

Gene Section

Review

GATA1 (GATA binding protein 1 (globin transcription factor1))

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Abstract

We provide a survey of the disease entities associated with GATA1 mutations.

Keywords

GATA1; Transcription; Hematopoiesis; erythroid development; megakaryocytic development; Down syndrome; Transient abnormal myelopoiesis associated with Down Syndrome; Myeloid leukemia associated with Down syndrome; Diamond-Blackfan anemia; Dyserythropoietic anemia

Identity

Other names: ERYF1, GF1, NFE1

HGNC (Hugo): GATA1

Location: Xp11.23

DNA/RNA

Description

Genomic sequence 7,757 bases, mRNA six exons (five coding); Plus strand

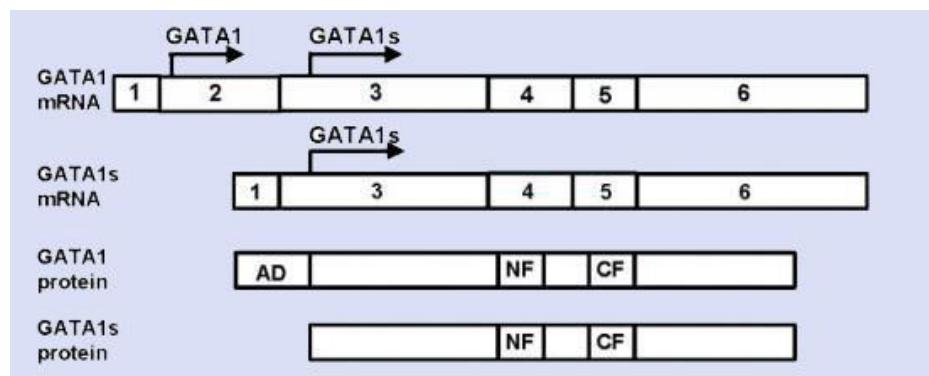


Figure 1. Alternative models for generation of GATA1 isoforms. The full GATA1 protein can only be translated from the full GATA1 mRNA, whereas the GATA1s protein can be translated either from the full gata-1mRNA or from the shorter splice variant in which exon 2 is skipped.

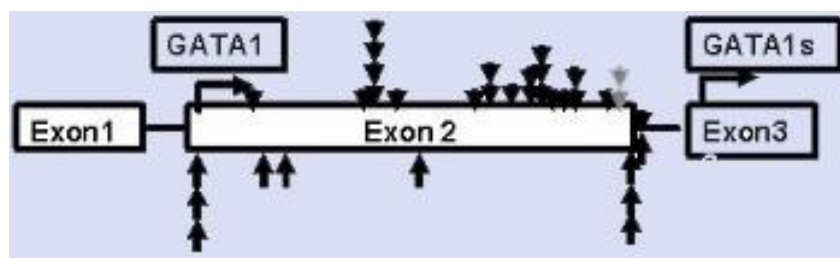


Figure 2. Example to the distribution of the mutations in children with M7 and DS described in Rainis et al.

Transcription

mRNA 1497bp

Protein

Description

GATA1 is physiologically present as two protein isoforms that are derived from alternative splicing of the mRNA and the usage of an alternative translation initiation sites as shown in the Figure. The full length GATA1 protein is comprised of 413 amino acids with a predicted molecular weight of 42.7 KDa. The shorter form of the GATA1 protein (GATA1s) lacks the first 83 amino acid residues, which contains the so-called N-terminal activation domain (AD) (Gruber TA et al., 2015).

Both proteins contain two Zinc finger domains mediating protein interactions and DNA binding. The expression level and ratio of both GATA1 isoforms are thought to be important in directing the appropriate erythromegakaryocytic development.

Expression

Bone marrow: erythroid, megakaryocytic, mast cell and eosinophilic precursors.

Testis: Sertoli cells

Localisation

Nuclear

Function

Transcription Factor, essential for erythroid and megakaryocytic development

Homology

A member of the GATA-binding factor (GATA) family.

Mutations

Germinal

Implicated dyserythropoietic anemia with thrombocytopenia/ Macrothrombocytopenia, and in Diamond-Blackfan anemia

Somatic

Myeloid proliferation associated with Down syndrome, including:

- transient abnormal myelopoiesis associated with Down syndrome, and
- myeloid leukemia associated with Down syndrome

Implicated in

Myeloid proliferation associated with Down syndrome, including transient abnormal myelopoiesis associated with Down Syndrome and myeloid leukemia associated with Down syndrome

Acquired somatic mutations resulting in the exclusive production of the short-form GATA1 protein (GATA1s) are pathognomonic in myeloid proliferation associated with Down syndrome (MP-DS) (Ahmed M et al, 2004; Groot J et al, 2003; Rainis L et al, 2003; Wechsler J et al, 2002). These mutations are often in the forms of nonsense or frame-shift mutations that result in premature stop codons in exon 2 or 3, while sparing the alternative start codon further downstream in the exon 3. GATA1 mutations can be detected in umbilical cord blood of DS patients and in fetal liver of aborted DS embryos; therefore, these mutations are thought to occur in-utero, likely during fetal liver hematopoiesis (Ahmed M et al, 2004; Taub JW et al, 2004). The presence of GATA1s in the absence of full length GATA1 is thought to block megakaryocytic differentiation and promote the proliferation of megakaryoblasts (Vyas P et al, 1999; Li Z et al, 2005; Lee WY et al, 2018). This disease entity only occurs in DS patients; however, the genes on chromosome 21 that enables the development of this disease are not known. MP-DS mostly occurs in children with DS younger than 5 years of age and manifests initially as transient abnormal myelopoiesis (TAM) within 7 days of birth. TAM is characterized by increased circulating megakaryocytic blasts, thrombocytopenia, and leukocytosis. The majority of cases of TAM undergo clonal extinction and spontaneously remit. However, about a third of the cases eventually recur within 3 years as myeloid leukemia associated with Down syndrome (ML-DS), which phenotypically resembles acute megakaryocytic leukemia and requires therapy. Next generation sequencing

studies comparing the genomic landscape of TAM and ML-DS have established the GATA1 mutations as the 'first-hit' mutations that presents phenotypically as TAM, and the subsequent gain of additional hits leads to the progression as ML-DS (Nikolaev SI et al, 2013; Yoshida K et al, 2013).

Diamond-Blackfan anemia

Diamond-Blackfan anemia (DBA) is a congenital condition characterized by isolated erythroid hypoplasia. Approximately half of the DBA cases are associated with germline mutations that result in haploinsufficiency of ribosomal proteins. A smaller subset of DBA cases, all of which are X-linked, is associated with germline GATA1 mutations, including substitution or splice site mutations involving exon 2 or 3 (Ludwig LS et al, 2014; Parrella S et al, 2014; Klar J et al, 2014; Sankaran VG, 2012). These mutations, similar to those seen in MP-DS (see above), create missense or nonsense mutations at the first start codon or premature stop codons before the second alternative start codon, thereby precluding the production of the full length GATA1 and leading to the exclusive production of the short form of GATA1 (GATA1s). Interestingly, several studies have suggested that in DBA with ribosomal protein haploinsufficiency exhibits altered translation of GATA1 mRNA, providing a possible converging mechanism of DBA (Ludwig LS et al, 2014; Khajuria RK et al, 2018).

Dyserythropoietic anemia

Dyserythropoietic anemia (DA), is a rare congenital red blood cell disorder characterized by anemia with erythrodysplasia (often abnormal forms with multinucleated nuclei) and varying degrees of macrothrombocytopenia with dysplastic megakaryocytes. There are several isolated case reports describing the roles of GATA1 mutations in a subset of DA, which often presents as severe fetal anemia requiring intrauterine transfusion (Zucker J et al, 2016; Abdulhay NJ et al, 2019; Kratz CP et al, 2008; Freson K et al, 2002; Nichols KE et al, 2000; Del Vecchio GC et al, 2005). Based on the limited case reports, there appears to be two different classes of GATA1 mutations that can cause DA. The first class of mutations (such as, V205M, G208R, and D218Y/G) appears to affect interaction with FOG-1 (Friends of GATA1), a transcriptional co-factor required for normal erythroid and megakaryocytic differentiation. The second class of mutations appears to affect the splicing of GATA1 transcripts that result in the preferential production of the short form of GATA1 protein, in a similar manner seen in DBA (see above). Mutations altering the pattern of splicing were described to involve the 5' untranslated region and in the fifth intron. Of note, these cases are distinctly different from congenital dyserythropoietic anemia type I, II, and III. Some

have proposed to include the GATA1 mutated DA cases as congenital dyserythropoietic anemia variants.

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