OTX2 (orthodenticle homeobox 2)

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Identity

Other names: MCOPS5, MGC45000
HGNC (Hugo): OTX2
Location: 14q22.3

Local order:
Chr14:57267427-57277184 (isoform a),
Chr14:57267427-57277097 (isoform b).
From plus strand: C14orf101, OTX2, EXOC5, MUDENG.

DNA/RNA

Description
Total gene sequence: 9757 bp.

Transcription
From minus strand. Isoform a: 5 exons, 4 introns; isoform b: 3 exons, 2 introns.
Isoform a: Full-length unspliced transcript: 9757 bp; spliced transcript: 2209 bp;
Isoform b: Full-length unspliced transcript: 9670 bp; spliced transcript: 2082 bp.

Pseudogene
OTX2P1 located at 9q21.

Protein

Note
Isoforms a and b share the same coding exons, therefore both isoforms encode full-length (289 amino acid) Otx2 protein.

Description
289 amino acids, see diagram for domain organization.

Expression
Rostral neural tube (mid-late gestation; Larsen et al., 2010), hippocampus, cerebellar rhombic lip, choroid plexus (Larsen et al., 2010), retinal pigment epithelium (Glubrecht et al., 2009; Larsen et al., 2009). Characterized in rodents: epiblast (Fossat et al., 2006), anterior neural ectoderm and anterior visceral endoderm (Fossat et al., 2006), external granular layer of the postnatal cerebellum (Frantz et al., 1994), posterior lobes of the adult cerebellum (Fossat et al., 2006).

Localisation
Predominately nuclear but in some cell types can be retained in the cytoplasm (Baas et al., 2000) as well as transferred from cell to cell (Sugiyama et al., 2008).

Otx2 protein domains. Domains were defined based on sequence conservation and, when possible, functional analysis as described in Chau et al., 2000 and Chatelain et al., 2006. Conserved OTX family domain identified in the CDD database (Marchler-Bauer et al., 2009). Domain abbreviations and boundaries are as follows: HD: Paired-class homeobox domain, spans amino acids (aa) 37-97; NRS: nuclear retention signal, spans aa 117-146; grey box: WSP domain, spans aa 150-159; OTX: OTX family domain, spans aa 178-243; TA: transactivation domain, comprised of two separate transactivation motifs spanning aa 255-267 and aa 273-285; b: basic regions (aa 36-42, aa 89-94, and aa 107-114); Q: polyglutamine repeat (aa 95-101).
**Function**

Homeobox transcription factor, binds the DNA sequence TAATCC (Chatelain et al., 2006). OTX2 plays a critical role in anteroposterior patterning of the embryo (Matsuo et al., 1995), anterior neuroectoderm formation (Acampora et al., 1995), neuronal differentiation in various CNS compartments (Vernay et al., 2005; Omodei et al., 2008), and experience-induced plasticity (Sugiyama et al., 2009).

**Homology**

Shares sequence homology and general domain organization with OTX family members Otx1 and Crx.

**Mutations**

**Germinal**

Dominant-inherited OTX2 mutations exhibiting variable penetrance have been associated with developmental defects of the eye (Ragge et al., 2005; Wyatt et al., 2008; see the "Implicated in" section below for further discussion) and pituitary (Diaczok et al., 2008) as well as recurrent seizure disorders (Ragge et al., 2005). None associated with hereditary tumor predisposition syndromes.

**Somatic**

None detected in medulloblastoma.

**Implicated in**

**Pediatric CNS cancer (medulloblastoma)**

**Prognosis**

5-year survival rates average 50-60%; predictors of poor outcome include young age (younger than 3 years old) and presence of metastases. OTX2 copy number gain has been associated with shorter survival (Adamson et al., 2010).

**Cytogenetics**

Various broad and focal copy number changes have been identified in medulloblastoma (reviewed in: Northcott et al., 2010), whereas OTX2 is the most common target of focal copy number gain in the medulloblastoma genome (Adamson et al., 2010).

**Oncogenesis**

Otx2 is overexpressed in the majority (~74%) of medulloblastomas (Adamson et al., 2010). A subset of these tumors (~21%) harbor copy number gains of the OTX2 genomic locus; the mechanism of Otx2 overexpression in the remaining tumors remains unidentified. Otx2 is distinctly overexpressed in Shh-independent medulloblastomas (i.e. tumor subtypes not expressing gene signatures of Shh pathway activation; Adamson et al., 2010). Otx2 has been implicated in medulloblastoma tumor progression and is required for tumor maintenance. One mechanism of Otx2 oncogenic activity is transcriptional activation of MYC (Adamson et al., 2010).

**Retinoblastoma**

**Cytogenetics**

Secondary events cooperating with loss of Rb gene function have remained elusive. However, genomewide copy number analysis has revealed recurrent regions of gain or loss at the megabase resolution, and chromosome 14 aberrations have indeed been described (Zielinski et al., 2005).

**Oncogenesis**

Considering the restricted expression pattern of OTX2 mRNA in adult tissues (Boon et al., 2002) and the well-established oncogenic function of Otx2 in medulloblastomas (Adamson et al., 2010), expression of Otx2 in retinoblastoma may indicate a role for this gene in retinoblastoma pathogenesis (Glubrecht et al., 2009). Interestingly, Otx2 is expressed in the most undifferentiated compartments of retinoblastomas (Glubrecht et al., 2009). Although, Otx2 is expressed broadly among retinoblastoma samples, its potential role as an oncogene in this tumor type has not been experimentally assessed; the possibility that Otx2 is solely a cell lineage marker maintained in transformed retinal progenitor cells has yet to be excluded based on functional studies.

**Coloboma**

**Note**

Developmental defects of the eye.

**Disease**

Coloboma, defined as a fissure in the ocular tissue (Onwochei et al., 2000). These result from incomplete closure of the fetal fissure (an invagination of the optic stalk and optic vesicle), whose function is to provide a scaffold for the formation of the optic cup and for the vessels responsible for retinal vascularization. Colobomata are predominately developmental defects that present at birth. Various genes, including OTX2, have been implicated in hereditary syndromes predisposing to coloboma (Onwochei et al., 2000; Wyatt et al., 2008), and sporadic cases have implicated teratogens, though evidence implicating particular agents is generally anecdotal (Onwochei et al., 2000).

**Cytogenetics**

Germline OTX2 mutations have been identified in patients with bilateral eye defects including colobomata and anophthalmia (Wyatt et al., 2008).

**Anophthalmia and microphthalmia (absent or small eyes, respectively)**

**Note**

Developmental defects of the eye.

**Disease**

Microphthalmia is clinically defined as an eye with an axial diameter measuring at least two standard
deviations below the mean for the corresponding age group (Onwochei et al., 2000), whereas anophthalmia/microphthalmia is diagnosed when no clinically apparent eye structure is present. Those affected generally harbor bilateral malformations. Like coloboma, some forms of anophthalmia/microphthalmia are clearly inheritable, while for other cases environmental factors have been implicated but not definitively so (Verma et al., 2007). Anophthalmia/microphthalmia can present as secondary malformations following coloboma.

**Cytogenetics**

Various genes have been implicated, including SOX2 (autosomal dominant inheritance), OTX2 (autosomal dominant), CHX10 (autosomal recessive), and RAX (autosomal recessive; Verma et al., 2007; Wyatt et al., 2008).

**References**


This article should be referenced as such: