Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Mini Review

PEG3 (paternally expressed 3)

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Identity

Other names: DKFZp781A095, KIAA0287, PW1, ZNF904, ZSCAN24

HGNC (Hugo): PEG3

Location: 19q13.43

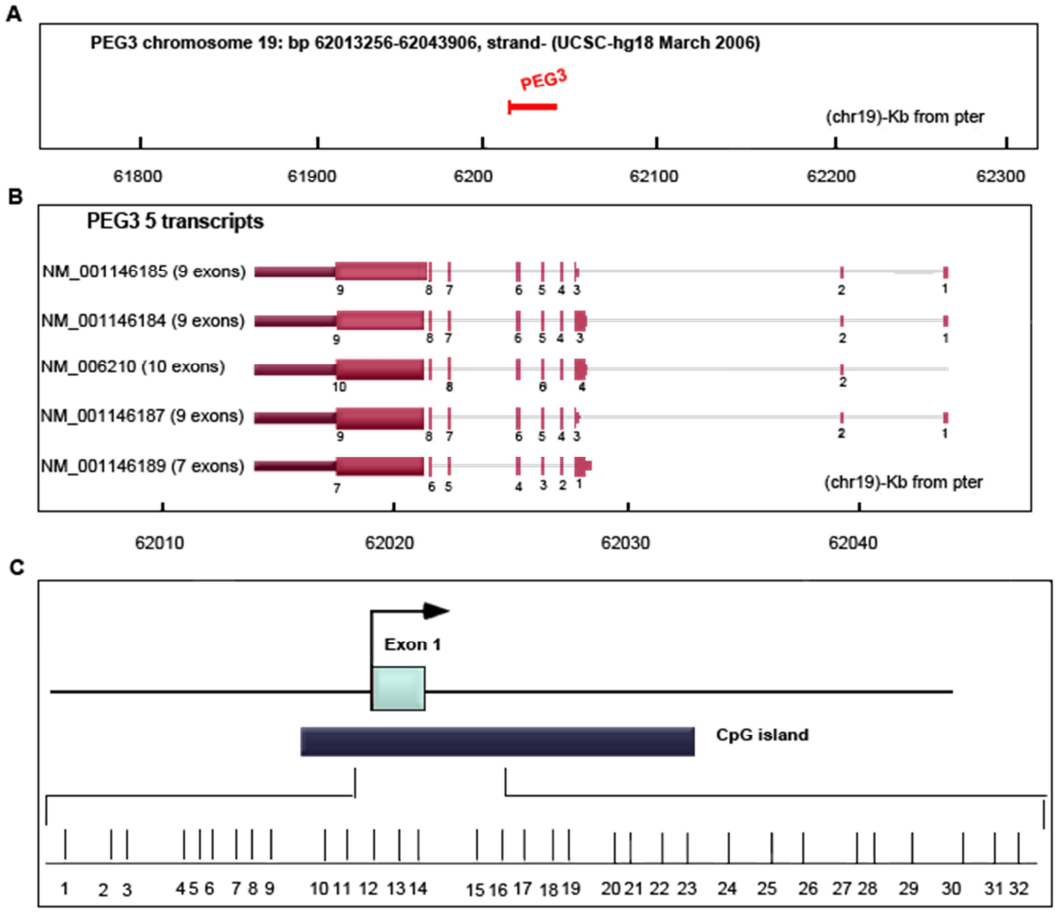

Figure A. PEG3 DNA located on chromosome 19, starts at 62013257 and ends at 62043906 bp. **Figure B.** The PEG3 gene contains 7-10 exons with 5 different transcripts. **Figure C.** PEG3 promoter and first exon. The transcription start site and direction are indicated with an arrow. The horizontal bars are 32 CpG sites. The dark blue box is a CpG island surrounded the first exon (Figure modified from Feng et al., 2008).

DNA/RNA

Description

Human PEG3 was originally identified as an ortholog of murine Peg3 that is the first imprinted gene detected in mouse chromosome 7. Human PEG3 is located ~2 Mb proximal of the 19q telomere, which is rich in Krüppel-type ZNF genes (Kim et al., 1997). Bisulfite sequencing across PEG3 revealed that all CpG dinucleotides examined were differentially methylated in human fetal brain, kidney, liver, and pancreas. PEG3 is monoallelically expressed during fetal development, it is a maternal-imprinted gene (Murphy et al., 2001).

Transcription

The PEG3 gene contains 7-10 exons with 5 different transcripts.

Pseudogene

There are no known pseudogenes, but an antisense transcript gene (APEG3), which is transcribed in the opposite direction of PEG3, has been identified from human. It is confirmed the presence of APEG3 in total RNAs from brain thalamus and testis. The functional significance of APEG3 is not known. The paternal allele-specific expression of anti-sense Peg3 (imprinting) was detected in mouse brain, but not in human yet (Choo et al., 2002).

Protein

Description

PEG3 is maternal-imprinted and paternally expressed. The imprinted status of PEG3 throughout development and adult life. PEG3 may be a susceptibility locus for cancer and for neurobehavioral deficits (Murphy et al., 2001).

Expression

PEG3 is expressed at higher levels in ovary and placenta (Kim et al., 1997; Hiby et al., 2001). It was also strongly expressed in the adult brain (Kohda et al., 2001).

Localisation

High levels of PEG3 have localized to the layer of villous cytotrophoblast cells in the human placenta, PEG3 expression is also detected in the ovary stroma (Hiby et al., 2001).

Function

PEG3 is an imprinted gene expressed exclusively from the paternal allele. The precise function of PEG3 is not clear, but recent evidence suggests that it plays an important role in the p53/c-myc-mediated apoptosis pathway.

PEG3 is a maternally imprinted tumor suppressor gene that is downregulated in gliomas, ovarian cancers, breast cancers and other gynecologic cancers (Kohda et al., 2001; Dowdy et al., 2005; Feng et al., 2008).

There are several studies revealed murine Peg3 acts as an intermediary between p53 and Bax in a cell death pathway activated by DNA damage in primary mouse cortical neurons, inhibiting Peg3 activity blocks p53-induced apoptosis (Johnson et al., 2002). Pw1/Peg3 interacts with a p53-inducible gene product Siah1a. Coexpression of Pw1/Peg3 with Siah1a induces apoptosis independently of p53. Inhibiting Pw1/Peg3 activity blocks p53-induced apoptosis (Relaix et al., 2000). Since human PEG3 is highly conserved with murine Peg3, PEG3 may have same function, Jiang et al. (2010) demonstrated that enforced overexpression of PEG3 mRNA during zebrafish embryogenesis decreased beta-catenin protein expression and inhibited Wnt-dependent tail development. Peg3/Pw1 also inhibited Wnt signaling in human cells by binding to beta-catenin and promoting its degradation via a p53/Siah1-dependent, GSK3beta-independent proteasomal pathway. Hypermethylation of the PEG3 promoter in primary human gliomas led to a loss of imprinting and decreased PEG3 mRNA expression that correlated with increasing tumor grade (Jiang et al., 2010).

The transcription factor YY1 can bind to the first intron of human PEG3, and specifically to the paternal allele of the gene. YY1-binding sites are methylated only on the maternal chromosome. YY1-binding region may function as a methylation-sensitive insulator that could influence the imprinted expression of PEG3 (Kim et al., 2003).

Homology

Human PEG3 is known to have orthologs in mice and cow. Human PEG3 gene sequences revealed a high level of conservation with Murine Peg3 (83% similarity), but one of the two proline-rich repeats is absent from the human PEG3 (Kim et al., 1997).

Mutations

Note

Mutations have not been detected.

Implicated in

Glioma, glioblastoma

Note

A significant decrease in PEG3 expression was more commonly observed in glioma cell lines as compared with that in primary cultures of astrocytes. Transfection of PEG3 cDNA in a glioma cell line resulted in a loss of tumorigenicity in nude mice (Kohda et al., 2001). The epigenetic silencing of PEG3 expression in glioma cell lines depends on aberrant DNA methylation of an exonic CpG island. Treatment of glioma cell lines with the DNA demethylating agent 5-aza-2'-deoxycytidine

reversed the silencing of PEG3 biallelically (Maegawa et al., 2001). Re-expression of PEG3 in glioma cells suppresses their proliferation. Hypermethylation of the PEG3 promoter in primary human gliomas led to a loss of imprinting and decreased PEG3 mRNA expression that correlated with tumor grade (Jiang et al., 2010). The lower gene expression was confirmed statistically in glioblastoma (Otsuka et al., 2009).

Endometrial cancer, cervical cancer, choriocarcinomas

Note

PEG3 is silenced in all endometrial and cervical cancer cell lines studied. In contrast, loss of maternal imprinting and relatively high PEG3 expression levels were detected in all four choriocarcinomas cell lines studied (Dowdy et al., 2005).

Breast cancer, ovarian cancer

Note

Five of the eight ovarian cancer cell lines were found to be PEG3 negative, the remaining three express low levels of PEG3 mRNA (Dowdy et al., 2005). PEG3 was down-regulated in 75% of ovarian cancers. PEG3 was hypermethylated in 11 of 42 ovarian cancers (26%), and PEG3 expression was down-regulated in 10 of those 11 cancers. LOH was detected in 5 of 25 informative cases for PEG3 (20%). Re-expression of PEG3 markedly inhibited ovarian cancer growth. PEG3 expression could be restored by treatment with 5-aza-2'-deoxycytidine and trichostatin A (Feng et al., 2008).

Hydatidiform moles

Note

PEG3 is not mutated in women with familial recurrent hydatidiform moles, there is allele-specific methylation of the CpG island and expression from the paternal allele in two independent informative pedigrees (Van den Veyver et al., 2001).

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