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Genomic Medicine applications for diagnosis and discovery in rare diseases

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Genomic Medicine (GM) is an interdisciplinary medical specialty, whose goal is applying genomic information to clinics and research. Genome data, such as those generated by microarray (MA) and next generation sequencing (NGS), are natively digital and thus well suited for computational analysis and sharing. Nonetheless, their volume and complexity require ad hoc computational approaches and bioinformatics infrastructures. Commercial and academic organizations have developed several tools for common diagnostic purposes; however, more complex analyses are still poorly covered.

Since our activity is dedicated to patients with rare diseases who manifest complex phenotypes and undergo multiple genomic assays, we have to assemble ad-hoc custom analytical pipelines.

We developed genePryor, a prioritization tool for NGS variants. genePryor is aimed to quickly identify known pathogenic variants, as well as highlight potential new disease-causing genes and variants. genePryor integrates information from multiple public and user-provided sources, considers inheritance analysis on multiple pedigrees of variable complexity, and integrates results from MA and NGS. genePryor has been used to analyze data from the Telethon Undiagnosed Disease Program (TUDP - about 1800 WES), contributing to the high diagnostic yield of the program, with about 50% conclusive diagnoses and novel genetic diseases identified. Planned improvements regard integrating tools to automatically match patient-gene phenotypes, considering non-Mendelian patterns of inheritance (like digeny), improving identification of variants with potential regulatory effects.

To study copy number variants (CNV) with a potential positional effect, we challenged the hypothesis that CNV may affect gene expression and determine a clinical phenotype by altering the genomic region between disease-genes and their enhancers. We studied 1900 CNVs from the cytogenetic units of Federico II and identified 27 CNVs located in gene-enhancer intervals. After manual curation, we found a consistent match between the gene and the patient phenotypes for a deletion located in the locus of Sonic Hedgehog (SHH) gene carried by a patient with a complex phenotype. For this CNV, the Strings-and-Binders model supported a slight reduction of gene-enhancer interactions, consistent with a potential positional effect of the variant. We plan to repeat the analysis on data from public repositories to verify the generalizability of our hypothesis and to refine the workflow.

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