Hematopoietic malignancies with germline predisposition diagnosis with filtered Whole Exome Sequencing and *in silico* panel analysis

In the frame of the development of new analytical methods for the diagnostic of patients suffering of suspected inherited malignancies with poor access to rapid diagnosis due to a restricted number of analytical sites or the current use of non-comprehensive targeted panels, we aimed at developing a new NGS panel for the analysis of several haematological diseases based on a filtered whole exome sequencing approach.

Clinical exome is sequenced with the SureSelect Hulan Exome V6, recovering information for about 20k genes, representing ca. 180k exons. A newly designed variant filter based on an in house pipeline tree (Alissa Interpret) for the flagging of retained variants, allows for the selection and labeling of 100 variants (in average) per patient. Variants are categorized following the ACMG guidelines for the interpretation of inherited variants and reported in the context of the patient malignancies.

Haematological diseases incorporated in the panel include myelodysplasic syndromes, acute myeloid leukemia, inherited bone marrow failure syndromes, Fanconi anemia, Diamond Blackfan anemia, dyskeratosis congenita, Telomeropathies and severe congenital neutropenia.

The set of genes has been selected from a deep insight to the most recent literature and guidelines and covers 85 full (exonic) genes. Interestingly, some deep intronic regions and UTRs with relevant clinical significance have been included as well, including non-coding regions from RETL1 or TERC.

The analytical pipeline considers the analysis of single patients, corroboration of relevant inherited germline mutations from fibroblasts and/or trio analysis including first or second relatives. Applications cover from simple diagnostic from single patients to familiar studies or donor compatibility analysis.

Inherited Haematological Malignancies are a heterogeneous group of malignancies not yet fully understood and in constant evolution. In this context, flexibility is a key concept to avoid analytical obsolescence. Due to the wide range of genes covered by the WES approach, significant genes could be further updated, with a minimal effort, to the panel.

We therefore aim to provide physicians with a comprehensive diagnostic panel for the diagnostic work-up of patients affected (or suspected to be affected) by inherited haematological malignancies, and related diseases enhancing the patient's chances to benefit from a personalized medicine approach; together with a view to increase the knowledge about those (rare) conditions.