Rubinstein-Taybi syndrome (RTS)

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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, downsloping 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

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

Protein

<table>
<thead>
<tr>
<th>Patient NO</th>
<th>Mutation Location</th>
<th>Mutation Type</th>
<th>Protein Domain</th>
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<tbody>
<tr>
<td>Missense Mutations</td>
<td>Exon 15</td>
<td>A961T (GGCA/CA)</td>
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<td>Splice site Mutations</td>
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<td>IYS27-2C/GS</td>
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<td>del17bp + ins20bp5</td>
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<tr>
<td>Intron 27</td>
<td>K1320X4 (AAG/AGG)</td>
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</table>

1 Last column refers to numbers of the different functional domains of CBP gene by Sibils RH et al., 1997 (9); NRBD: Nuclear receptor binding domain; ND: N-terminal transactivation domain; CEB: CREB binding domain; HATD: Histone acetyltransferase domain; E1ABD: E1A binding domain - 3rd Cys-His rich region - 2nd Zinc finger; CR: C-terminal region; CTG: 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: ATACAGGAGAGAGAA
Mutated sequence: ATACCCAGGAGAGAGAA
3 Normal sequence: ATACAGGAGAGAGAA
Mutated sequence: ATACAGGAGAGAGA
4 Missense mutation affecting the donor splice site (see Results Section)

References


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Lacombe B


This article should be referenced as such: