Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Cancer Prone Disease Section

Mini Review

Rubinstein-Taybi syndrome (RTS)

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Published in Atlas Database: June 2001

Online updated version : http://AtlasGeneticsOncology.org/Kprones/RubinsTaybiID10063.html
DOI: 10.4267/2042/37768

Identity

Alias: Broad thumb - hallux syndrome

Note: The Rubinstein-Taybi syndrome is a well-defined entity characterized by growth and mental retardation, broad thumbs and halluces, typical face, and various malformations.

Inheritance: The prevalence at birth was estimated to be 1 in 125,000 living newborn infants. RTS is caused by an autosomal dominant mutation.

Clinics

Phenotype and clinics

The main clinical features of RTS are facial dysmorphism, broad thumbs, broad big toes, and growth and mental retardation.
The facial appearance is different in the newborn, but the most striking facial features in childhood include microcephaly, downslanting palpebral fissures, prominent and beaked nose with low nasal septum, highly arched palate, and mild micrognathia.
Broad thumbs and broad halluces are present in almost all cases. Other extremities abnormalities include angulation deformities of the thumbs and halluces, broad distal phalanges of other fingers, clinodactyly of the 5th finger, persistent fetal fingertip pads and overlapping toes.
Growth retardation is generally marked during infancy with feeding problems, and with a tendency to overweight in later childhood and adulthood. Constipation, recurrent upper respiratory infections and conjunctivitis are frequent problems in infancy.
Retarded motor and mental development become apparent in the first year of life. The average IQ of the patients is between 35 and 50, but some patients may have a better outcome. The performal IQ is higher than the verbal IQ.
Other findings may include eye abnormalities (tear duct obstruction, ptosis, strabismus, glaucoma, coloboma, cataract, refractive error), congenital heart defects (PDA, VSD, ASD), urinary tract malformations, specific dental abnormalities, epilepsy, and skin features (naevus flammeus, hirsutism, keloid scarring).

Neoplastic risk

An increased risk for different tumors has been noticed. Tumors are reported in about 5 % of RTS patients. The reported tumors include brain tumors as meningioma, acute lymphocytic leukemia, pheochromocytoma, rhabdomyosarcoma (nasopharyngeal), and intraspinal neurilemmoma. An increased frequency of pilomatrixoma is also known in the syndrome.

Treatment

There is no specific treatment in RTS.

Cytogenetics

Note
Chromosome analysis is usually normal in RTS. Some cytogenetic rearrangements involving chromosome 16p13.3 have been described leading to the identification of the causing gene. An interstitial submicroscopic deletion of this region is found in approximately 12 % of the patients, using two-color FISH and the cosmid RT1 (D16S237).

Genes involved and proteins

Note
The gene for the human CREB binding protein, the transcriptional co-activator CREBBP (cAMP

Responsive Element Binding Binding Protein), is included in the RT1 cosmid, and mutations in CREBBP have been described in RTS patients.

Protein

CBP

Location
16p13.3

Patient N°	Mutation Location	Mutation Type	Protein Domain[1]
Missense Mutations			
29	Exon 15	A981T (GCAÆ ACA)	
30	Exon 31	N1978S (AAC ÆAGC)	GR
58	Exon 31	M2221L (ATG ÆCTG)	GR
50	Exon 31	A2243V (GCCÆ GTC)	GR
Nonsense Mutations			
69	Exon 1	S23X (TCG ÆTAG)	NRBD
40	Exon 4	R370X (CGA ÆTGA)	NTD
75	Exon 5	R413X (CGA ÆTGA)	NTD
18	Exon 21	K1269X (AAG ÆTAG)	HATD
35	Exon 27	R1498X (CGAÆ TGA)	HATD
64	Exon 27	Y1466X (TAT ÆTAA)	HATD
57	Exon 31	Q2043X (CAG ÆTAG)	CTD
8	Exon 14	2827delC	
39	Exon 30	4945delA	E1ABD
52	Exon 2	138delA+ins13bp[2]	NRBD
68	Exon 3	840insT	NTD
51	Exon 10	2045insA	CBD
33	Exon 16	3096insT	
Splice site Mutations			
6	Intron 27	IVS27-5CÆG	HATD
44	Intron 17	del7bp + ins2bp[3]	
12	Intron 19	IVS19+3AÆT	HATD
66	Intron 25	IVS25+2TÆC	HATD
65	Exon 27	K1520R[4] (AAG ÆAGG)	

[1]Last column refers to numbers of the different fuctional domains of CBP given by Giles RH *et al.*, 1997 (9). NRBD : Nuclear receptor binding domain; NTD : N-terminal transactivation domain; CBD : CREB binding domain; HATD : Histone acetyltransferase domain; E1ABD : E1A binding domain - 3rd Cys/His rich region - 2nd Zinc finger; GR : Gln-rich region; CTD : C-terminal transactivation domain. Some of the mutations are not related to any protein domain since certain regions of CBP gene have not been assigned to any functional domain.

[2]Normal sequence : ATACCCAATGGAGGAGAA
Mutated sequence : ATACCC - TCATCATGAGCTGATGGAGGAGAA

[3]Normal sequence : ATCCAGTAAGTTAATTCAT
Mutated sequence : ATCCCA - - - - - TAATTCAT

[4]Missense mutation affecting the donor splice site (see Results Section)

Mutations in the CBP gene detected by PCR and direct sequencing in French patients with RTS (Coupry et al., 2002)

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This article should be referenced as such:

Lacombe B. Rubinstein-Taybi syndrome (RTS). Atlas Genet Cytogenet Oncol Haematol. 2001; 5(3):218-220.