ERCC6L2-Related Bone Marrow Failure and Myeloid Malignancies: A Cohort of 18 Patients from Consanguineous Families

Alfadil Haroon, Ahmed Alotaibi Mansour Alfayez, ,Ayman Saad, Hazza Alzahrani, Ahmed Binsalman, Mahmoud Aljurf and Syed Osman Ahmed

1-Adult Hematology, Stem Cell Transplant and Cellular Therapy Section, Cancer Center of Excellence King Faisal Specialist Hospital and Research Center ,Riaydh, Saudi Arabia

Introduction

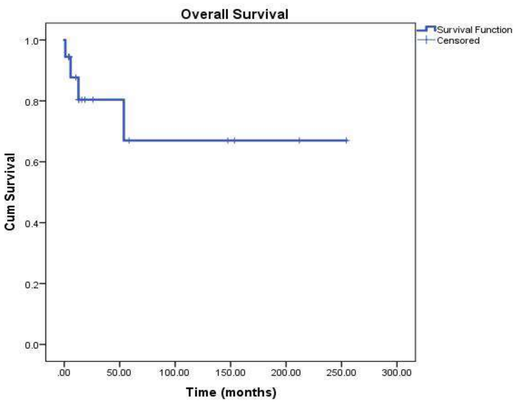
Excision repair cross-complementing 6 like 2 (ERCC6L2) ,serves as an ATP-dependent DNA translocase. Biallelic variants in ERCC6L2 has recently been described and predispose individuals to bone marrow failure, myeloid malignancies, and neurological dysfunction.

Aim

To characterize the clinical, hematologic, and genetic spectrum of ERCC6L2-associated BMF and myeloid malignancies and to evaluate treatment outcomes

Methods

Clinical data was extracted from the KFSH-Riyadh Inherited Marrow Failure Registry. Whole exome sequencing was performed to identify causative mutations.



Summary

ERCC6L2 biallelic mutations predispose to BMF and MM. In 18 patients and MDS/AML seen 61.1% and BMF in 33.3%.TP53 mutations seen in 33% .HSCT offered potential benefit, with 2-year survival of 71.6%, highlighting importance of early detection and surveillance.

References

1-ERCC6L2 mutations link a distinct bone-marrow-failure syndrome to DNA repair and mitochondrial function. The American Journal of Human Genetics,
2-A nonsense mutation in the DNA repair factor causes mild bone marrow failure and microcephaly. Journal of Experimental Medicine

Results

We reported 18 patients from 10 families, the median age was 14 years (range 6-37). There were 9 females and 9 males, all of whom carried a homozygous ERCC6L2 mutation. Six (33.3%) of the patients had BMF, 4 (22.2%) had AML, 3 (16.6%) Hypoplastic MDS, 3 (16.6%) MDS-EB, one (5.5%) had quadriplegia and one with normal CBC. Anemia was observed in 16 (88.8%) patients, thrombocytopenia in 15 (83.3%), and leucopenia in 9 (50%) patients. Bone marrow was hypocellular in 12 (66.6%) cases, and hypercellular in 3 (16.6%) cases. TP53 mutation was seen in 6 patients, complex karyotype was seen in three patients and two patients had monosomy 7. non-hematological features noticed in 6 patients includes erythema nodosum, short stature with or without microcephaly, global developmental regression and quadriplegia.

Nine of the patients underwent HSCT. Among them, 4 patients with MSD, 2 patients with MUD; one patient underwent haploidentical HSCT and one patient received HSCT from umbilical cord blood. Seven of them have been treated conservatively or with immunotherapy while four patients died, 3 during induction chemotherapy and one post HSCT. The 2-years overall survival was 71.6%.

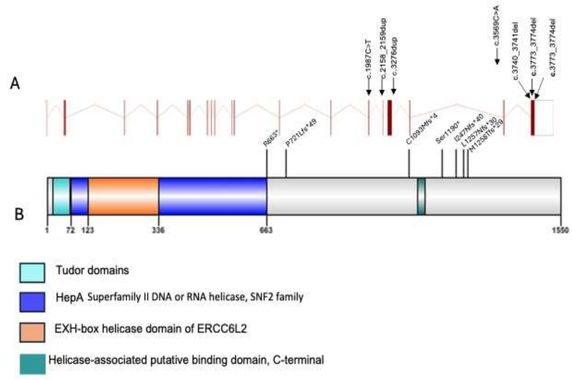


Figure 1- A-B sketch for *ERCC6L2* transcript and protein domains, arrows denotes the position of mutated exon and the corresponding variant amino acid. Figure created based on DOG 1.0: illustrator of protein domain structures*

*DOG 1.0: illustrator of protein domain structures, Jian Ren, Longping Wen, Xinjiao Gao, Changjiang Jin, Yu Xue, Xuebiao Yao.Cell Research 2009 (19)271-273

Discussion/Conclusion

Early detection of ERCC6L2 mutations is important to prevent the use of immunosuppressive therapy. Surveillance with annual bone marrow biopsy and cytogenetics in required. If the disease progresses into MM, HSCT should be considered. This report opens further possibilities for the detailed study of this mutation.