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Gene Section
Review

CHD6 (chromodomain helicase DNA binding protein 6)

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Abstract

CHD6 is a chromatin remodeling protein characterized to play a role in transcriptional repression of genes and viruses.
It occurs in a nuclear location as a component of a larger complex which associates with RNA Pol II. Mutations in CHD6 are associated with motor coordination defects, and development of cancers following substitutions and translocations.

Keywords
Chromodomain Helicase DNA Binding protein 6 - CHD6

Identity

Other names: CHD-6, CHD5, RIGB

HGNC (Hugo): CHD6

Location: 20q12

DNA/RNA

Description

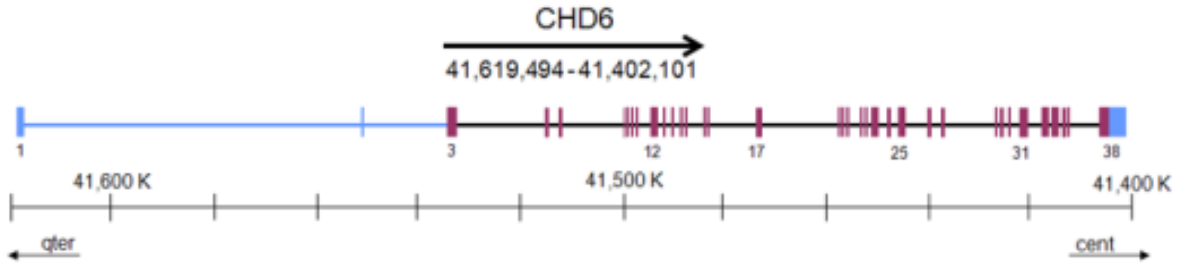
The CHD6 gene is encoded by 38 exons spanning 216394 bp. In addition to the full length transcript there are 5 predicted but not specifically reported splice variants of human CHD6. The CHD6 cDNA sequence spans 10826 bp, with a 5' untranslated region of 179 bp, an open reading frame of 8148 bp, and a 3' untranslated region of 2492 bp (NCBI: NM_032221.4) (Schuster and Stöger, 2002).

Transcription

CHD6 mRNA is found in all tissues examined, with the greatest levels found on reproductive tissues, digestive tissues, brain, bone marrow, muscle, lymph node, and spleen (EMBL-EBI: E-MTAB-1733).

Pseudogene

CHD6 in humans has no identified pseudogene.



CHD6 is a located on chromosome 20q12 in humans. The transcript contains 38 exons. Exons are indicated relative to size in red, 5' and 3' untranslated regions are indicated in blue. Exon number is indicated below graphic. Position of the gene on the chromosome and the location of the centromere and q terminus are indicated (adapted from the NCBI graphics viewer).

CHD6 protein functional domains. Chromodomains are highlighted in purple, the highly conserved SNF2-like ATPase region is indicated in light blue, and the DNA binding domain (green oval) contains BRK binding sights, indicated by the red diamonds.

Protein

Description

CHD6 is a member of the very homologous SNF2 superfamily of chromatin remodeling enzymes (SWI2/SNF2, ISWI, and CHD enzyme families). These enzymes all contain a highly conserved HELICc DEAD-like helicase/ATPase with seven conserved catalytic regions (Brown et al., 2007; Marfella and Imbalzano, 2007).

The nine CHD family members all contain n-terminal chromodomains and the HELICc ATPase/helicase region, and are split into three subfamilies, distinguished by the additional functional domains in each (Marfella and Imbalzano, 2007; Stanley et al., 2013). CHD6 contains a DNA binding region in its c-terminal region with conserved BRK domains (Schuster and Stöger, 2002).

CHD6 is localized to the nucleus and is found in large multi-protein chromatin remodeling complexes, including the Nrf2 transcription factor (Nioi et al., 2005).

Additionally, CHD6 is a DNA dependent ATPase. CHD6 protein is expected to function as a transcriptional repressor and it has been shown to be interact with RNA Pol II proteins (Lutz et al., 2006) and to be involved in the cellular repression of viral replication (Fertey et al., 2010; Alfonso et al., 2011; Alfonso et al., 2013). Size: 2715 amino acids; 305412 Da.

Expression

CHD6 protein is expressed in all tissues assayed including, monocytes, lymphocytes, kidney, liver, lung, colon, bone, brain, ovary, prostate, cervix, and breast (Data sourced from MOPED, PaxDb, and MaxQB, by GeneCards.org Version: 3.12.142 28 July 2014). Low dose radiation induces CHD6 expression in the lymphoblastoid cell line AHH-1, and both A549 and HeLa cell lines (Wang et al., 2006).

Localisation

Nuclear.

Function

Chromatin remodeling, transcription co-factor binding, suppression of gene expression.

Homology

CHD6 has homologues in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, and frog.

Mutations

Note

There have been no reports of naturally occurring homozygous inactivation of CHD6. Mutations have been identified in several types of cancer, however, no nonsense or frameshift mutations exclusive to CHD6 have been associated with cancer to date (Cosmic database). Haploinsufficiency in CHD6 has been reported in miscarriage and mental retardation (Yamada et al., 2010) and mutation of the ATPase region in mice resulted in an ataxia phenotype (Lathrop et al., 2010).

Implicated in

Acute myeloid leukemia (AML)

Note

The presence of a fusion gene between LMBRD1 and CHD6 was identified in a case report of AML. Development of AML from an acute MDS/MPD diagnosis occurred over two years. FISH mapping of increasingly specific bacterial artificial chromosomes was used to identify the breakpoints of this AML between exons 1 and 2 of CHD6 (Douet-Guilbert et al., 2014).

Hybrid/Mutated gene

Fusion gene between LMBRD1-CHD6 (6;20)(q13;q12).

Myeloproliferative disorder (MPD)/ myelodysplastic syndrome (MDS)

Note

Chromosome 20q12 is a common breakpoint associated with the development of MPD/MDS, however with the increased specificity of chromosome mapping techniques the frequency of the CHD6 gene specifically mutated in this disease is still being more precisely determined (Huh et al., 2010; Padhi et al., 2013).

Colorectal cancer

Note

CHD6 has been implicated in two studies using

genome wide analysis of colorectal cancer cell lines. A comparison between tumor cell lines and primary tumors found that cell lines accurately reflect the diversity of mutations associated with primary tumor samples (Mouradov et al., 2014). Additionally this study determined that mutations in chromatin state regulators (including CHD6) are commonly found in colorectal cancer.

Further research examined the copy number variation (CNV) found between colorectal cancer and normal tissue samples (Ali Hassan et al., 2014). Significant alterations in CNV were observed on chromosomes 8, 13, and 20.

The gain of copies on chromosome 20q12 was the most significant finding, occurring in 45% of tumor tissues examined, specifically over a 2445 kbp region containing eight genes that include PTPRT, TOP1, and CHD6 (Ali Hassan et al., 2014).

Bladder transitional cell carcinoma (TCC)

Note

Analysis of multiple TCC tissues identified a group of chromatin remodeling enzyme genes with mutations occurring in 59% of patients.

CHD6 was found mutated in multiple lines examined, however, only in one line was the mutation exclusive to CHD6. Linked mutation of CHD6 and two other genes, ANK2 or LRP2 was found to correlate with the development of TCC (Gui et al., 2011).

Various cancers (malignant melanoma, glioma, cervical cancer, lung, urinary tract, large intestine, and others)

Note

Whole genome analysis of tumor tissues and culture cell lines have identified point mutations within CHD6.

These mutations and copy number variations occur at low frequencies and are often not likely pathologically associated with the development of the cancers.

The alterations have been found in the following tissues: malignant melanoma (5 substitution mutations: NCBI ClinVar Database, last update 04-24-2014), multiple tumor tissue sources identifying 283 mutations in haematopoietic and lymphoid (0.23% of tested samples), central nervous system (0.74%), cervix (14.3%), endometrium (8.5%), prostate, urinary tract (14.3%), ovary, breast, lung (7.0%), stomach (6.4%), skin, kidney, large intestine (10.6%), liver, oesophagus, and pancreas. The bulk of mutations are composed of nonsense substitution: 7.42%, missense substitution: 68.90%, synonymous substitution: 27.92%, deletion frameshift: 2.12% (COSMIC Database, v69). This database further identified copynumber variants in the following tissues; haematopoietic and lymphoid, central nervous system, breast, lung, endometrium, kidney, large intestine, lung, ovary, and pancreas tumor tissues, with gain of copy number, more common than loss of copy number (COSMIC Database, v69).

Influenza/human papillomavirus

Note

CHD6 has been identified as playing a role in the repression of influenza A infections. It associates with viral ribonuclear proteins in infected cells (Alfonso et al., 2011). Loss of CHD6 by siRNA silencing results in an increased viral replication, while in lungs of infected mice, CHD6 is degraded upon infection and exposure to the three subunits of the viral polymerase (Alfonso et al., 2013). Recent reports also indicate that CHD6 interacts with human papillomavirus proteins, binding and repressing the expression of oncogenes (Fertey et al., 2010). This suggests that CHD6 plays a role in gene suppression and is important in the response to viral infection.

Ataxia

Note

Mutations in CHD6 that affect functional subunits are linked to the development of an ataxic phenotype. The deletion of the ATPase region of CHD6 in a mouse model resulted in deficiencies in coordinated movement, which did not progress over time (Lathrop et al., 2010). Additionally, a recent study utilizing genome wide analysis of genes associate with coordination defects in ADHD identified CHD6 as one of the most relevant target genes (Fliers et al., 2012).

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