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Gene Section
Review

AUTS2 (autism susceptibility candidate 2)

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Abstract

Review on AUTS2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: FBRSL2

HGNC (Hugo): AUTS2

Location: 7q11.22

Local order: AUTS2 is close to (about 2.1 Mb) – and proximal to- POM121 (another gene involved in PAX5 translocations in leukemia), and to the Williams-Beuren syndrome critical region.

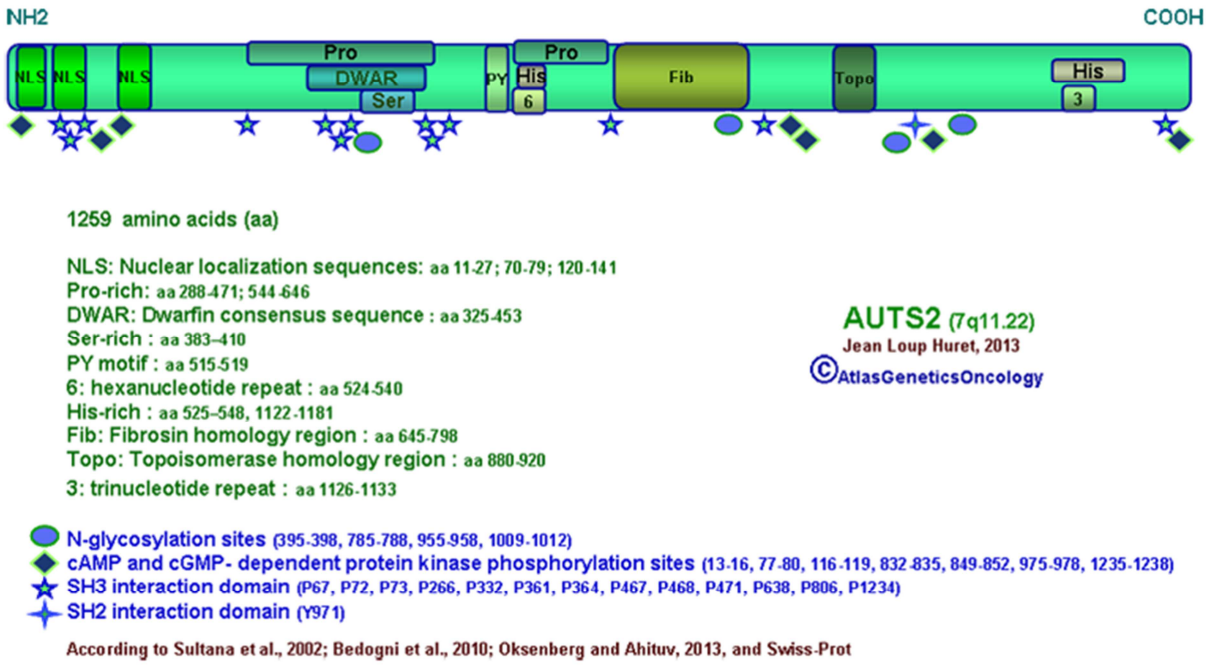
DNA/RNA

Description

The gene spans 1.19 Mb. 19 coding exons.

Transcription

There are 16 transcripts (splice variants). Six transcripts contains an open reading frame.



AUTS2 protein and domains.

Protein

Description

1259 amino acids (aa); from N-term to C-term, AUTS2 contains: nuclear localization sequences (aa: 11-27; 70-79; 120-141); Pro-rich regions (aa: 288-471; 544-646); a Dwarfin consensus sequence (aa: 325-453); a Ser-rich region (aa: 383-410); a PY motif (aa: 515-519); a hexanucleotide repeat (aa: 524-540; (cagcac/cagcac/cagcac/cagcac/acc/cac/cagcac/cagcac/cagcac) at nucleotide 1901-1949 (exon 9)); His-rich regions (aa: 525-548, 1122-1181); a Fibrosin homology region (aa: 645-798); a topoisomerase homology region (aa: 880-920); a trinucleotide repeat (aa: 1126-1133 (cac)8, at nucleotide 3701-3732 (exon 19)), and also N-glycosylation sites (aa 395-398, 785-788, 955-958, 1009-1012), cAMP and cGMP- dependent protein kinase phosphorylation sites (aa: 13-16, 77-80, 116-119, 832-835, 849-852, 975-978, 1235-1238), SH3 interaction domains (P67, P72, P73, P266, P332, P361, P364, P467, P468, P471, P638, P806, P1234), and a SH2 interaction domain (Y971) (Sultana et al., 2002; Bedogni et al., 2010b; Oksenberg and Ahituv, 2013).

Expression

AUTS2 is primarily expressed in the central nervous system, and also in skeletal muscle and kidney, and with lower expression in other tissues (placenta, lung, and leukocytes) (Sultana et al., 2002). AUTS2 is highly expressed in the embryo, and in more restricted areas in the adult (Oksenberg and Ahituv, 2013).

Auts2 in the mouse embryo is expressed in the cortical preplate, in frontal cortex, hippocampus and cerebellum, including Purkinje cells and deep nuclei, in developing dorsal thalamus, olfactory bulb, inferior colliculus and substantia nigra (Bedogni et al., 2010a).

Localisation

AUTS2 is a nuclear protein.

Function

TBR1, a postmitotic projection-neuron specific transcription factor, binds the AUTS2 promoter and activates AUTS2 in developing neocortex in vivo (Bedogni et al., 2010b; Srinivasan et al., 2012). Suppression of auts2 in zebrafish embryos caused microcephaly, and a reduction in developing midbrain neurons and also in sensory and motor neurons (Beunders et al., 2013; Oksenberg et al., 2013). ZMAT3 (a target gene of TP53) downregulation produced significant reductions in AUTS2 mRNA levels (Sedaghat et al., 2012).

Enhancers that were mutated in patients with dyslexia or with autism spectrum disorder were described; AUTS2 has been found as a rapidly evolving gene in homo sapiens sapiens, compared to Neanderthals, and non-human primates. It is suggested that AUTS2 has an important role in the evolution of human cognitive traits (Oksenberg et al., 2013).

Implicated in

t(7;9)(q11;p13) PAX5/AUTS2

Note

PAX5 is involved in B-cell differentiation. Entry of common lymphoid progenitors into the B cell lineage depends on E2A, EBF1, and PAX5. Genes repressed by PAX5 expression in early B cells are restored in their function in mature B cells and plasma cells, and PAX5 repressed (Medvedovic et al., 2011).

Disease

Pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL).

Prognosis

Three cases to date, two boys and one girl, aged 0.6, 2.8, and 3.1 years (Kawamata 2008; Coyaud et al., 2010; Denk et al., 2012). Two patients presented with a high WBC, and also had a central nervous system involvement at a time during course of the disease. Patients were assigned to different risk arms of the respective clinical trials, as noted by Denk et al., 2012. The three patients achieved complete remission (CR), but two (those with high risk features) relapsed and died at 1.7 and 3.4 years after diagnosis, indicating a rather poor outcome (Denk et al., 2012). Only one patient is still in CR and well 2.2 years after diagnosis.

Cytogenetics

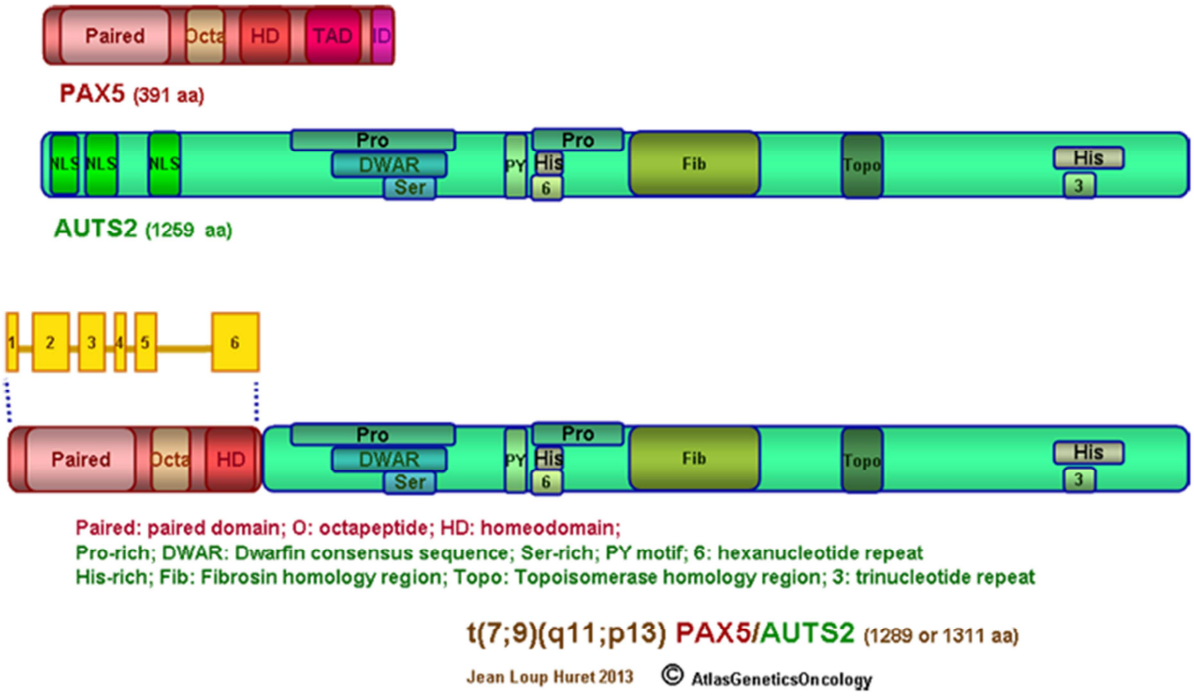
The t(7;9)(q11;p13) was the sole abnormality in one case. Unbalanced translocation in two cases, due to the loss of the der(7)t(7;9).

Hybrid/Mutated gene

5' PAX5-3' AUTS2. Fusion of PAX5 exon 6 to AUTS2 exon 4 or 6.

Abnormal protein

1289 or 1311 amino acids depending on whether exon 6 or 4 of AUTS2 is fused to PAX5. The predicted fusion protein contains the paired domain, the octapeptide, and the homeodomain of PAX5 and the proline rich, the Dwarfin consensus sequence, the serine rich, the PY motif, the hexanucleotide repeat, the histidine rich, the fibrosin homology region, the topoisomerase homology region, and the trinucleotide repeat of AUTS2.



Fusion protein PAX5/AUTS2.

Other cancers

Disease

Loss of heterozygocity was found in an adenocarcinoma of the lung, but more data is needed (Weir et al., 2007).

Copy number variation was found in a single case of mixed germ cell tumor containing yolk sac tumor and teratoma (Stadler et al., 2012).

Syndromic phenotype, mental retardation, neurodevelopmental and psychiatric disorders, including autism spectrum disorder

A review in Oksenberg and Ahituv, 2013 shows a map of the gene with the structural variants and abnormalities in relation to the various phenotypes described.

Disease

Syndromic phenotype: A study on 24 patients with deletions of part of AUTS2 allowed the identification of a variable syndromic phenotype including intellectual disability, autism, short stature, microcephaly, cerebral palsy, and facial dysmorphisms.

The authors delineated an "AUTS2 syndrome severity score" of the phenotypic diversity, that correlated with genotypic data: individuals with deletions in the 5' part of the gene showed a milder phenotype than those with a deletion in the 3' part of the gene (Beunders et al., 2013).

Mental retardation: A patient with developmental delay had an intragenic deletion within AUTS2 (Jolley et al., 2013).

Three unrelated mentally disabled patients were found to carry a balanced translocation that truncates AUTS2. Patients were borderline or severely mentally retarded and carried different deletions in AUTS2 (Kalscheuer et al., 2007). AUTS2 has been found disrupted in balanced chromosomal abnormality in patients with abnormal neurodevelopment (Huang et al., 2010; Talkowski et al., 2012).

Autism spectrum disorder (ASD): Small copy-number variations (CNVs) that disrupt AUTS2 (duplications or deletions of exons) were found in two patients with developmental delay, and two with autism spectrum disorder (Nagamani et al., 2013). AUTS2 has been found disrupted in a monozygotic twin pair concordant for autism (Sultana et al., 2002). Duplication in the AUTS2 gene was identified in a family with ASD (Ben-David et al., 2011).

Pathological behaviour: A variant in AUTS2 was associated with excessive alcohol consumption (Edenberg and Foroud, 2013; Kapoor et al., 2013). AUTS2 variants (rs6943 allele A) are correlated with heroin dependence, and reduced AUTS2 gene expression might confer increased susceptibility (Chen et al., 2013). rs6943555 A allele was also found associated with alcohol consumption (Schumann et al., 2011), and with suicide committed after drinking (Chojnicka et al., 2013).

Amino acids sequence variant in AUTS2 were found in a large family with high risk for suicide, but also with a significant co-morbidity for affective disorders, alcohol disorders, psychotic disorders, and drug abuse disorders (Coon et al., 2013).

Epilepsy: AUTS2 deletions were identified in one patient with juvenile myoclonic epilepsy and in another patient with an unclassified 'non-lesional epilepsy with features of atypical benign partial epilepsy' (Mefford et al., 2010).

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