Abstract

Review on t(11;11)(q14;q23) and inv(11)(q14q23) KMT2A/PICALM, with data on clinics and the genes involved.

KEYWORDS
Chromosome 11; KMT2A; PICALM; acute myeloid leukemia; acute lymphoblastic leukemia.

Clinics and pathology

Disease
Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL).

Clinics
There was the case of a 12-week-old female infant with acute monocytic leukemia (M5b) and inv(11)(q14q23), dead at day 11 (Wechsler et al., 2003).

Otherwise, in a large study of cases of chromosomal rearrangements involving the human KMT2A (MLL) gene, a t(11;11)(q14;q23) or inv(11)(q14q23) KMT2A/PICALM was found in 1 out of 440 infant ALL patients, 1 out of 105 infant AML patients, 1 out of 205 pediatric AML patients, 1 out of 272 adult AML patients, and none in 202 pediatric AML patients, nor in 333 adult ALL patients (Meyer et al., 2013). Note: the case by Meyer et al., 2006 was reused in Meyer et al., 2013.

Genes involved and proteins

PICALM (clathrin assembly lymphoid myeloid leukemia gene)
Location
11q14.2
DNA/RNA
24 transcripts
Protein

PICALM codes for a 652-aa protein, and shorter isoforms. It is an endocytosis adaptor, in the initial stages of coated pit invagination together with clathrin, AP2 (adapter related protein complex subunits) and PtdIns(4,5)P2 (phosphatidylinositol-4,5-bisphosphate) containing membranes. PICALM interacts with CLTC (clathrin heavy chain) promoting assembly of clathrin triskelia into clathrin cages. Clathrin is the major binding partner of PICALM (Archangelo et al., 2006). PICALM is required for erythroid maturation and transferrin internalization.

**PICALM domains:** PICALM contains an AP180 N-terminal homology (ANTH) domain (or ENTH domain for epsin NH2-terminal domain)) (note: "AP180" is SNAP91, and epsin is EPN1, EPN2 or EPN3) and an assembly domain (AD). ANTH: amino acids (aa) 1-289; AD: aa 290-652.

**ANTH:** The ANTH domain is folded; it binds phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P2) via a lysine-rich motif, and vesicle associated membrane proteins (VAMPs). There are nine alpha helices forming a solenoid (aa 20-30, 40-50, 56-67, 71-90, 91-100, 115-142, 160-180, 191-222, 225-258). In addition, there are PtdIns(4,5)P2-binding residues at aa 28, 38, 40, 41 (K, K, K, H).

**AD:** The AD has two subdomains; a central clathrin and adaptor protein binding (CLAP) domain and the remainder is an unnamed domain (ADACLAP). CLAP domain: aa 290-525, with CLAP motifs: DIF, DLL, DPF (see below), and FESVF: aa 488-493.

Unnamed domain (ADACLAP): aa 526-652. ADACLAP is basic. The assembly domain (AD) has a role of clathrin and AP2 binding.

**Other domains:** transcriptional activation domain (TAD) (aa 408-572). PICALM is O-GlcNAc modified at aa 454 (S). Nuclear export signal (NES) LANLVLGNGLI: aa 544-553. The NES consensus sequence is ΦX1-3ΦX2-3ΦXΦ, where Φ is most often leucine. The NES is the factor which contributes to PICALM/MLLT10 mediated leukemogenesis.

**Protein interaction domains:** PICALM binds directly to various vesicle associated membrane proteins: VAMP2, VAMP3, VAMP4, VAMP7 and VAMP8. PIMREG (FAM64) interaction domain: aa 221-294; FHL2 interaction domain: aa 294-335; proteins with an EPS15 homology domain interaction domain: NPF (Asp-Pro-Phe) motif (aa 437-439). Clathrin binding motifs (CBM): Binding of clathrin heavy chain (CLTC) involves primarily aa 413-652, however, the entire AD is required for efficient clathrin binding. PICALM has one DLL (Asp-Leu-Leu) motif (aa 392-394); one DIF (Asp-Ile-Phe) motif (aa 375-377) which could bind clathrin, but also AP2A (AP2 alpha subunit); and one DPF (Asp-Pro-Phe) sequence (aa 420-422), which can also bind AP2A1. Other clathrin binding sequences involve L/I (Leu/Ile) in aa 540-553 and aa 649-652 (Tebar et al., 1999; Ford et al., 2001; Archangelo et al., 2006; Pašaliç et al., 2011; Moshkanbaryans et al., 2014; Moshkanbaryans et al., 2016).
KMT2A (myeloid/lymphoid or mixed lineage leukemia)

Location

DNA/RNA
37 exons, spanning about 120 kb; 13-15 mRNA

Protein
3969 amino acids, 431 kDa; Transcriptional regulatory factor. MLL is known to be associated with more than 30 proteins, including the core components of the SWI/SNF chromatin remodeling complex and the transcription complex TFIID. MLL binds promoters of HOX genes through acetylation and methylation of histones. MLL is a major regulator of hematopoesis and embryonic development, through regulation of HOX genes expression regulation (HOXA9 in particular).

Result of the chromosomal anomaly

Hybrid gene
Description
The KMT2A breakpoint was in intron 9 in 2 cases, and in intron 10 in the 2 other cases (Meyer et al., 2013). The full-length KMT2A/PICALM transcript was 5409 bp long, including 4218 bp from KMT2A exons 1-7 and 1191 bp from PICALM (exons 8-20) in Wechsler et al., 2003.

Fusion protein
t(11;11)/inv(11) (q14;q23) KMT2A/PICALM

Description
The KMT2A/PICALM fusion protein was contained 1803 amino acids and included 1406 amino acids from KMT2A A-T hooks and repression domain, and a PICALM-derived clathrin-binding domain in Wechsler et al., 2003.

References

This article should be referenced as such: