Studying the phenotypic variability of ERCC6L2 deficiency in a genetic island

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Introduction

- ERCC6L2 belongs to the Snf2 family of helicase-like proteins that are involved in nucleotide excision repair, mitochondrial function and transcription regulation.
- Pathogenic variants in this gene have been related to bone marrow failure (BMF) with variable phenotypic expression, age of onset and somatic genetic findings in bone marrow.
- Up to date about 31 patients with bi-allelic variants in ERCC6L2 have been reported in the literature. Clinical representation varied from myelodysplastic syndrome (MDS) which progressed to acute myeloid leukemia (AML) in some of the patients. Neurological and developmental findings were reported in one patient.

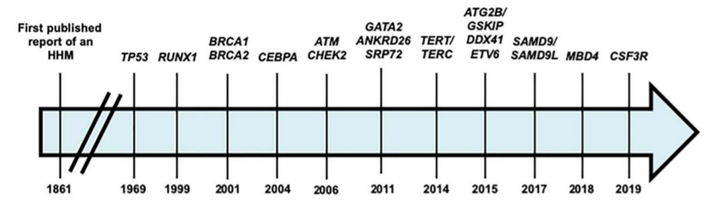


Figure 1. Timeline of discovery of genes that predispose to the development of hereditary hematopoietic malignancies (HHMs). The first description of an HHM in the medical literature appeared in 1861, and the first molecular description of an inherited gene mutation was published in 1999. The application of next-generation sequencing to patients and families has accelerated disorder discovery in the past several years.

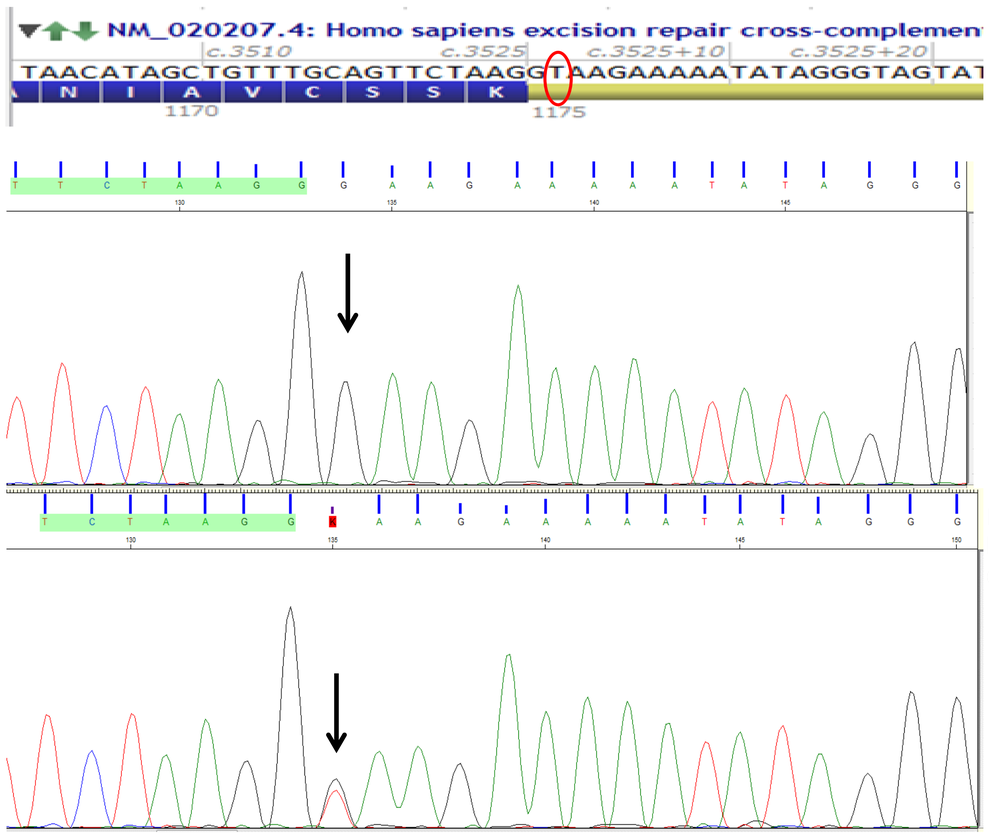
Feurstein et al., Germline predisposition to hematopoietic malignancies, Human Molecular Genetics, review, 2021

Patients

Recently we have enrolled in our institute three patients from two unrelated families who reside in the same village, in northern Israel:

- The first patient is a 7 y.o. girl, referred to genetic counseling due to mild developmental delay, behavioral disorders and pancytopenia. Bone marrow karyotype was normal.

Exome sequencing revealed a homozygous splicing variant, c.3525+2T>G in *ERCC6L2*, predicted to damage splicing completely.



Carrier testing for healthy individuals from the same village revealed 7 carriers out of 104 tested (1:15).

REF	# cases	Age of onset	AML	Neurodevelopmental symptoms
Tummala, 2014	2	12,19	Not reported	2/2
Zhang, 2016	1	13	Not reported	1/1
Shabanova, 2018	1	7	Not reported	1/1
Douglass 2019	8	14-65	5/8	Not reported
Blutau 2018	7	2-22	1/7 (3 HSCT)	1/7
Järviaho, 2017	2	8	Not reported	Not reported
Tummala, 2018	8	3-18	1/8	Not reported

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- The second patient is a 16 y.o. boy who presented with MDS, progressed to AML after three months and passed away. Bone marrow demonstrated complex karyotype with 5qdel. Sequencing using a panel of genes mutated in inherited bone marrow failure using patients' skin fibroblasts revealed the same c.3525+2T>G variant.
- Segregation analysis exposed a 24 y.o. "healthy" sister that was found homozygous for the same variant. She is now under close hematological follow up.

- There is a consensus among the hematological community that early hematopoietic stem cell transplantation (HSCT) is warranted for patients with MDS in order to eliminate the progression of the disease to aggressive AML.
- Our data emerge the urgent identification of pre-symptomatic homozygous individuals to study the penetrance and the course of the disease in order to give accurate genetic and hematological counseling to the patients and family, and early treatment when indicated.