Gene Section

Review

PAX6 (paired box 6)

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Published in Atlas Database: August 2009


DOI: 10.4267/2042/44797

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Identity

Other names: AN; AN2; DI1S812E; MGC17209; MGDA; Oculorhombin; WAGR

HGNC (Hugo): PAX6

Location: 11p13

DNA/RNA

Description

The PAX6 coding region extends over a genomic interval of 16-17 kb and comprise 10 (isoform a) and 11 exons (isoform b).

Transcription

Three transcripts have been identified, originating from alternative promoter usage (variant 3) or alternative splicing (variant 2, additional in-frame coding 42 bp exon downstream of exon 5 of variant 1); transcription is from centromere to telomere.

Protein

Description

PAX6 belongs to the paired box family of transcription factors, contains two DNA binding domains, a paired box (PD) and a paired-type homeodomain (HD), and a carboxyl-terminal transactivation domain rich of proline, serine, and threonine (PST).

Expression

PAX6, predominately in form of PAX6a, is expressed in the developing sensory organs (including eye, nasal and olfactory tissues), central nervous system (including forebrain, hindbrain, and spinal cord), and endocrine system (including anterior pituitary gland and pancreas) in human and rodent (Walther and Gruss., 1991; Stoykova and Gruss., 1994; Davis and Reed., 1996; Terzic and Saraga-Babic., 1999; Pinson et al., 2005). PAX6 expression is sustained into adulthood in certain areas of the brain, including, hippocampal dentate gyrus (Maekawa et al., 2005; Nacher et al., 2005), ependymal layer and the subventricular zone of the lateral ventricle (Hack et al., 2005; Kohwi et al., 2005), radial glia-like cells (Gubert et al., 2009), and in mature endocrine cells in pancreas (St-Onge et al., 1997). PAX6 transcription is regulated by two promoters, P0 and P1, which are remarkably conserved in evolution in both of their nucleotide sequence arrangement and functional control of special and temporal expression of PAX6 in development (Xu and Saunders, 1997; Okladnova et al., 1998a; Williams et al., 1998; Xu and
There are two isoforms of PAX6, PAX6a and PAX6b with additional 14 extra amino acids in the paired box DNA binding domain. PAX6a, 423 amino acids, ~47 kDa; PAX6b, 436 amino acids, ~49 kDa.

Saunders, 1998; Kammandel et al., 1999; Plaza et al., 1999a; Xu et al., 1999; Tyas et al., 2006), involving multiple transcription factors, such as Pou factor Bm-3B, TFCP2, SP1, the basic helix-loop-helix transcription factor NeuroD/BETa2, CCCTC binding factor CTCF, PPARgamma (Plaza et al., 1999b; Zheng et al., 2001; Schinner et al., 2002; Marsich et al., 2003; Li et al., 2006; Wu et al., 2006), PAX6 expression is also regulated by a long range downstream enhancer (Kleinjan et al., 2006) and is under autoregulation (Grocott et al., 2007) and post modification by HIPK2 and protein phosphatase 1 (Kim et al., 2006; Yan et al., 2007). A promoter-associated polymorphic repeat was found to modulate PAX6 expression in human brain (Okladnova et al., 1998b).

**Localisation**

Nuclear.

**Function**

Loss of Pax6 function in rodent mutant and knock-out model revealed that Pax6 is a key regulator of a multitude of developmental processes of sensory system, including eye, nasal and olfactory (Hill et al., 1991; Grindley et al., 1995; Quinn et al., 1996; van Raamsdonk and Tilghman, 2000; Singh et al., 2002; van Heyningen and Williamson, 2002; Collinson et al., 2003; Davis et al., 2003; Brill et al., 2008), CNS (Matsuo et al., 1993; Schmahl et al., 1993; Stoykova et al., 1996; Grindley et al., 1997; Osumi et al., 1997; Mastick et al., 1997; Warren and Price, 1997; Gotz et al., 1998; Sun et al., 1998; Engelkamp et al., 1999; Kawano et al., 1999; Pratt et al., 2000; Stoykova et al., 2000; Estivill-Torrus et al., 2002; Pratt et al., 2002; Talamillo et al., 2003; Quinn et al., 2007), pituitary (Bentley et al., 1999; Kioussi et al., 1999) and pancreas (Sander et al., 1997; St-Onge et al., 1997; Dohrmann et al., 2000; Zhang et al., 2003). Pax6 function in development of fundamental sensory processes and central nervous system, particularly of the photoreceptive organ, are remarkably conserved in evolution (Halder et al., 1995; Gehring et al., 2005). PAX6 function in development were found to be under control of Shh, notch and EGFR signaling (Ericson et al., 1997; Kumar and Moses, 2001; Onuma et al., 2002; Li and Lu, 2005), essential for neural stem cell proliferation, multipotency, and neurogenesis in many regions of the central nervous system (Warren et al., 1999; Bishop et al., 2000; Toresson et al., 2000; Marquardt et al., 2001; Yamasaki et al., 2001; Yun et al., 2001; Estivill-Torrus et al., 2002; Heins et al., 2002; Simpson and Price, 2002; Tyas et al., 2003; Collinson et al., 2004; Haubst et al., 2004; Nomura and Osumi, 2004; Schuurmans et al., 2004; Maekawa et al., 2005; Bel-Vialar et al., 2007; Duparc et al., 2007; Quinn et al., 2007; Canto-Soler et al., 2008; Oron-Karni et al., 2008; Osumi et al., 2008), and appears to control the balance between neural stem cell self-renewal and neurogenesis under a dose-dependent manner (Sanson et al., 2009).

PAX6 binds as a monomer to relatively long (15-22 bp) DNA binding sites, and the 14 aa insertion in the paired domain allows different binding affinity to DNA sequences between PAX6a and PAX6b (Epstein et al., 1994a; Epstein et al., 1994b). Through binding to different DNA sequences via usage of various DNA binding motifs alone or in combination, PAX6 controls the expression of various downstream target genes involved in complex gene regulatory networks for cell proliferation, adhesion, migration, and neurogenesis (Schmahl et al., 1993; Caric et al., 1997; Sander et al., 1997; Sax et al., 1997; Tang et al., 1997; Duncan et al., 1998; Beimesche et al., 1999; Meech et al., 1999; Singh et al., 2000; Sivak et al., 2000; Zhou et al., 2000; Chauhan et al., 2002; Mishra et al., 2002; Skala-Rubinson et al., 2002; Zhou et al., 2002; Andrews and Mastick, 2003; Davis et al., 2003; Horie et al., 2003; Tyas et al., 2003; Cvekl et al., 2004; Grinchuk et al., 2005; Mayes et al., 2006; Holm et al., 2007; Tuoc and Stoykova, 2008). Not only reduced, but also increases level of PAX6 gene dosage also cause defects in developmental processes that are sensitive to PAX6 dosage, including eye organogenesis and corticogenesis (Schedl et al., 1996; Berger et al., 2007; Manuel et al., 2007).

**Homology**

PAX6 shares homology through the conserved paired box domain with the other members of the nine PAX gene family.

**Mutations**

**Germinal**

Heterozygous intragenic mutation of PAX6, that causes loss of function of one copy of the PAX6 gene, is the cause of aniridia syndrome (Ton et al., 1991; Glaser et al., 1992; Prosser and van Heyningen, 1998; Robinson et al., 2008; Hingorani et al., 2009; MRC Human Genetics Unit) and cerebral malformation, olfactory dysfunction, absence of the pineal gland and unilateral polymicrogyria (Sisodiya et al., 2001; Free et al., 2003; Mitchell et al., 2003; Bamiou et al., 2007a; Bamiou et al., 2007b).
PAX6 3’ deletion also results in aniridia, autism and mental retardation (Davis et al., 2008).

### Implicated in

**Brain cancer**

**Note**
The expression level of PAX6 in human glioma cell lines was shown to be negatively associated with the degree of tumorigenicity. PAX6 expression level is lower in glioblastoma compared to the adjacent normal tissue and to the anaplastic astrocytoma previously formed in the same patient (Zhou et al., 2003). Ectopic expression of PAX6 in glioma cell lines suppressed cell anchorage independent growth, ability to survive under oxidative stress induced by cell detachment, ability to invade partially by suppression of MMP2 gene expression, ability to induce angiogenesis by initiating a new signaling pathway independent of PI3K/Akt-HIF1A signaling to suppress VEGFA, and overall tumor growth after intracranial implantation in immunocompromised mouse brain (Zhou et al., 2005; Mayes et al., 2006; Chang et al., 2007; Zhou et al., 2009). Mutation analysis for PAX6 in gliomas failed to identify PAX6 mutation in its coding and regulating regions, suggesting involvement of epigenetic mechanisms in the silencing of PAX6 in glioma (Pinto et al., 2007). PAX6 expression is activated in glioma cell line with re-introduction of a normal ch.10, suggesting that PAX6 is regulated by a gene(s) on ch.10 (Zhou et al., 2005).

**Prognosis**
PAX6 is a factor related to a longer survival prognosis for astrocytic gliomas (Zhou et al., 2003).

**Pancreatic cancer**

**Note**
PAX6 is expressed in pancreatic adenocarcinoma and is downregulated during induction of terminal differentiation (Lang et al., 2008). In pancreatic carcinoma cell lines, PAX6 bind directly to an enhancer element in the MET promoter and activate the expression of the MET gene (Mascarenhas et al., 2009).

**Bladder cancer**

**Note**
Methylation of PAX6-promoters is increased in early bladder cancer and in normal mucosa adjacent to pTa tumours (Hellwinkel et al., 2008).

**Familial adenomatous polyposis (FAP) related carcinoma**

**Note**
PAX6 gene is methylated in FAP-related carcinoma. Patients with familial adenomatous polyposis (FAP) have a high risk of developing duodenal carcinomas (Berkhout et al., 2007).

### WAGR syndrome

**Note**
WAGR syndrome can have aniridia due to deletion of chromosome 11 including PAX6 (Gronskov et al., 2001; Chao et al., 2003). However, PAX6 mutation is only found in aniridia patient, not WAGR syndrome associated anomalies (Robinson et al., 2008).

### References

- Walther C, Gruss P. Pax-6, a murine paired box gene, is expressed in the developing CNS. Development. 1991 Dec;113(4):1435-49
- Schmahal W, Knoedlseder M, Favor J, Davidson D. Defects of neuronal migration and the pathogenesis of cortical malformations are associated with Small eye (Sey) in the mouse, a point mutation at the Pax-6-locus. Acta Neuropathol. 1993;86(2):126-35
- Epstein JA, Glaser T, Cai J, Jepeal L, Walton DS, Maas RL. Two independent and interactive DNA-binding subdomains of the Pax6 paired domain are regulated by alternative splicing. Genes Dev. 1994 Sep 1;8(17):2022-34
- Grindley JC, Davidson DR, Hill RE. The role of Pax-6 in eye and nasal development. Development. 1995 May;121(5):1433-42


Sander M, Neubüser A, Kalaramas J, Ee HC, Martin GR, German MS. Genetic analysis reveals that PAX6 is required for normal transcription of pancreatic hormone genes and islet development. Genes Dev. 1997 Jul 1;11(13):1662-73


Xu ZP, Saunders GF. PAX6 intrinsic sequence targets expression to the spinal cord. Dev Genet. 1998;23(4):259-63


Xu PX, Zhang H, Heaney S, Yoon A, Michelson AM, Maas RL. Regulation of Pax6 expression is conserved between mice and flies. Development. 1999 Jan;126(2):383-95


Chao LY, Mishra R, Strong LC, Saunders GF. Missense mutations in the DNA-binding region and termination codon of PAX6. Hum Mutat. 2003 Feb;21(2):138-45


Atlas Genet Cytogenet Oncol Haematol. 2010; 14(7)
Collinson JM, Chanas SA, Hill RE, West JD. Corneal development, limbal stem cell function, and corneal epithelial cell migration in the Pax6(+/-) mouse. Invest Ophthalmol Vis Sci. 2004 Apr;45(4):1101-8
Bel-Vialar S, Medevielle F, Pituello F. The on/off of Pax6 controls the tempo of neuronal differentiation in the developing spinal cord. Dev Biol. 2007 May 15;305(2):659-73
Holt PC, Mader MT, Haubst N, Wizenmann A, Sigvardsson M, Götz M. Loss- and gain-of-function analyses reveal targets...


Quinn JC, Molinek M, Martynoga BS, Zaki PA, Faedo A, Bulfone A, Hevner RF, West JD, Price DJ. Pax6 controls cerebral cortical cell number by regulating exit from the cell cycle and specifies cortical cell identity by a cell autonomous mechanism. Dev Biol. 2007 Feb 1;302(1):50-65


Hellwinkel OJ, Kedia M, Isbarn H, Budäus L, Friedrich MG. Methylation of the TPEF- and PAX6-promoters is increased in early bladder cancer and in normal mucosa adjacent to pTa tumours. BJU Int. 2008 Mar;101(6):753-7


Tuoc TC, Stoykova A. Er51 is a downstream target of Pax6 in cortical progenitors. BMC Dev Biol. 2008 Feb 28;8:23


This article should be referenced as such: Zhou YH. PAX6 (paired box 6). Atlas Genet Cytogenet Oncol Haematol. 2010; 14(7):645-651.