t(12;12)(p13;q13) ETV6/BAZ2A

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Clinics and pathology

Disease

Acute leukemias

Clinics

Out of 5 cases herein taken into account, 3 cases presented with a rearranged ETV6 gene, and only one of these cases was identified to carry an ETV6/BAZ2A hybrid gene. This case was a 3-year-old girl with a pre-B acute lymphoblastic leukemia (CD10+ ALL). She achieved complete remission (CR), and was remaining in CR 18 months after diagnosis (Panagopoulos et al., 2006).

The 2 other ETV6+ cases were acute myeloid leukemia (AML) cases: a 77-year-old male patient with AML-M2. Complete remission was achieved; he relapsed and died of sepsis (Saitoh et al., 2002); and a 46-year-old female patient with treatment related AML-M2, developing years after treatment for breast cancer; the patient has been in continuous relapse for the last 4 months after onset of AML (Manola et al., 2008).

The 2 last cases were: a 4-years-old boy with ALL; the patient was alive 27 months after diagnosis (Heerema et al., 1985); and a 62-years-old female patient with AML-M6 with a 2 months survival (Mazzella et al., 1998).

Altogether, this makes 2 pediatric ALL cases, and 3 adult AML cases, with perhaps different prognoses between the two categories. Excluded here is a case of refractory anemia with excess blasts with HMGA2 involvement (Odero et al., 2005), although the 4 above mentionned cases where BAZ2A was not studied may also have had a HMGA2 rearrangement.

Cytogenetics

Cytogenetics morphological

In the case where ETV6/BAZ2A rearrangement was ascertained, the rearrangement between 12p13 and 12q13 was cryptic (Panagopoulos et al., 2006). The other ALL case also had a trisomy 16 and a trisomy 21. The t(12;12)(p13;q13) was an additional anomaly to a t(11;19)(q23;p13.1) in the treatment related AML-M2 case.

The apparently de novo AML-M2 case have had a del(7q) prior to the t(12;12). The M6-AML case had a del(5q), a del(20q) and a complex karyotype.

Genes involved and proteins

ETV6

Location

12p13.2

Protein

ETV6 is a transcriptional repressor belonging to the ETS family. ETV6 displays a HLH domain (also referred to as the pointed (PNT) or sterile alpha motif (SAM) domain), responsible for hetero- and homodimerization, a central domain involved in the recruitment of a repression complex including NCOR2 and SIN3, and an ETS domain, responsible for sequence specific DNA-binding to DNA-responsive elements.

Repression involves the recruitment of co-repressor complexes and HDACs or the recruitment of L3MBTL-containing polycomb group-complexes that facilitate repression by chromatin remodeling. ETV6
binds to nuclear receptors RARA and RXRA and represses gene activation. ETV6 is a selective and essential regulator of stem cells, important in vitelline angiogenesis and in bone marrow hematopoiesis. ETV6 expands erythroid precursors and stimulates hemoglobin synthesis (Knezevich, 2005; Eguchi-Ishimae et al., 2009; Meester-Smoor et al., 2011).

**BAZ2A**

**Location**
12q13.3

**Protein**

BAZ2A comprises from N-term to C-term a MBD (methyl-CpG-binding) domain, 2 AT hooks, a DDT (DNA binding homeobox and different transcription factors), 2 AT hooks again, a PHD-type zinc finger, and a bromo domain. The bromo domain and the PHD-type zinc finger recognize and bind histone H4. These 2 domains play a central role in the recruitment of chromatin silencing proteins such as DNMT1, DNMT3B and HDAC1 (Swiss-Prot). The NoRC (nucleolar remodeling complex) comprises BAZ2A and SMARCA5. A mechanism for silencing active ribosomal RNA (rRNA) genes is the recruitment by TTF1 (transcription termination factor-1) of NoRC to the promoter of rRNAs in the nucleolus. PARP1, component of the machinery that establishes and maintains silent rDNA chromatin during cell division, binds to BAZ2A (Guetg et al., 2012). BAZ2A is up-regulated in patients with chronic lymphocytic leukemia (Hanlon et al., 2009).

**Result of the chromosomal anomaly**

**Hybrid gene**

Transcript consisting of exons 1 and 2 of ETV6 and a sequence from intron 1 of BAZ2A. This transcript is not expected to produce any chimeric protein.

**Fusion protein**

The transcript may encode a truncated form of ETV6, containing the first 54 amino acids (aa) of ETV6, followed by 16 aa from the 3' fusion sequence.

**Oncogenesis**

The production of a truncated form of ETV6 is reminiscent of ETV6 fusions with MDS2, FCHO2, PER1, and STL, according to Panagopoulos et al., 2006. BAZ2A may also be deregulated.

**References**


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