Letter to the Editor

Floating-Harbor syndrome: SRCAP mutations are not restricted to exon 34

To the Editor:

Floating-Harbor syndrome (FHS; OMIM #136140) is a rare autosomal dominant disorder characterized by short stature, delayed bone age, speech delay, and dysmorphic facial features. FHS is caused by mutations in SRCAP which encodes the SNF2-related CREBBP activator protein (1). To date, eight different SRCAP mutations have been reported in 20 unrelated FHS patients. All mutations were either nonsense or frameshift variants, and they were all located within a small region (between codons 2407 and 2622) of exon 34, the last exon of SRCAP (1–3). Here, we report on the first FHS patient who carries a SRCAP mutation that is not located in exon 34, but in the penultimate exon 33.

The patient was born after an uneventful pregnancy at a postmenstrual age of 42 1/7 weeks by vacuum extraction to healthy and non-consanguineous German parents. He had normal birth measurements [weight 3540 g (30th centile), body length 54 cm (61th centile), occipitofrontal circumference (OFC) 37.5 cm (86th centile)]. Apart from glandular hypospadias, no other malformations were noted at birth. He started walking at the age of 24 months, and also speech development was delayed. On examination at the age of 8 years 9 months, height (119 cm) was just below the 3rd centile, while weight (26.8 kg; 25th centile) and OFC (53 cm; 75th centile) were normal. Dysmorphic features included a metopic ridge, pits of ear lobules, a typical nose (broad base, prominent nasal bridge, hypoplastic alae nasi, bulbous tip, low-hanging columella), short philtrum, and thin upper lip. He also had bilateral fifth finger clinodactyly, generalized hypertrichosis and atopic dermatitis (Fig. 1). He was able to speak in three-word sentences, to write single letters, and he attended a school for children with intellectual disability. Parents reported temperament and behavior difficulties with (auto)aggressive outbursts. Brain magnetic resonance imaging, sonography of the abdomen, electroencephalography, ophthalmologic examination and hearing tests revealed normal results. Blood pressure measurements, blood creatinine, urine analysis and sonography of the kidneys showed normal results at the age of 10 6/12 years. Hand X-ray at the age of 8 2/12 years revealed a bone age corresponding to 5 3/12 years. Conventional chromosome analysis and SNP array analysis (Affymetrix Genome-Wide Human SNP Array 6.0; Affymetrix, Santa Clara, CA) failed to reveal any abnormalities. A clinical diagnosis of FHS was made.

Molecular genetic analysis of all 34 exons of SRCAP (NM_006662.2) was performed by conventional Sanger sequencing according to standard protocols which revealed a de novo heterozygous stop mutation (c.7000C>T; p.Gln2334*) in exon 33. Exon 33 has a size of 84 bps, and the distance of this mutation to the following exon–intron boundary is 9 bps.

The patient reported here carried the first SRCAP mutation that is not located in the last exon (exon 34), but in the penultimate exon (exon 33) of this gene. The clinical signs of this patient are in accordance with those of the 20 previously published FHS patients with SRCAP mutations (1–3). All published mutations, as well as the nonsense mutation reported here, presumably lead to truncated proteins that lack the three C-terminal AT-hook DNA binding motifs of SRCAP, and a dominant-negative disease mechanism was suggested (1). Complete heterozygous deletion of the SRCAP gene has apparently no major clinical
effect (1), and the same is probably the case with nonsense or frameshift mutations in the proximal (i.e. 5′) exons of the gene that would result in nonsense mediated mRNA decay. Indeed, one SRCAP frameshift variant with a frequency of approximately 0.4% was identified in the probands of the Exome Variant Server (http://evs.gs.washington.edu/EVS/). On the other hand, specific SRCAP missense mutations could also exert dominant-negative effects, but the resulting clinical problems might be different from typical FHS. Similar effects have recently been reported for NOTCH2, where truncating mutations in the last exon cause Hajdu–Cheney syndrome, and missense mutations in other exons are associated with Alagille syndrome (4).

In conclusion, the patient reported here shows for the first time that SRCAP mutations are not restricted to the last exon of this gene. Functional studies and reports of patients with additional SRCAP mutations will eventually lead to a better understanding of biological mechanisms underlying this disorder.

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References

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