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Gene Section
Review

EP300 (E1A binding protein p300)

Gloria Negri, Cristina Gervasini

Department of Health Science, Medical Genetics, Universita degli Studi di Milano, Milano, Italy

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Abstract

Review on EP300, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: P300, KAT3B

HGNC (Hugo): EP300

Location: 22q13.2

DNA/RNA

Description

p300 was first discovered on the basis of its interaction with the adenoviral protein E1A and EP300 locus was subsequently mapped to the long arm of chromosome 22, spanning about 88 kb (Whyte et al., 1989; Eckner et al., 1994).

Transcription

EP300 has only one splice variant derived from the splicing of its 31 exons with an mRNA of 9585 bp which includes 1219 and 1121 bp of 5'UTR and 3'UTR, respectively.

Pseudogene

No pseudogenes are known.

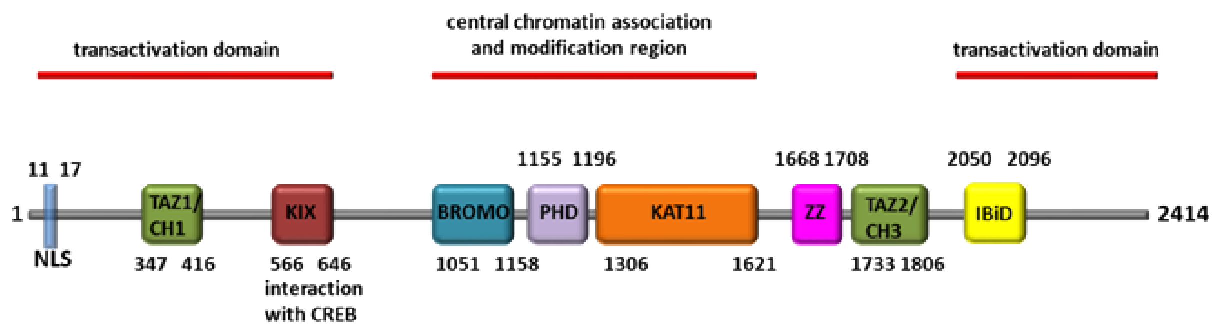
Protein

Description

p300 is a large size protein of about 264 kDa belonging to the KAT3 (lysine or K-acetyltransferase) family (Valor et al., 2013).

p300 shares a modular organization consisting in several conserved domains including a central chromatin association and modification region which includes the bromodomain/PHD finger module and the KAT11 domain (Rack et al., 2014) which is flanked by four transactivation domains (TADs): i) the CH1 that encompasses the TAZ1 domain, ii) the KIX domain, iii) another CH3 containing the TAZ2 domain and a ZZ domain, and iv) the IBiD (Bedford et al., 2012; Wang et al., 2013).

Schematic representation of EP300 gene. Black boxes represent exons and gray ones 5' and 3' UTRs. Thin black lines represent introns. (Modified from Zimmerman et al., 2007).



Schematic structure of p300 protein including its functional and structural domains and their localization. NLS (nuclear localization signal), CH1 (cysteine/histidine-rich region 1, also known as transcriptional-adaptor zinc-finger domain 1 or TAZ1), KIX (kinase inducible domain of CREB interacting domain), BROMO (bromodomain), PHD (plant homeodomain finger), KAT11 (lysine acetyltransferase domain), ZZ (ZZ-type zinc finger domain), TAZ2 (transcriptional-adaptor zinc-finger domain 2; ZZ and TAZ2 together are sometimes referred to as CH3 or cysteine/histidine-rich region 3), and IBiD (IRF3-binding domain). Aminoacid positions are from UniGene NP_001420.2.

The Bromodomain mediates p300 binding to acetylated histones, nucleosomes and transcriptional factors and could therefore play a role in tethering p300 to specific chromosomal sites (Kalkhoven et al., 2004; Rack et al., 2014) moreover, the associated PHD finger is an integral part of the enzymatic core of the protein influencing its ability to recognize and acetylate both itself as well as histones and non-histone substrates (Kalkhoven et al., 2004; Wang et al., 2013; Rack et al., 2014). The KAT11 catalytic domain can acetylate p300 itself and a variety of histonic and non-histonic proteins and the CH rich regions are able to bind zinc and are involved in protein-protein interaction (Valor et al., 2013; Wang et al., 2013).
p300 has also multiple specific interaction domains for different transcriptional factors such as the KIX domain that mediates CREB-p300 interaction and CREB phosphorylation at serine 133 residue but also for the Retinoic Acid Receptor-related orphan receptor A (RORA) and for ALX1 at the N-term end of the protein and for Interferons at C-term end.

Expression

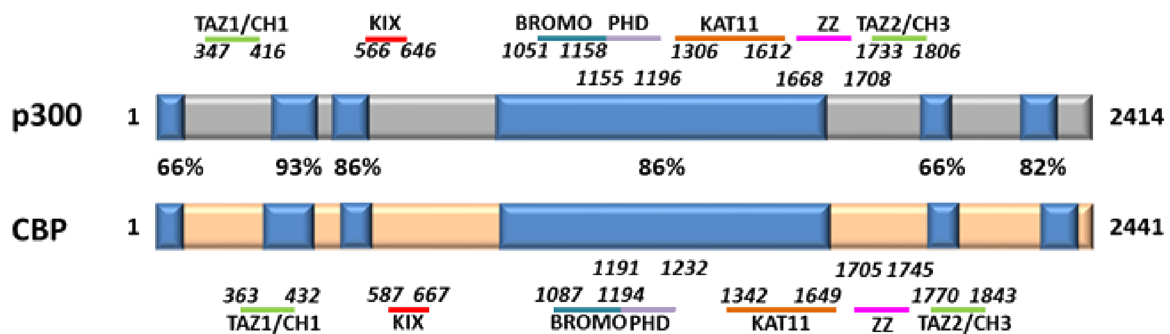
p300 is ubiquitously expressed in human tissues (Kalkhoven et al., 2004; Valor et al., 2013). p300 is highly evolutionary conserved and present in many multicellular organisms including flies, worms and plants but not in lower eukaryotes such as yeasts (Kalkhoven et al., 2004).

Localisation

p300 is a nuclear protein which resides in a specific nuclear structure called nuclear body (Chan and La Thangue, 2001).

Function

p300 is a transcriptional coactivator with intrinsic lysine acetyltransferase activity able to regulate transcription and gene expression in different ways.
1) Acetylation of histones tails: p300 can enable transcription through the catalytic activity of its KAT domain which is able to acetylate promoter nucleosomal histones resulting in chromatin remodelling and relaxation and in increased accessibility of the DNA to other essential regulators (Kalhoven et al., 2004; Wang et al., 2013).
Thanks to its ability in modifying chromatin structure by histone acetylation, p300 can be defined as "writer" of the epigenetic code (Berdasco et al., 2013).
2) Acetylation of other target proteins: p300 can also acetylate other kinds of proteins, such as transcriptional factors, modulating their activity positively or negatively, or coactivators.
Acetylation of non-histone substrates can result in either positive or negative effects on transcription by affecting protein-protein interactions (activator of thyroid and retinoid receptors ACTR), protein-DNA interactions (the high mobility group protein HMGI), nuclear retention (the hepatocyte nuclear factor HNF4) or protein half-life (E2F).
For example some acetylated p300 targets regulate the expression of histone methyltransferase leading to chromatin condensation and gene silencing.
3) RNA Polymerase II stabilization: p300 functions as a "bridge" linking the DNA-bound transcription factors (activators) to the basal transcription machinery through direct interaction with TFIID, including TATA-binding protein (TBP) and 13 TBP-associated factors (TAFs) and TFIIB promoting the pre-initiation complex (PIC) assembly (Wang et al., 2013).
p300 has also some more indirect chromatin-related roles:
4) DNA replication and repair: p300 interacts with various replication and repair proteins, including proliferating cell nuclear antigen (PCNA), the Recq4 helicase, Flap endonuclease 1 (Fen1), DNA polymerase b and thymine DNA glycosylase, with the latter three also serving as acetylation substrates.



Comparison of p300 and CBP amino acidic sequences. The blue regions indicate the areas of highest homology with the percentage of amino acid identity specified in between. Position of the corresponding domains are taken from UniGene (NP_001420.2 for EP300 and NP_004371.2 for CREBBP). (Modified from Chan and La Thangue, 2001).

5) Cell cycle regulation: p300 associates with the complex formed between cyclin E and cyclin-dependent kinase 2 (cdk2) regulating proper progression of the cell cycle.
6) p53 activity regulation: p300 is involved in p53 degradation, which depends on the murine double minute 2 protein (MDM2). Degradation and ubiquitination of p53 is dependent on MDM2, and a ternary complex between these two proteins and p300 regulates the turnover of p53 itself in cycling cells. Furthermore, the CH-1 region of p300 displays polyubiquitin ligase activity towards p53, and could therefore play a key role in controlling p53 levels.
7) Nuclear import: p300 can acetylate two proteins involved in regulating nuclear import, the importin-α1 isoform Rch1 and importin-α7, and could therefore play a role in this process.
Because of its ability of interacting with more than 400 partner proteins, p300 can be considered a "hub" (Bedford et al., 2014). Its interactome includes pro-proliferative proteins and oncoproteins: c-Myc, c-Myb, CREB, c-Jun and c-Fos; transforming viral proteins: E1A, and E6; as well as tumor suppressors and pro-apoptotic proteins: Forkhead box class O (FoxO) transcription factors FoxO1, FoxO3a, and FoxO4, signal transducers and activators of transcription (STAT) 1 and STAT 2, Hypoxia-inducible factor 1α (HIF-1α), breast cancer 1 (BRCA1), SMA/MAD homology (Smad) proteins, the Runt-related transcription factor (RUNX), E2 Transcription Factor (E2F), and E-proteins (Wang et al., 2013).

Homology

p300 is highly homologous to the cyclic AMP response element-binding (CREB) binding protein (CBP) with 63% identity and 75% similarity at amino-acid level (Narayanan et al., 2004; Wang et al., 20113). CREBBP/CBP locus was mapped on 16p13.3, a region of extensive homology to the one on chromosome 22 where EP300/p300 resides (Chan and La Thangue, 2001; Gervasini, 2010).

Mutations

Germinal

Rubinstein-Taybi Syndrome (RSTS; OMIM #180849, #613684).

Somatic

Cancers derived from almost all tissues and organs, such as those of hematopoietic and lymphoid organs, cancers of eye, skin, bones, thyroid, salivary and adrenal glands, central nervous system (CNS) including meninges, and nervous system (NS) including automatic ganglia, esophagus, upper aerodigestive tract, lung and pleura, stomach, liver, pancreas, biliary tract, large and small intestine, kidney, urinary tract and breast, endometrium, cervix, ovary and prostate.

Epigenetics

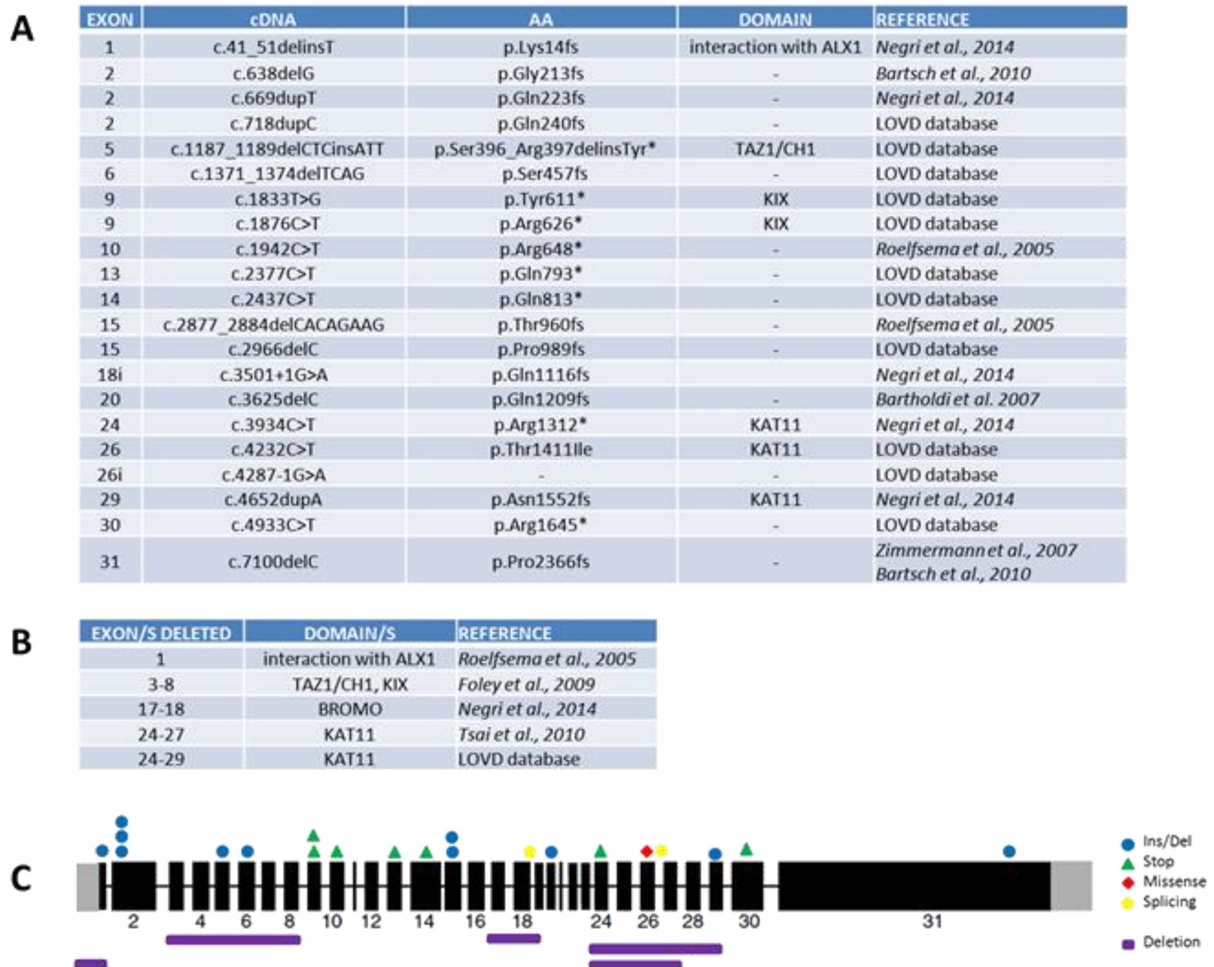
The identification of mutations in epigenetic genes, classified as writers, readers and erasers based on their function (Berdasco and Esteller, 2013), represents a link between the cancer epigenome and genetic alterations acting as "driver" or "passenger" mutations in cancer development.
Actually, many genetic alterations in cancer epigenetic regulators cause cancer-associated phenotype via epigenetic dysfunction (Roy et al., 2014).

Implicated in

Rubinstein-taybi syndrome (RSTS; OMIM #180849, #613684)

Note
Germinal mutations leading to loss of function/haploinsufficiency.

Disease
Rubinstein-Taybi syndrome is a rare (1:125000 live birth) autosomal dominant neurodevelopmental disorder.



A

EXON	cDNA	AA	DOMAIN	REFERENCE
1	c.41_51delinsT	p.Lys14fs	interaction with ALX1	Negri et al., 2014
2	c.638delG	p.Gly213fs	-	Bartsch et al., 2010
2	c.669dupT	p.Gln223fs	-	Negri et al., 2014
2	c.718dupC	p.Gln240fs	-	LOVD database
5	c.1187_1189delCTCinsATT	p.Ser396_Arg397delinsTyr*	TAZ1/CH1	LOVD database
6	c.1371_1374delTCAG	p.Ser457fs	-	LOVD database
9	c.1833T>G	p.Tyr611*	KIX	LOVD database
9	c.1876C>T	p.Arg626*	KIX	LOVD database
10	c.1942C>T	p.Arg648*	-	Roelfsema et al., 2005
13	c.2377C>T	p.Gln793*	-	LOVD database
14	c.2437C>T	p.Gln813*	-	LOVD database
15	c.2877_2884delCACAGAAG	p.Thr960fs	-	Roelfsema et al., 2005
15	c.2966delC	p.Pro989fs	-	LOVD database
18i	c.3501+1G>A	p.Gln1116fs		Negri et al., 2014
20	c.3625delC	p.Gln1209fs	-	Bartholdi et al. 2007
24	c.3934C>T	p.Arg1312*	KAT11	Negri et al., 2014
26	c.4232C>T	p.Thr1411Ile	KAT11	LOVD database
26i	c.4287-1G>A	-	-	LOVD database
29	c.4652dupA	p.Asn1552fs	KAT11	Negri et al., 2014
30	c.4933C>T	p.Arg1645*	-	LOVD database
31	c.7100delC	p.Pro2366fs	-	Zimmermann et al., 2007 Bartsch et al., 2010

B

EXON/S DELETED	DOMAIN/S	REFERENCE
1	interaction with ALX1	Roelfsema et al., 2005
3-8	TAZ1/CH1, KIX	Foley et al., 2009
17-18	BROMO	Negri et al., 2014
24-27	KAT11	Tsai et al., 2010
24-29	KAT11	LOVD database

EP300 germline mutations in Rubinstein-Taybi patients (2014 update). A) Point mutations, B) intragenic deletions and C) schematic of the gene with type and localization of all 26 mutations reported so far. (Modified from Negri et al., 2014).

It is characterized by postnatal growth retardation, intellectual disability (ID), skeletal anomalies (broad and/or duplicated distal phalanges of thumbs and halluces are a landmark sign) and distinctive facial dysmorphisms including down-slanting palpebral fissures, broad nasal bridge, beaked nose and micrognathia (Hennekam, 2006).

Prognosis

All EP300-mutated RSTS patients described in literature are alive (Roelfsema et al., 2005; Bartholdi et al., 2007; Zimmermann et al., 2007; Foley et al., 2009; Bartsh et al., 2010; Tsai et al., 2011; Negri et al., 2014).

Hybrid/Mutated gene

The identification of EP300 as the second RSTS causative gene in 2005 (Roelfsema et al., 2005) disclosed the heterogeneous nature of the syndrome. EP300 heterozygous point mutations and intragenic deletions have been detected in about 8% of RSTS CREBBP-negative cases (Negri et al., 2014). Fourteen patients are clinically and genetically described (Roelfsema et al., 2005; Bartholdi et al., 2007; Zimmermann et al., 2007; Foley et al., 2009; Bartsh et al., 2010; Tsai et al., 2011; Negri et al., 2014), while 12 additional alterations are reported in the LOVD database .

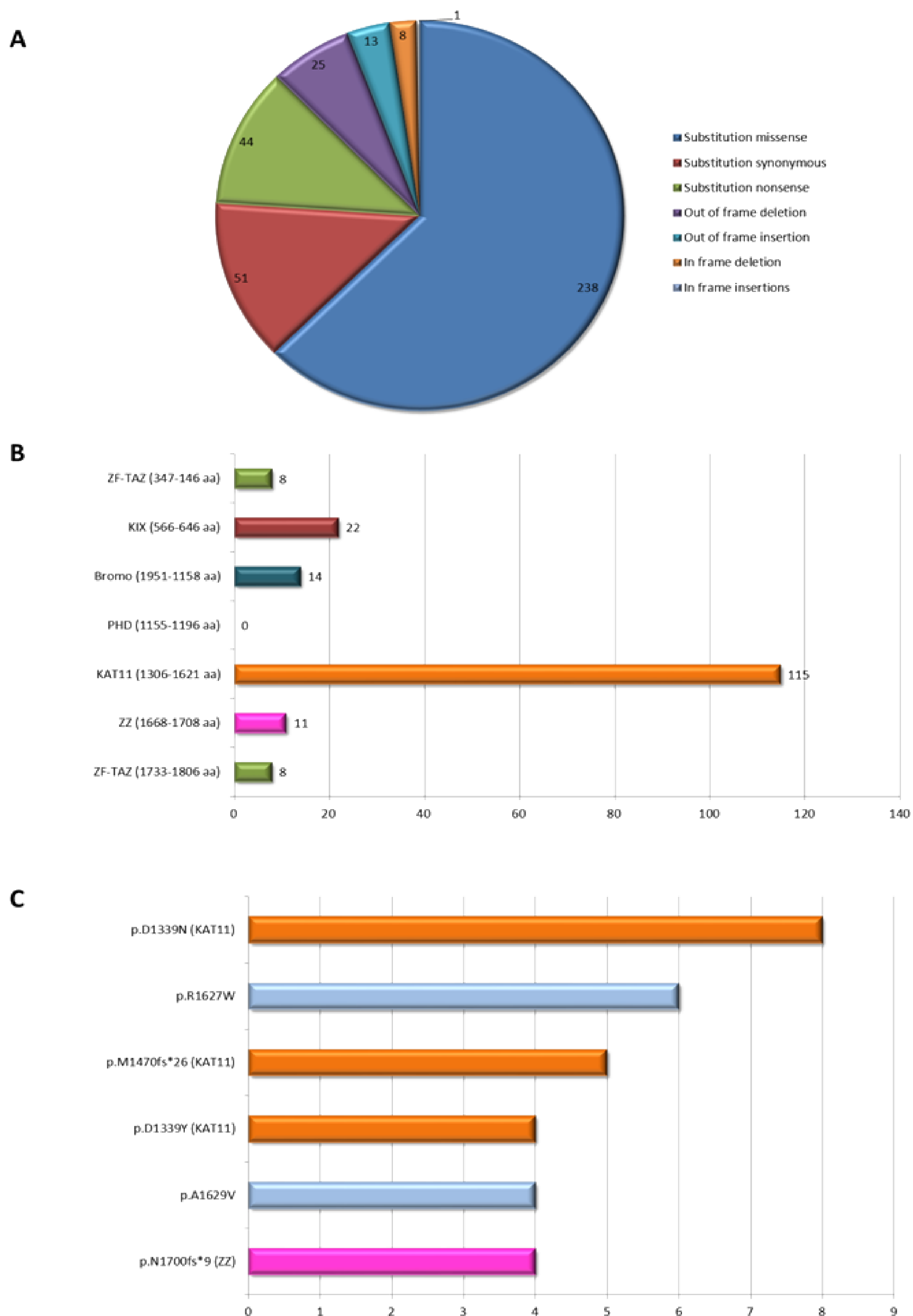
Oncogenesis

RSTS patients (estimated incidence 5%) have an increased predisposition to malignancies like leukemia, neuroblastoma, meningioma and pilomatrixoma, developed either in the first years of life or in mid-adulthood (30-40 years) (Siraganin et al., 1989; van de Kar, 2014). Glaucomas and keloids are reported too; in particular, EP300-mutated RSTS patients show a slight increase in developing skin anomalies such as keloids (Van Genderen et al., 2000; van de Kar, 2014; Negri et al., 2014).

Various cancers

Note

All data are taken from COSMIC database (Catalogue of Somatic Mutations In Cancer) (Release v70 August 2014).



EP300 somatic point mutations load. A) Pie chart of the main kinds of point mutations and relative numbers, B) bar chart of the distribution of the mutations within the gene domains and C) recurrent mutations and localization. Data are reworked from COSMIC database.

Disease

EP300 point mutations, copy number variations (CNVs) but also gene expression profile alterations have been detected in almost all human cancers independently of the embryonic origin. Out of >14.000 tumor samples tested, those derived from hematopoietic and lymphoid organs, lung, central nervous system (CNS), breast, intestine and ovary show the highest prevalence of EP300 mutations.

Hybrid/Mutated gene

The majority of EP300 point mutations detected in tumoral samples are heterozygous (Aumann et al., 2014).

With about ~400 unique somatic alterations reported, point mutations appear to be the most represented kind of EP300,mutations: in particular, missense mutations account for >60% of all mutations, followed by synonymous (~13%) and nonsense (~11%) mutations. In detail, transitions justify about 70% of all substitutions. Out of frame insertion/deletions (ins/del) represent together 38% and in frame ins/del about 4%.

Mutations are widespread across the gene with a great concentration in the large KAT11 domain, which clusters about 26% of all alterations. Few recurrent mutations are reported: the most frequently mutated amino acid residue is the aspartic acid at position 1339 in the KAT11 domain which is replaced by either asparagine (eight samples) or tyrosine (four samples).

CNVs are described too. In particular, losses are reported in 31 samples including breast, endometrium, ovary, large intestine and lung cancer, while gains seem to be rarer being described in 11 samples including breast, hematopoietic and lymphoid, and lung cancer.

Alterations in EP300 gene expression are recorded too: in particular over expression was described in 94 samples, while under expression in 104 samples, both in cancers derived from breast, endometrium, ovary, CNV, haematopoietic and lymphoid organs, kidney, large intestine and lung.

Oncogenesis

The oncogenic mechanism by which EP300 mutations act is not yet clear, but as the most frequently mutated region is the lysine acetyltransferase domain, which catalyzes acetylation of histones and other essential proteins, aberrant acetyltransferase activity may be a key feature. In vitro studies demonstrated reduced H3K18 acetylation, as well as decreased ability to acetylate p53 and BCL6, in p300- mutated cells (Peifer et al., 2012). Because of p300 multiple functions and diverse interactions, many intertwisted mechanisms could play a role in the different mutations' effects.

t(11;22)(q23;q13) resulting in MLL1-EP300 fusion gene

Note

Somatic mutations.

Disease

Therapy-related leukemias and myeloid neoplasms.

Cytogenetics

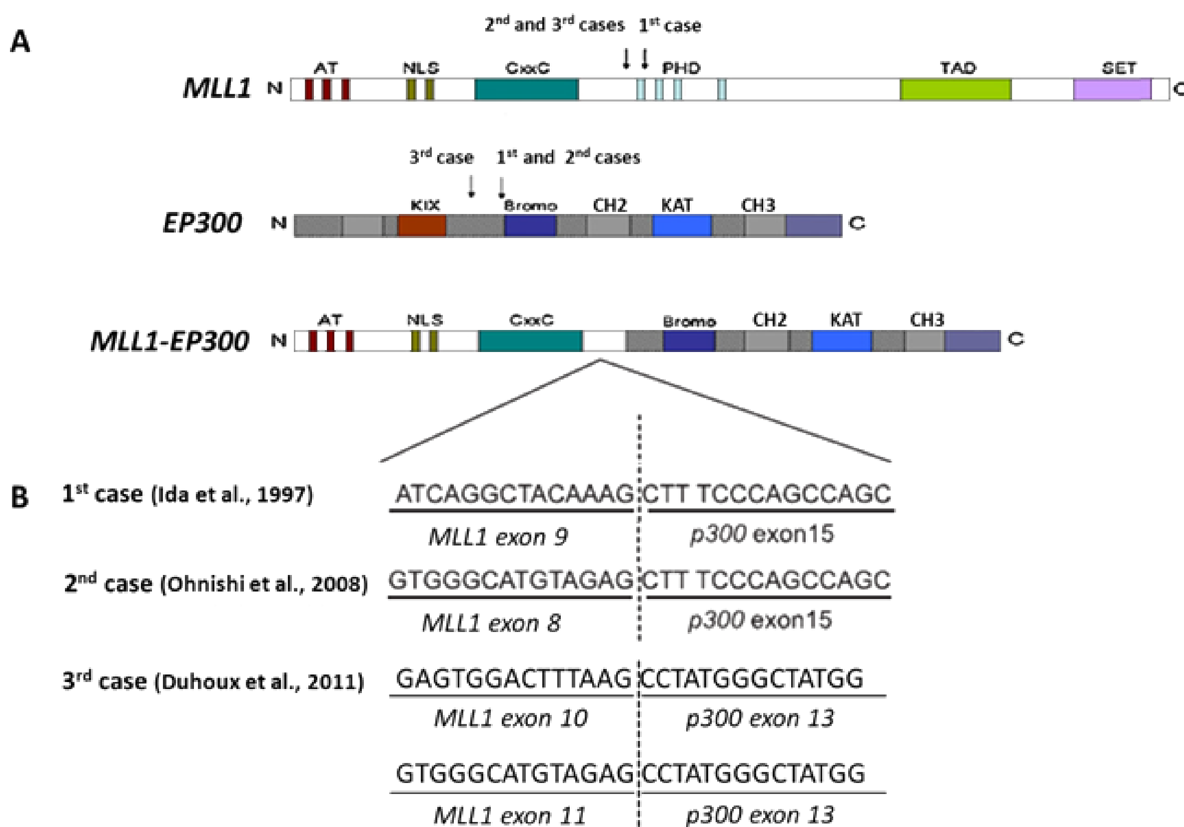
Ida et al., described the first patient presenting the karyotype 48,XY,+8,+8,(11;22)(q23;q13); the same group (Ohnishi et al.) described a second patient with 46,XX,t(1;22;11)(q44;q13;q23), t(10;17)(q22,q21), while a third patient, with 46;XY,t(11;22)(q23;q13)[15]/47,idem,+8[2], was reported by Duhoux et al.

Hybrid/Mutated gene

Rearrangements of the mixed lineage leukemia (MLL1 or KMT2A; gene ID: 4297) locus are frequently encountered in acute leukemias and at least 104 different chromosomal rearrangements involving MLL1 itself with more than 64 translocation partner genes have been described (Meyer et al., 2009) while rearrangements of EP300 gene locus seem to be rare events.

Only three cases of MLL1-EP300 fusion genes have been described, all in therapy-related leukemia patients following chemoterapy with topoisomerase II inhibitors. The first patient was initially diagnosed as having non-Hodgkin lymphoma and, after conventional chemotherapy, he developed secondary AML which was cytogenetically characterized as t(11;22)(q23;q13) producing a chimeric MLL1-EP300 gene in which the exon 9 of MLL1 was juxtaposed to EP300 exon 15 (Ida et al., 1997). The second case is a girl who developed AML after chemotherapy for neuroblastoma. She presented a complex karyotype 46,XX,t(1;22;11)(q44;q13;q23),t(10;17)(q22,q21) with the fusion of MLL1 exon 8 to EP300 exon 15 and also a less expressed clone in which exon 7 of MLL1 is fused with exon 15 of EP300, which was considered to be generated by alternative splicing (Ohnishi et al., 2008). The third patient presented AML with myelodysplasia-related changes evolving after chemotherapy in acute myelomonocytic leukaemia (AMML). Leukemic cells were cytologically characterised as 46;XY,t(11;22)(q23;q13)[15]/47,idem,+8[2] including the fusion of exon 10, or exon 11 resulting from alternative splicing, of MLL1 with exon 13 of EP300 (Duhoux et al., 2011).

All chimeric proteins retain almost the same part of both MLL1, including the AT-hook, the DNA methyltransferase and the transcriptional repression domains and p300, i.e. the bromodomain, the catalytic KAT and TADs



t(11;22)(q23;q13) leads to fusion of MLL1 gene to EP300. A) Schematic representation of MLL1, p300 and the predicted MLL1-p300 fusion proteins of all reported cases (Ida et al., 1997; Ohnishi et al. 2008; Duhoux et al., 2011). B) Nucleotide sequences of the hybrid junctions of the chimeric MLL1-EP300 genes and relative references. Breakpoints are indicated by arrows; AT: AT hooks, NLS: nuclear localization signals, CxxC: motif recognizing unmethylated CpG dinucleotides, PHD: plant homeodomain fingers, TAD: transactivation domain, SET: histone methyltransferase active sites; CH: cystidine/histidine-rich; KIX: kinase inhibitory domain, Bromo: bromodomain, KAT: Lysine acetyltransferase domain. (Modified from Duhoux et al., 2011).

Oncogenesis

The fusion of MLL1 with the lysine-acetyltransferase p300 supposedly leads to hyperacetylation of chromatin which contributes to increase the transcriptional output conferring a significant oncogenic advantage to the cells. Furthermore, nuclear factors, such as p300, have transcriptional activity and their function might be deregulated by the fusion with MLL1 (Ohnishi et al., 2008; Duhoux et al., 2011).

The translocation t(11;22)(q23;q13) involving MLL1-EP300 is characteristic of therapy related leukemias where it is likely driven by topoisomerase II inhibitors, rather than of de novo leukaemias.

t(8;22)(p11;q13) resulting in MOZ-EP300 fusion gene

Note

Somatic mutations.

Disease

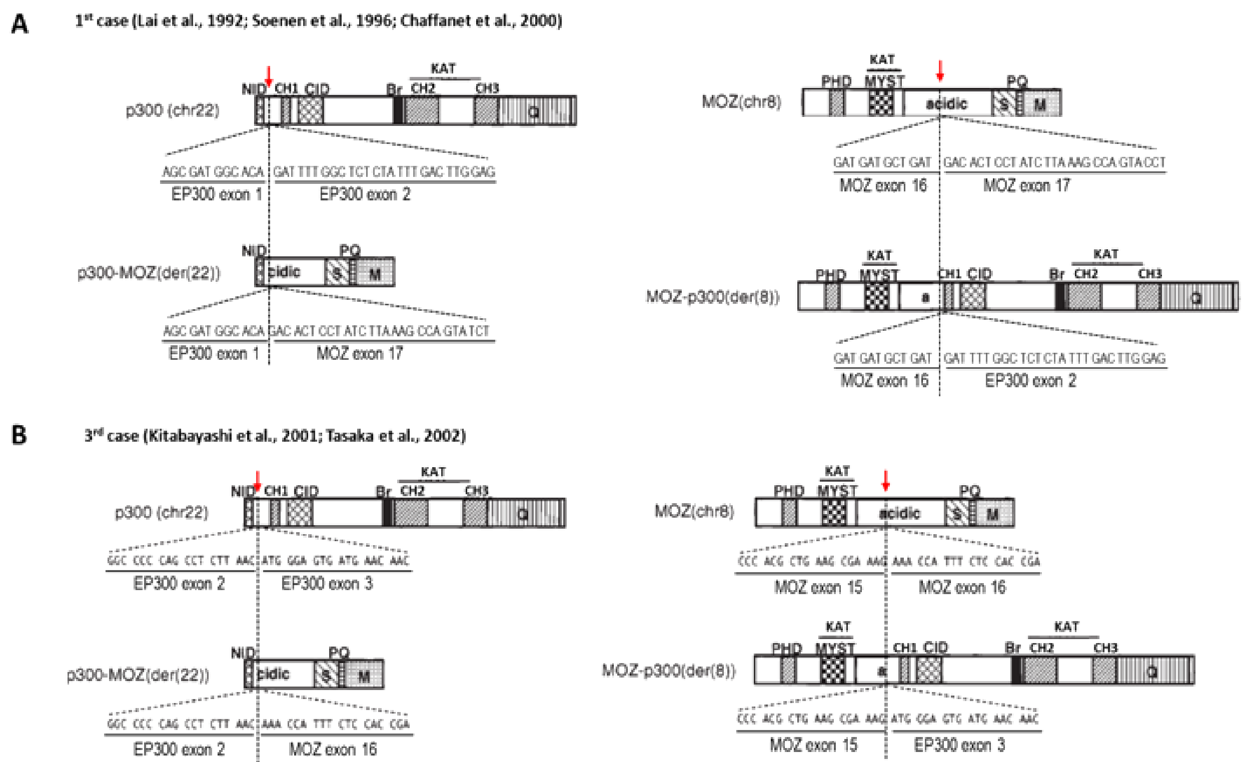
de novo, progression or therapy-related AML.

Cytogenetics

The t(8;22)(p11;q13) is a rare translocation found in acute myeloid leukaemia (AML) described in only three patients (Lai et al., 1992; Soenen et al., 1996; Chaffanet et al., 2000; Kitabayashi et al., 2000; Tasaka et al., 2002). The first patient was diagnosed as having a de novo AML with karyotype 47, XY,+8,t(8;22)(p11;q13), while the second patient suffered from a chronic myelomonocytic leukaemia (CMML) which evolved in AML with the abnormal karyotype: 46,XY,t(8;22)(p11;q13)/idem,+der(8)t(8;22)(p11;q13)del(17)(p11) (Lai et al., 1992; Soenen et al., 1996; Chaffanet et al., 2000). The third case is a man with primary macroglobulinemia who developed a secondary AML during chemotherapy, with the karyotype: 47, XY, t(8;22)(p11.2;q13.1),+der(8)t(8;22)(22qter→22q13.1::8p11.2→8q13::8q22→8qter),add(19)(p13.3) (Kitabayashi et al., 2001; Tasaka et al., 2002).

Hybrid/Mutated gene

Monocytic leukemia zinc finger gene (MOZ, Gene



Schematic representation of the p300, MOZ, MOZ-p300 and p300-MOZ proteins. A) p300, MOZ, p300-MOZ and MOZ-p300 diagram of the first case and B) p300, MOZ, p300-MOZ and MOZ-p300 diagram of the third one. Red arrows indicate the breakpoints of the translocations and nucleotide sequences of WT and hybrid junctions are reported. The functional domains of MOZ and p300 as well as those of fusion proteins are indicated above and beneath the diagrams. NID: nuclear receptor interaction domain, CH1-3: cysteine/histidine-rich domain, CID: CREB-interaction domain, B: bromodomain, KAT: lysine acetyltransferase domain, Q: glutamine-rich region, PH: PHD class zinc finger, MYST: MOZ, YB1, SAS, TIP homology domain, S: serine-rich region, PQ: proline/glutamine region, M: methionine-rich region. (Modified from Kitabayashi et al., 2001).

ID: 7994) codifies for a Myst (MOZ, Ybf2 (Sas3), Sas2, Tip60)-type lysine acetyltransferase (KAT) also named KAT6A (lysine acetyltransferase 6A).
The gene underlies chromosomal translocation with different partners, generating fusion genes, such as MOZ-TIF2, MOZ-CBP and MOZ-EP300 in acute myeloid leukemia (AML). All MOZ fusion partner genes are involved in histone modification and transcriptional regulation (Katsumoto et al., 2008).
To date, only three cases of t(8;22)(p11;q13) involving MOZ and EP300 have been reported and investigated at DNA and RNA levels in two of them (Lai et al., 1992; Soenen et al., 1996; Chaffanet et al., 2000; Kitabayashi et al., 2001; Tasaka et al., 2002).
In Chaffanet et al., and in Kitabayashi et al., MOZ-EP300 fusion genes result from the hybrid junction between exon 16 and exon 15 of MOZ with exons 2 and 3 of EP300, respectively.
In both cases, the MOZ breakpoints are located in or around its acidic domain resulting in the retention of its N-terminal region and the replacement of the C-terminal end with the p300 fusion partner. The N-terminal region of MOZ contains a H15 (histone H1/H5) domain related to nuclear localization, a PHD (plant homeobox-like domain) zinc finger involved in binding to methylated histones, a basic domain and a Myst-type KAT domain. The KAT domain contains C_2HC zinc finger and helix-turn-helix motifs that bind to nucleosomes and DNA. Because of the early truncation of EP300 , almost all its functional domains are conserved, including the KAT, the bromodomain and the CH1-3, resulting in a fusion protein with both MOZ and p300 KAT domains.
In the reciprocal fusion genes, EP300-MOZ, exon 1 or 2 of EP300 are juxtaposed to exons 17 and 16 of MOZ, respectively. In both cases, the N-terminal region including only the nuclear receptor interaction domain (NID) of p300 and the C-terminal of MOZ encompassing its serine, proline-glutammine and methionine-rich regions are conserved (Chaffanet et al., 2000; Kitabayashi et al., 2001).

Oncogenesis

The conservation of MOZ and p300 KAT catalytic domains in the hybrid proteins MOZ-p300 may result in abnormal acetylation of histonic and non histonic proteins with a consequent alteration in gene expression regulation, leading to leukaemogenesis;

furthermore, MOZ-p300 fusion proteins retain the domains required for the interaction with AML1 thus affecting AML1-dependent transcription whose deregulation may be implicated in leukaemogenesis too (Kitabayashi et al., 2001).

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