FMS-Related Tyrosine Kinase 3

Alternative Names
FLT3
Stem Cell Tyrosine Kinase 1
STK1
FLK2

Record Category
Gene locus

WHO-ICD
N.B.: Classification not applicable to gene loci.

Incidence per 100,000 Live Births
N/A to gene loci

OMIM Number
136351

Mode of Inheritance
N/A

Gene Map Locus
13q12.2

Description
The FLT3 gene is located on chromosome 13q12.2, where it codes for a protein with 993 amino acids. This gene is expressed in immature hematopoietic cells and is important for the normal development of stem cells and the immune system. FLT3 is a class III receptor tyrosine kinase (RTK), structurally related to the receptors for platelet derived growth factor (PDGF), colony stimulating factor 1 (CSF1), and KIT ligand (KL). The ligand for FLT3 is expressed by marrow stromal cells and other cells. FLT3 receptor function can be defined by the activity of its ligand (FL); it synergizes with other growth factors to stimulate proliferation of stem cells, progenitor cells, dendritic cells, and natural killer cells.

Defects in the FLT3 receptor result in acute myeloid leukemia and acute lymphoblastic leukemia.

Molecular Genetics
The FLT3 gene consists of 24 coding exons, and spans approximately 97 kb in the genomic DNA. Somatic mutations of the FLT3 gene are the most frequent genetic aberrations that have been described in patients with acute myelogenous leukemia (AML). These mutations lead to constitutive activation of the FLT3 receptor and they fall into two classes. The most common mutations involve small tandem duplications of amino acids within the juxtamembrane domain of the receptor and result in constitutive tyrosine kinase activity. The second category of mutations includes point mutations, usually involving the kinase domain (KD) and resulting in a constitutively activated kinase. These mutations cause constant signaling leading to uncontrolled proliferation of abnormal, immature white blood cells, a hallmark of acute myeloid leukemia.

Epidemiology in the Arab World
Iraq
Al-Husseinawi (2014) evaluated the frequency of FLT3-ITD mutation in acute lymphoid leukemia (ALL) patients using conventional polymerase chain reaction (PCR) in Iraq. The study included 25 individuals (16 children with ALL and nine adults with ALL), attending two teaching hospitals in Baghdad. FLT3-ITD mutation was detected in two patients. These cases were an 8-year-old girl and a 7-year-old boy, L2 subtype, who had achieved complete hematological remission throughout the study. All the other ALL cases showed absence of the mutation.

Saudi Arabia
Gari et al. (2008) carried out direct DNA sequencing analysis for 129 patients with acute myeloid leukemia (AML) in Saudi Arabia. Internal tandem duplication (ITD) mutations with lengths varying between 24-60 bp were identified within exons 14 and 15 of the FLT3 gene in 15 AML patients. The FLT3-ITD mutations were either a part or whole stretch of tyrosine-rich sequence of the FLT3 gene located between codons 589-599. Also a G>C point mutation of exon 20, resulting in

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p.Asp835Tyr substitution, was identified in 11 AML patients. These mutations lead to constitutive activation of the FLT3 receptor.

Elyamany et al. (2014a) analyzed the prevalence of activating ITD and point mutations in the FLT3 gene in a sample of 77 patients with ALL in Saudi Arabia and tried to assess their prognostic significance. Only two of the 77 patients examined showed FLT3 mutations, giving an overall prevalence of 3%. One of these was a 14-year old male patient with an ITD mutation, who was diagnosed as acute mixed-lineage leukemia. The second patient was a 4-year old female who was found to have the D835 mutation. Cytogenetic studies showed no association with balanced translocations or MLL rearrangement. Both patients responded well to treatment and achieved complete remission. Elyamany et al. (2014a) concluded that there was no prognostic significance of FLT3 mutations in ALL patients. Elyamany et al. (2014b) also did a similar study in 97 Saudi patients with AML, and found 18 cases positive for FLT3 mutations, giving an increased prevalence of 19%. Of these, 14 had FLT3-ITD mutations, while the remaining had the D835 mutation. Interestingly, these FLT3 mutations were found more in males (72%) than that in females (28%) in this study.

References

Al-Husseinawi EK. A pilot study for the detection of FLT3-ITD mutation frequency in 25 Iraqi patients with acute lymphoid leukemia in 2 Iraqi hospitals. J Pediatr Hematol Oncol. 2014; 36(4):e207-11. PMID: 24390456 [AB]

Elyamany G, Awad M, Alsuhaibani O, Fadalla K, Al Sharif O, Al Shahrani M, Alabbas F, Al-Abulaaly A. FLT3 Internal Tandem Duplication and D835 Mutations in Patients with Acute Lymphoblastic Leukemia and its Clinical Significance. Mediterr J Hematol Infect Dis. 2014a; 6(1):e2014038. PMID: 24959335 [FT]

Elyamany G, Awad M, Fadalla K, Albalawi M, Al Shahrani M, Al Abdulaaly A. Frequency and Prognostic Relevance of FLT3 Mutations in Saudi Acute Myeloid Leukemia Patients. Adv Hematol. 2014b; 2014:141360. PMID: 24696688 [FT]

Gari M, Abuzenadah A, Chaudhary A, Al-Qahtani M, Banni H, Ahmad W, Al-Sayes F, Lary S, Damanhouri G. Detection of FLT3 oncogene mutations in acute myeloid leukemia using conformation sensitive gel electrophoresis. Int J Mol Sci. 2008; 9(11):2194-204. PMID: 19330068

Related CTGA Records

Leukemia, Acute Lymphoblastic
Leukemia, Acute Myeloid

External Links

http://ghr.nlm.nih.gov/gene/FLT3
http://www.genecards.org/cgi-bin/carddisp.pl?gene=FLT3

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