HK J Paediatr (new series) 2024;**29**:47-50

Case Report

Menke-Hennekam Syndrome: A Case Report and Literature Review

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Abstract *CREBBP* pathogenic variants were known to be associated with Rubinstein-Taybi syndrome (RTS). However, missense variants in exon 30 or 31 of *CREBBP* were identified to cause a distinctive phenotype different from classical RTS. In 2016, Menke et al first reported 11 individuals with de novo missense variants in the last part of exon 30 or at the beginning of exon 31 of *CREBBP.* These affected individuals were found to have variable developmental delay, short stature, microcephaly, feeding problems, recurrent upper airway infection and various congenital malformations but lack the hallmark features of RTS including grimacing smile, broad thumb and/or broad halluces. Initially described as atypical RTS, the condition was later revised as Menke-Hennekam syndrome (MHS). To date, less than 30 affected individuals were identified worldwide. In this case report, we wish to illustrate a patient suffering from molecularly confirmed MHS who presented with developmental delay, failure to thrive, undescended testis, scoliosis, inguinal and umbilical hernia.

Key words *Atypical RTS, CREBBP, Menke-Hennekam syndrome*

Clinical Report

Our proband is a 15-year-old gentleman who was the second child of a healthy, non-consanguineous Chinese couple. Family history was unremarkable. He was born as a full-term baby with a birth weight of 2.5 kg after an uneventful pregnancy. He was found to have undescended testis and inguinal hernia shortly after birth. He also had sternomastoid tumour of the right and bilateral hip joint contractures. He was referred to Clinical Genetic Service at 4 months of age for dysmorphic features. On physical examination, he had failure to thrive with body weight and body height both below the 3rd centile, while the head circumference was at the 3-10% centile. He was also noted to have dysmorphic features including bilateral ptosis, short palpebral fissures, telecanthus, a broad and flat nasal bridge, thin alae nasi, thin lips and low-set ears, but did not have broad thumbs or halluces (Figure 1). He had bilateral myopia of -1.5 diopters over the left and -5.0 diopters over the right. He also had right-sided convergent squint and was followed up by the ophthalmologist. He had global developmental delay with discrepant speech development and had no single words during the latest assessment at 15 years old. His clinical course was complicated with scoliosis, torticollis and valgus deformity of both feet and was followed up by orthopaedic surgeons.

Investigations

Medical exome sequencing was performed on DNA extracted from the peripheral blood of the patient. It revealed a likely pathogenic variant in NM_004380.2 (CREBBP): c.5602C>T p.(Arg1868Trp) [PS1, PM2, PP3,

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Received August 12, 2021

PP5]. This missense variant was previously reported in the literature and ClinVar.[1,2] Parental testing confirmed this as a de novo variant. This variant was classified as likely pathogenic according to the ACMG guideline. The diagnosis of CREBBP-related Menke-Hennekam syndrome (MHS) was substantiated.

Discussion

Variants in the CREBBP were traditionally known to be associated with Rubinstein-Taybi syndrome (RTS). However, recent studies discovered that variants in the last part of exon 30 and the beginning of exon 31 are associated with a different phenotype. In 2016, Menke et al first described 11 individuals carrying missense variants in the last part of exon 30 or the beginning of exon 31 in CREBBP. These affected individuals had a distinctive phenotype that was different from RTS. They presented to medical attention due to developmental delay, growth failure, microcephaly, feeding problems, recurrent upper airway infections and various congenital malformation including cardiac and urogenital malformations. However, they did not have a grimacing smile or broad angulated thumbs and halluces, which were considered the hallmarks of RTS.[1] Rather, they were frequently noted to have short palpebral fissures, telecanthus, short nose with anteverted nares, short columella and a long philtrum.[3] These affected individuals were identified to harbour de novo missense variants between base pairs 5,128 and 5,614 of CREBBP (codons 1,710 and 1,872), which encompassed the ZNF2 (codons 1,701 to 1,744) and ZNF3 (codons 1,764 to 1,853) domains, which were conserved regions of the protein. (Figure 2). These domains contained cysteine residues involved in helical folding stabilisation and facilitate the interactions with different transcriptional regulatory proteins.[4,5] Variants in these regions would cause instability in the structural organisation of the domain.[4,6] It was postulated that these missense variants were involved a gain of function mechanism with disturbed protein-protein interaction.[1] In 2018, Menke et al further reported 13 individuals with an atypical RTS phenotype, of which 11 individuals were found to carry variants in the exon 30 and 31 of the CREBBP gene.[3] The remaining 2 individuals were found to harbour variants in the homologous regions of EP300. Further studies are required for delineation of the borders for variants in EP300 causing atypical RTS as there were only a limited number of reports available. Apart from variants in the ZNF2 and ZNF3 domains, Wang et al recently reported a Chinese patient with atypical RTS harbouring an in-frame deletion in the histone acetyltransferase (HAT) domain at the beginning of exon 30 of CREBBP, postulating gain-of-function variants in HAT domains could also lead to atypical RTS.[7] Precise determination of the margins in CREBBP coding sequence in which gain of function variants could result in atypical RTS requires further studies.

To date, less than 30 affected individuals were reported worldwide.[1,2,3,8] Their clinical characteristics were summarised in Table 1. All of them had intellectual

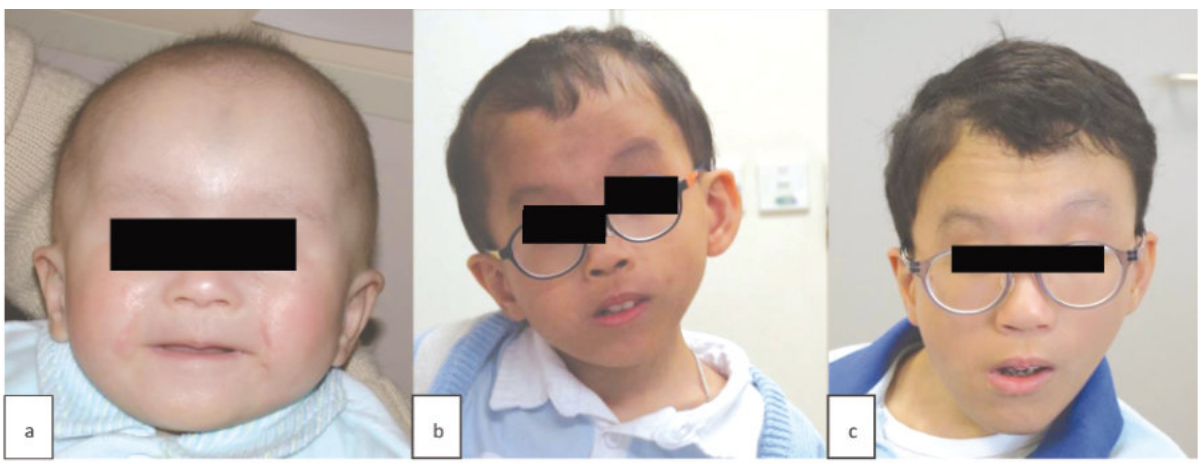

Figure 1 Clinical photo of our proband at the age of a) 8 months, b) 6 years old and c) 15 years old respectively. Note the presence of dysmorphic features including bilateral ptosis, short palpebral fissures, telecanthus, hypoplastic alae nasi, broad and flat nasal bridge, thin lips and low-set ears.

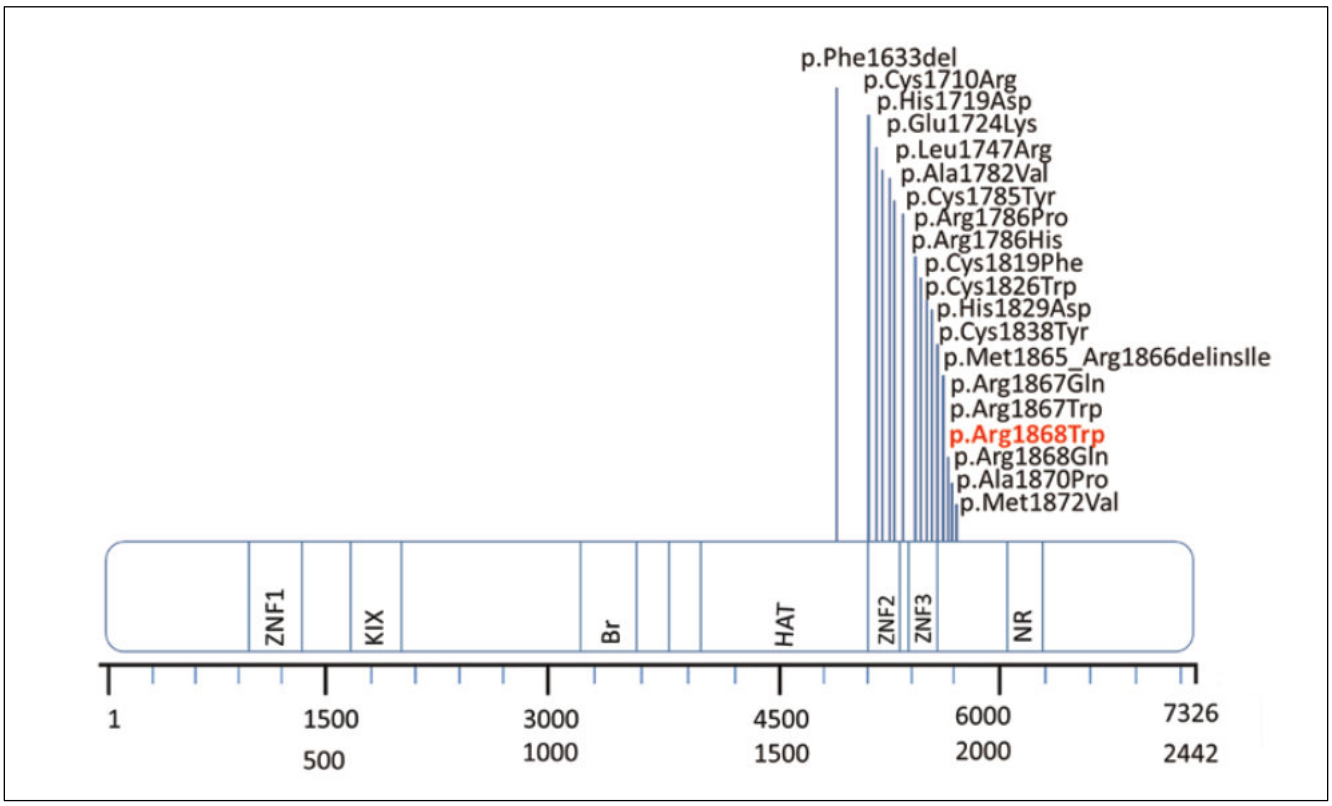

Figure 2 Summary of all reported CREBBP variants related to atypical RTS or Menke-Hennekam syndrome and their respective distribution in the protein's domain. The variant in our proband is highlighted in red.

Table 1 Summary of clinical characteristics of previously reported individuals with Menke-Hennekam syndrome

	Menke et al. 2016 & 2018[1,3]	Angius et al. 2018[8]	Banka et al. 2019[2]	Our patient	Total incidence
Developmental delay / Intellectual disability	19/21-24 (80-90%)	1/1	3/3	1/1	24/26-30 (80-92.3%)
Prenatal growth retardation	4/24 (16.7%)	0/1	2/3	0/1	6/29 (20.7%)
Postnatal growth retardation	10/24 (42%)	0/1	3/3	1/1	14/29 (48.2%)
Obesity	2/24 (8.4%)	1/1	0/3	0/1	3/29 (10.3%)
Microcephaly	10/23 (43%)	0/1	3/3	1/1	14/28 (50%)
Epilepsy	5/24 (21%)	0/1	0/3	0/1	5/29 (17.2%)
Autism / autism-like behaviour	13/20-24 (54-65%)	0/1	1/2	0/1	14/24-28 (50-58.3%)
Cardiovascular anomalies	4/24 (17%)	0/1	0/2	0/1	4/28 (14.3%)
Cryptorchidism	6/13 (46%)	0/1	2/2	1/1	9/17 (53%)
Urinary tract anomalies	5/24 (21%)	0/1	1/2	0/1	6/28 (21.4%)
Scoliosis	6/24 (25%)	0/1	1/3	1/1	8/29 (27.6%)
Recurrent upper airway infection	10/24 (42%)	0/1	N/A	0/1	10/26 (38.5%)
Feeding problems	18/24 (75%)	0/1	3/3	0/1	21/29 (72.4%)
Cleft palate	2/24 (8%)	1/1	0/3	0/1	3/29 (10.3%)
Hearing impairment	13/24 (54%)	0/1	1/3	0/1	14/29 (48.3%)
Inguinal / umbilical hernia	4/24 (16.7%)	0/1	0/3	1/1	5/29 (17.2%)
Joint contractures	4/24 (16.7%)	0/1	0/3	1/1	5/29 (17.2%)

disability. The most consistently described dysmorphic features would include ptosis, telecanthus, short and upslanted palpebral fissures, depressed nasal bridge, short nose, anteverted nares, short columella and long philtrum, which were seen in our patient as well. All affected individuals were described to have a minimal resemblance to the classical RTS phenotype after expert review. With an increasing readiness of exome sequencing, it is expected that more affected individuals with atypical RTS will be picked up, thereby broadening our understanding of the genotype-phenotype correlations in MHS.

Conflict of Interest

All authors have disclosed no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Informed Consent

Informed consent for publishing clinical photo and clinical information was obtained from the proband and his parents.

Funding / Support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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