Letter to the Editor

Pitt–Hopkins syndrome should be in the differential diagnosis for males presenting with an ATR-X phenotype

To the Editor:

Pitt–Hopkins syndrome [PTHS (OMIM 610954)] is characterized by severe intellectual disability (ID), distinct facial features (a wide mouth, fleshy lips, beaked nose with broad nasal bridge and anteverted nares) and periods of hyperventilation followed by apnea (1–6). PTHS was found to be caused by haploinsufficiency of the transcription factor 4 [TCF4 (OMIM 602272)] in 2007 (1, 2). More than 95% of patients have severe ID and PTHS facial features (7). PTHS has been considered as an important differential diagnosis of well-known developmental disorders such as Angelman syndrome [AS (OMIM 105830)], Rett syndrome (OMIM 312750) and Mowat–Wilson syndrome (OMIM 235730), because some characteristic features of PTHS overlap with these syndromes (1, 2, 8–11). We have also suggested that PTHS be included in the differential diagnosis of X-linked α-thalassemia ID [ATR-X (OMIM 301040)] because one of our patients had been suspected of having ATR-X based on his clinical features of severe ID, open mouth expression, a tented upper lip, a full lower lip, a depressed nasal bridge with anteverted nares and wide-spaced incisors (Fig. 1 in Ref. 12).

In follow-up to this observation, we analyzed 79 male patients who were submitted for ATRX testing and had negative findings. A heterozygous frameshift mutation, c.624delC (p.S209Afssx25), was found in one male patient. The patient is a 9-year-old male with severe developmental delay and hypotonia (Fig. 1). His unrelated parents and 7-year-old sister are healthy. There is no family history of developmental delay or neuromuscular disease. The pregnancy was uneventful. He was born by emergency caesarean section at 41 weeks following 4 days of labor induction. His birth weight was 3740 g (50th–75th percentile), birth length was 53 cm (75th–90th percentile CDC growth charts for boys). He required some facial oxygen and antibiotics in the immediate neonatal period, but there were no significant neonatal complications. His developmental delay and hypotonia were noticed in the newborn period and he was followed by the neurologist. Chromosomal analysis, fragile X analysis, FISH testing for 15q11q13 deletion and DNA methylation analysis of the PWS/AS critical region were negative. The result of a muscle biopsy, carried out as part of an extensive neurologic evaluation, was not suggestive of any specific diagnosis.

Our patient has typical clinical features of PTHS, severe ID with language impairment, hypotonia, seizure and constipation, which are also major symptoms of ATR-X. Particularly, his facial features, depressed nasal bridge with anteverted nares, a wide mouth with an everted upper lip and a full lower lip, wide-spaced teeth with prominent central incisors and upswept frontal hair overlap with those of patients with ATR-X (Fig. 1).

Periods of hyperventilation are not constantly observed in patients with PTHS but are highly specific for this syndrome (1, 2). This patient has had

Fig. 1. Facial features of the patient at the age of 8 years. Note the depressed nasal bridge with anteverted nares, a short philtrum, a wide mouth with an everted upper lip and a full lower lip, wide-spaced teeth with prominent central incisors, lumpy ear helices and upswept frontal hair.
episodic hyperventilation and breath-holding during wakefulness for several years. His mother had noticed them, but she did not mention this before his diagnosis of PTHS because they were not consistently present. Once patients are suspected of having PTHS, inquiring if there is a history of breathing anomalies may assist the diagnosis. In fact, clinicians might make an inquiry about respiratory problems standard for all individuals with severe ID. The present patient had regression episodes which were atypical for PTHS. Once he was able to say several single words and had acquired hand skills, but subsequently lost them.

In summary, we found a TCF4 mutation in 1 of 79 male patients referred for ATRX testing who had negative results. It is possible that additional TCF4 mutations may exist in this cohort because we did not screen for large or intragenic deletions. Thus, it is important to consider PTHS in the differential diagnosis of ATR-X. We suggest testing the TCF4 gene in male patients with an ATR-X phenotype but without an ATRX mutation.

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