RESEARCH TOPIC MECM_19

Integrated multi-omics and functional characterization of inherited bleeding disorders: towards personalized hemostatic medicine

Curriculum

MECM Standard

Research Area

Other

Laboratory name

Lab of Medical Genetics & RNA Biology

Research Supervisor

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Abstract

Inherited bleeding disorders (IBDs) are a heterogeneous group of rare conditions, ranging from relatively common diseases such as von Willebrand disease (VWD; prevalence ~1:1000) to ultra-rare coagulation factor deficiencies (rare bleeding disorders, RBDs; prevalence 1:1-2 million), as well as the recently defined category of bleeding disorders of unknown cause (BDUC). Despite advances in diagnostic and molecular approaches, significant gaps remain in understanding disease mechanisms, variability in clinical presentation, and patient-specific responses to therapy. Many patients still lack a definitive molecular diagnosis, while others exhibit phenotypic variability not fully explained by known genetic variants.

This PhD project aims to address these challenges through an integrated translational approach combining molecular genetics, functional assays, and multi-omics analyses. The research will focus on three complementary areas within inherited coagulation disorders.

First, the project will investigate the genetic determinants of VWD and hemophilia A and B, with particular attention to the pharmacokinetic variability of factor VIII in hemophilia A. Differences in factor VIII half-life, clearance, and distribution following infusion may be influenced by genetic variants and polymorphisms affecting both factor VIII and its clearance receptors, including von Willebrand factor-related pathways. Understanding these mechanisms will support the optimization of prophylactic treatments and promote individualized therapeutic strategies.

Second, the project will focus on ultra-rare inherited coagulation disorders, including deficiencies of fibrinogen and factors II, V, VII, X, XI, and XIII. Through comprehensive clinical, laboratory, and genetic characterization, the study aims to refine genotype–phenotype correlations and improve molecular diagnosis in these conditions.

Third, the project will address BDUC by applying a multi-omics strategy integrating whole-exome sequencing (WES) and RNA sequencing (RNA-seq). This approach will enable the identification of previously undetected coding, splicing, or regulatory variants that may escape standard diagnostic pipelines.

Additionally, the role of modifier genes (such as those encoding platelet receptors or other hemostatic mediators) will be investigated to better understand their contribution to all bleeding phenotypes.
The PhD candidate will be primarily involved in experimental laboratory work and will acquire a broad range of technical skills relevant to modern hemostasis research. These include nucleic acid extraction, DNA and RNA processing, targeted genotyping, Sanger sequencing validation, and preparation of samples for omics analyses. Functional studies will be conducted in mammalian cell systems, including recombinant expression of selected variants to assess their biological impact. Protein expression and function will be evaluated using immunological and biochemical techniques such as ELISA and Western blotting, alongside laboratory assays of coagulation factors and biomarkers.
In parallel, the candidate will develop foundational bioinformatics skills for the analysis of sequencing data. Training will include quality control, sequence alignment, variant annotation and prioritization, transcriptomic analysis, and integration of genomic and expression datasets. This dual expertise will enable the interpretation of molecular findings in the context of functional consequences and clinical phenotypes.
Overall, this project aims to generate new insights into the molecular basis and phenotypic variability of inherited bleeding disorders. By integrating experimental and computational approaches, it is expected to improve diagnostic accuracy, enhance understanding of genotype–phenotype relationships, and identify determinants of treatment response, ultimately contributing to the advancement of personalized hemostatic medicine.

Main technical approaches

- Usage of DNA databases (Genome Browser, 1000Genomes, HapMap, dbSNP, Exac)
- Bioinformatic analyses of nucleotide sequences (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)
- PCR, qPCR, digital-PCR
- Automated DNA sequencing (Sanger method)
- Library preparation for next-generation sequencing
- Molecular cloning
- Site-directed mutagenesis
- In-vitro cultures of eukaryotic cell lines
- Transfection experiments
- In-vitro functional assays

Scientific references

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Type of contract

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