Genetic variation contributes to individual risk for many complex diseases and is increasingly being used for predictive patient stratification. Previous work has shown that genetic factors are not equally relevant to human traits across age. Our project will examine the age-stratified genetic effect on many different pathologies, including some that represent a socio-economic burden, especially in the elderly. **Advanced diagnostics and precision medicine.** The P4 medicine (personalized, predictive, preventive, participatory) implies a deep understanding of inter-individual differences in health/disease that are due to genetic and environmental factors. Among others, our project tries to overcome the sex-related issue. We aim to dissect molecular mechanisms behind sex bias in different disorders (e.g., COVID-19 and myocardial infarction, both characterized by male prevalence; and PBC, in which we observe an extreme female preponderance), to reach the ultimate goal of changing treatment paradigms by taking into account sex-related factors. Thus, it belongs to the field of gender medicine, defined by WHO as the study of how sex-based biological and gender-based socioeconomic and cultural differences influence people health. In compliance with the principles of **open science and FAIR data policy**, all the data produced with this project will be deposited in ad-hoc data repository with dedicated accession numbers and associated with detailed metadata. The results of this project will be presented at national/international congresses and published in peer-reviewed open-access journals. In addition, the proximity and full integration among Humanitas

	University, Humanitas Hospital and Humanitas Research Center, with access to state-of-the -art technologies (e.g. omics and bioinformatics), will provide the ideal environment for the successful completion of the PhD program. All participants to this project will completely endorse and will be fully committed to PNRR priorities.
N. of months abroad (min. 6, max. 18) [**compulsory**]	6
Name of the research institution/company abroad	Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland
N. of months of internship (min. 6, max. 18) [compulsory only for D.M. 352/2022]	At least 6
Name of the company[3]	GenomSys Chemin de Vuasset 2, CH-1028 Prevenges Via Giacometti 1, CH-6900 Lugano www.genomsys.com
Scientific references	Asselta R, et al. X Chromosome Contribution to the Genetic Architecture of Primary Biliary Cholangitis. Gastroenterology. 2021 Jun;160(7):2483-2495.e26 Severe Covid-19 GWAS Group. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. N Engl J Med. 2020 Oct 15;383(16):1522-1534. Cappadona C, et al. MEDTEC Students against Coronavirus: Investigating the Role of Hemostatic Genes in the Predisposition to COVID-19 Severity. J Pers Med. 2021 Nov 9;11(11):1166. Do R, et al. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. Nature. 2015 Feb 5;518(7537):102-6. Paraboschi EM, et al. Rare variants lowering the levels of coagulation factor X are protective against ischemic heart disease. Haematologica. 2020 Jul;105(7):e365-e369.