A Case Of CREBBPExon 31 De Novo Missense Mutation Presented With Insomnia And Intellectual Disability Without Rubinstein-Taybi Syndrome Phenotype

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Background: The CREBBP (CREB Binding Protein) gene is ubiquitously expressed and is involved in the transcriptional coactivation of many different transcription factors. It binds to protein kinase A phosphorylated form of the cAMP-response element binding protein (CREB). CREBBP is known to play critical roles in embryonic development, growth control, and homeostasis by coupling chromatin remodeling to transcription factor recognition. The protein has intrinsic histone acetyltransferase activity and also acts as a scaffold to stabilize additional protein interactions with the transcription complex. The CREBBP encoding protein acetylates both histone and non-histone proteins. The functional domains in the CREBBP protein include Zinc finger domains (ZNF1, ZNF2, ZNF3), CREB-binding domain (KIX), Bromodomain (Br), histone acetyltransferase domain (HAT), and nuclear receptor coactivator domain (NR). Mutations in this gene are known to cause Rubinstein-Taybi syndrome (RTS). Case Study: The propositus was a 5 year-old Japanese female. She was born at full term via NSVD to non-consanguineous Japanese parents who were in good health. She weighed 2436g. Apgar scores were 71 and 85. Pregnancy history was unremarkable. Prenatal/perinatal history was remarkable for hospitalization in NICU for respiratory distress. Hypertonia, opisthotonus, round fingertips and 2nd and 3rd toe cutaneous syndactyly were noted as a neonate. She had recurrent aspiration pneumonia due to a cleft soft palate which was surgically corrected at age 2. Her development was remarkable for cognition and speech delay without significant gross motor delay: head control (3 mo), sit without support (10 mo), walking (15 mo), and first word spoken (20 mo). Characteristic behavioral abnormalities including insomnia, anorexia, and autistic features were noted as an infant. Physical examination at age 5 revealed multiple minor anomalies including narrow forehead, sparse eyebrows, telecanthus, deep-set eyes, epicanthal folds, depressed nasal bridge, anteverted nares, long philtrum, low set ears, prominent thumbs and great toes, and round fingertips. High resolution chromosome studies and CGH microarray studies were normal. NGS whole exome sequencing showed a heterozygous de novo CREBBP missense variant (c.5611A>C; p.Thr1871Pro) in the exon 31.

Discussion: Menke et al. (2016) reported 11 patients with mutations in CREBBP who showed minimal clinical findings resembling Rubinstein-Taybi syndrome. These cases reportedly had the similar features to our case in characteristic facial findings as well as behavioral and developmental problems including autistic behavior and feeding problems. All 11 reported cases also had a de novo missense mutation in the last part of exon 30 or beginning of exon 31 of CREBBP involving ZNF2, ZNF3 and the flanking domains. Our case further supports a separate entity (or entities) from the classical Rubinstein-Taybi syndrome due to missense mutations in the specific CREBBP region suggested by Menke et al.

Comments (un-moderated)

"last part of exon 30 or beginning of exon 31 of CREBBP involving ZNF2, ZNF3 and the flanking domains"
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