Rubinstein Taybi syndrome

Rubinstein-Taybi syndrome (RSTS) is characterized by distinctive facial features, broad and often angulated thumbs and great toes, short stature, and moderate to severe intellectual disability. The characteristic craniofacial features are downslanted palpebral fissures, low hanging columella, high palate, grimacing smile, and talon cusps. Prenatal growth is often normal; however, height, weight, and head circumference percentiles rapidly drop in the first few months of life. Obesity may occur in childhood or adolescence. IQ scores range from 25 to 79; average IQ is between 36 and 51. Other variable findings are coloboma, cataract, congenital heart defects, renal abnormalities, and cryptorchidism.

Data reveal that loss of CREBBP in cerebellar granule neuron progenitors (GNPs) during embryonic development of mice compromises GNP development, in part by downregulation of brain derived neurotrophic factor (Bdnf). Interestingly, concomitant cerebellar hypoplasia was also observed in patients with Rubinstein Taybi syndrome, a congenital disorder caused by germline mutations of CREBBP. By contrast, loss of Crebbp in GNPs during postnatal development synergizes with oncogenic activation of SHH signaling to drive MB growth, thereby explaining the enrichment of somatic CREBBP mutations in SHH MB of adult patients. Together, this data provide insights into time-sensitive consequences of CREBBP mutations and corresponding associations with human diseases [1].

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Merk DJ, Ohli J, Merk ND, Thatikonda V, Morrissy S, Schoof M, Schmid SN, Harrison L, Filser S, Ahlfeld J, Erkek S, Raithatha K, Andreska T, Weißhaar M, Launspach M, Neumann JE, Shakarami M, Plenker D, Marra MA, Li Y, Mungall AJ, Moore RA, Ma Y, Jones SJM, Lutz B, Ertl-Wagner B, Rossi A, Wagener R, Siebert R, Jung A, Eberhart CG, Lach B, Sendtner M, Pfister SM, Taylor MD, Chavez L, Kool M, Schüller U. Opposing Effects of CREBBP Mutations Govern the Phenotype of Rubinstein-Taybi Syndrome and Adult SHH Medulloblastoma. Dev Cell. 2018 Mar 9. pii: S1534-5807(18)30107-2. doi: 10.1016/j.devcel.2018.02.012. [Epub ahead of print] PubMed PMID: 29551561.