Germline mutations in inherited bone marrow failure

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Bone marrow failure (BMF) syndromes are a heterogeneous group of hematological disorders that may either be acquired or inherited (IBMF). Overlap between BMF and myelodysplastic syndromes (MDS) has long been recognized, BMF being intrinsically a situation that favours the expansion of clones with somatic mutations or chromosomal abnormalities such as monosomy 7/del(7q). While Fanconi anemia, dyskeratosis congenital, RUNX1-deficient disorders and others are well-recognized IBMF causes, the underlying genetic diagnosis can remain uncertain in many IBMF cases. However, recognizing the inherited nature of BMF and MDS is crucial to avoid immunosupressive therapy and adapt treatment such as HSCT, including donor choice. It also enables MDS/AML risk monitoring and family counselling. For translational research, identifying causal germline mutations in BMF and MDS can illuminate crucial biological pathways that are involved directly or indirectly in homeostasis and oncogenesis in the bone marrow.

We have systematically collected over 15 years the clinical data and primary samples from patients with BMF seen for diagnosis evaluation at the “French National Center of Bone Marrow Failure Syndromes” (Saint-Louis and Robert Debré Hospitals, Paris, France). In many patients, a “likely-inherited” nature of BMF was suspected based on familial history, physical signs, and/or a very young age (<2 yo), despite that no clear cause could be identified at initial diagnosis evaluation (Fanconi anemia being excluded). Using whole exome sequencing (WES) in non-hematopoietic (fibroblast) DNA on the resulting “unresolved” patient cohort of 179 patients, we were able to identify causal or likely-causal mutations in almost half the patients, and therefore to draw a broad molecular and clinical portrait of this heterogeneous group of patients with “likely-inherited” BMF (with or without MDS features).

Germline mutated genes included genes of familial hematopoietic disorders (*GATA2*, *RUNX1*), telomeropathies (*TERC, TERT, RTEL1*), ribosome disorders (*SBDS*, *DNAJC21*, *RPL5*), and DNA repair deficiency (*LIG4*). Many patients had an atypical presentation, and the mutated gene was often not clinically suspected. We also found mutations in *SAMD9* and *SAMD9L*, *MECOM/EVI1*, and *ERCC6L2*, each of which was associated with a distinct natural history; *SAMD9* and *SAMD9L* patients often experienced transient aplasia and monosomy 7, whereas *MECOM* patients presented early-onset severe aplastic anemia, and *ERCC6L2* patients, mild pancytopenia with myelodysplasia.

In conclusion, this and other recent studies have broadened the molecular and clinical portrait of IBMF syndromes and shed light on newly recognized IBMF/MDS disorders. Importantly, NGS systematic screen help to implement precision medicine at diagnosis and can improve patient management and family counselling.