Research letter

Additional causal *SNRPE* mutations in hereditary hypotrichosis simplex

DOI: 10.1111/bjd.20089

Dear Editor, Hereditary hypotrichosis simplex (HHS) refers to a group of monogenic isolated alopecias characterized by diffuse and progressive loss of scalp and/or body hair. They start in childhood and progress with age. Affected individuals typically present with sparse-to-absent scalp hair, and may have brittle eyebrows and eyelashes, as well as sparse body hair, without any characteristic hair shaft anomalies. HHS research has identified several causal genes.[1,2] In 2012, our group was the first to identify *SNRPE* as an underlying gene for HHS.[3] Since then, no further cases have been reported. However, we now report the identification of further heterozygous mutations in *SNRPE* (NM_003094) – two novel mutations and one known mutation – in three ethnically diverse cases.

This study was approved by the ethics committees of the University Hospital of Bonn, Germany, and Xinhua Hospital, Shanghai Jiaotong University School of Medicine, China. All study procedures were performed in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from the respective patient or legal guardian prior to inclusion.

The first case concerned a 6-year-old Chinese girl, who presented with sparse scalp hair, and a history of short and brittle eyelashes and eyebrows since birth. Her healthy parents reported that, from the age of 1·5 years, the girl had experienced a pronounced and progressive loss of hair from the scalp, eyebrows and eyelashes. On examination, a paucity of body hair was observed (Figure 1a, left). To determine the underlying genetic cause, multigene panel sequencing was performed for 596 monogenic skin disease genes. A *de novo* splice site variant c.54+2T>A in *SNRPE* was identified and confirmed by Sanger sequencing (Figure 1b). The mutation was not identified in 200 control chromosomes of Chinese origin. *In vitro* hybrid mini-genes were constructed to investigate the splicing effect. This revealed that the mutation activates a new donor splice site in the enhanced green fluorescent protein coding sequence present in the vector and a new acceptor splice site in *SNRPE* intron 1, resulting in complete skipping of exon 1 and a partial intron 1 (14 base pair) retention.

The second case concerned a 2·5-year-old Spanish boy with healthy parents. He had displayed hypotrichosis since birth (Figure 1a, middle). Sanger sequencing of HHS-associated genes revealed the missense variant c.221T>C;p.(Leu74Pro) in *SNRPE*. This variant is predicted to be pathogenic by the *in silico* tool MutationTaster (http://www.mutationtaster.org/). The mutation could not be detected in the parents, thus indicating a *de novo* status. The leucine in position 74 is highly conserved across animal species. According to protein modelling, the proline at the end of a beta strand would affect the adjacent loop. In turn, this would affect the adjacent beta strand, which is part of the interdomain beta leaflet, thus the SmE–SmF interface would be disturbed (Figure 1d). Neither of the novel mutations was present in dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/) or the 1000 Genomes database (https://www.internationalgenome.org/index.html).

The third case concerned a 21-year-old woman of Turkish origin. She presented with sparse hair and absent eyebrows (Figure 1a, right). Exome sequencing analysis and subsequent Sanger sequencing revealed the mutation c.1A>G;p.(Met1?), which affects the start codon of *SNRPE*. This variant was associated with HHS in our original study.[3]

The fact that we identified mutations in three ethnically diverse families suggests that mutations in *SNRPE* are a relatively frequent occurrence. It is thus surprising that no additional cases have been reported since our original publication.[3] As also observed in the cases at that time, there was wide phenotypic variation in the present ones.

Concerning the splice site mutation, c.54+2T>A directly affects one of the most conserved nucleotides of the 5′ splice site of intron 1. As the newly activated splice site donor, which allows exon 1 skipping, was found in the vector sequence, we cannot exclude the possibility that another mechanism is taking place *in vivo*. However, if the described aberrant transcript were to be produced, it may be either subjected to RNA decay or, more likely, allow the production of an in-frame 52 amino acid-long protein corresponding to a different small nuclear ribonucleoprotein polypeptide E (SNRPE) isoform (ENST00000367208·1). We suggest that the lower expression of wild-type protein, or the imbalance between the two isoforms, impacts on SNRPE function with respect to hair growth/development.[3]

Interestingly, a mutation in *SNRPE* was recently identified in a patient with primary microcephaly and intellectual disability.[2] None of the present cases showed either clinical feature. This study identified two novel heterozygous mutations, and one known mutation, in *SNRPE*. This expands the mutational and ethnic spectrum of HHS.

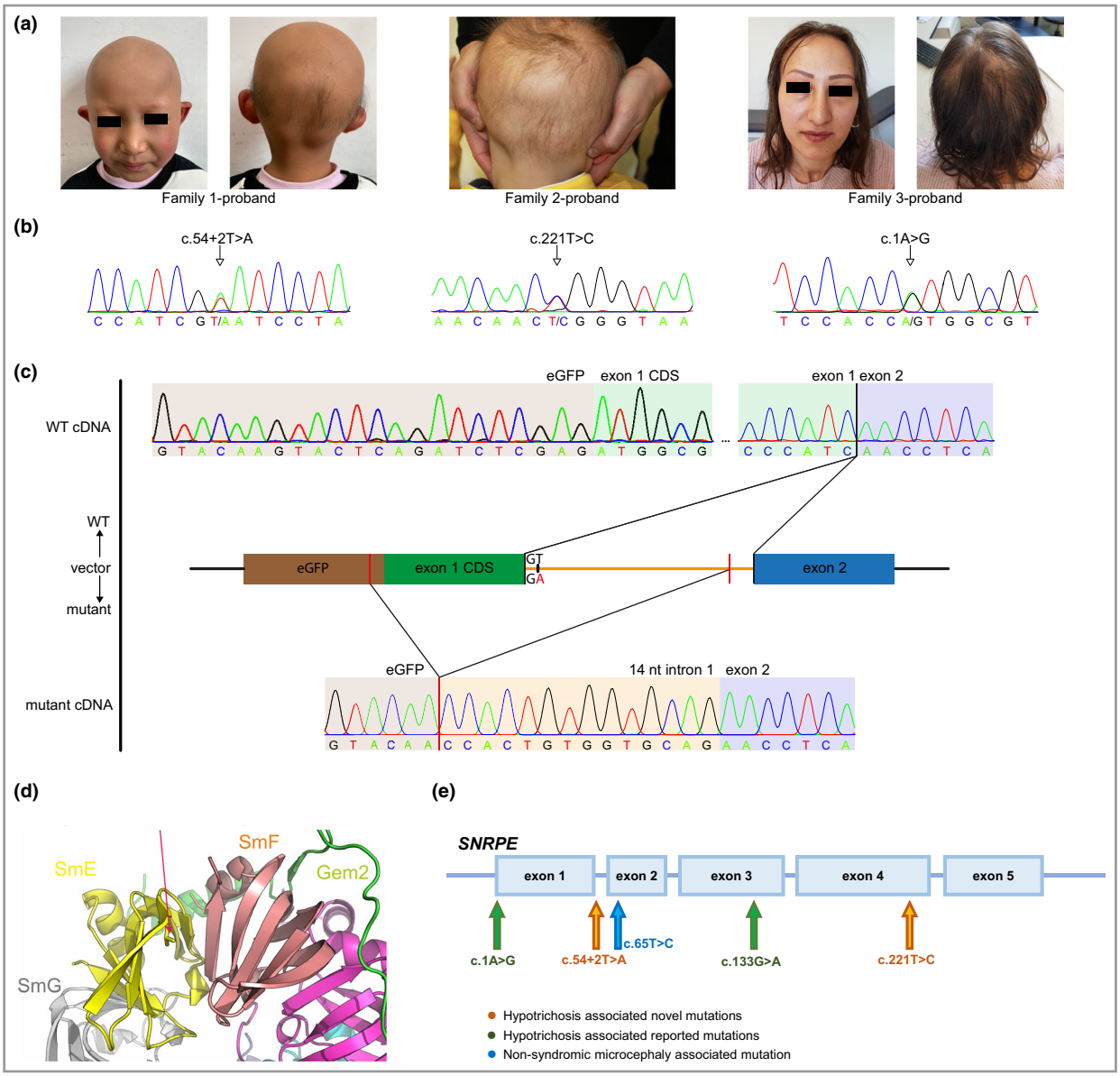

Figure 1 (a) Clinical photographs of the affected individuals. On the left, the 6-year-old girl of Chinese origin displayed sparse scalp hair, and short and brittle eyelashes and eyebrows. In the centre, the 2·5-year-old Spanish boy presented with hypotrichosis since birth. On the right, the 21-year-old woman of Turkish origin displayed sparse scalp hair and absent eyebrows. (b) Electropherograms of the three patients: (left) the c.54+2T>A mutation of the Chinese girl; (centre) the c.221T>C mutation in the boy of Spanish origin; and (right) the c.1A>G mutation in the woman of Turkish origin. (c) cDNA sequencing from the hybrid mini-gene experiment: schematic representation of the *in vitro* mini-gene strategy used to analyse the splicing behaviour of the c.54+2T>A mutation. The black lines underline the wild-type exon–exon junction and the red lines show the new splicing sites. (d) Protein model of small nuclear ribonucleoprotein polypeptide E (SNRPE), containing the mutation p.(Leu74Pro). The red arrow indicates proline in position 74. (e) Cartoon of all new and already known mutations of *SNRPE*.

Acknowledgments: We thank the patients and their families for their cooperation and participation in this study. Open Access funding enabled and organized by Projekt DEAL.

C. Pan,[1,2] A. Humbatova,[3] L. Zheng,[1,2] N. Cesarato,[3] C. Grimm,[4] F. Chen,[1,2] B. Blaumeiser,[5] A. Catalán-Lambán,[6] A. Patiño-García,[6] U. Fischer,[4] R. Cheng,[1] Y. Li,[1,2] X. Yu,[1] Z. Yao,[1,2] M. Li[1,2,7] and R.C. Betz[3]

[1]*Department of Dermatology, Xinhua Hospital;* [2]*Institute of Dermatology, Shanghai Jiaotong University School of Medicine, Shanghai, China;* [3]*Institute of Human Genetics, University of Bonn, School of Medicine and University Hospital Bonn, Bonn, Germany;* [4]*Department of Biochemistry, University of Würzburg, Würzburg, Germany;* [5]*Department of Medical Genetics, University of Antwerp, Antwerp, Belgium;* [6]*Department of Pediatrics, Clínica Universidad de Navarra, Pamplona, Spain; and* [7]*Center for Rare Diseases Diagnosis, Shanghai, China*

Correspondence: Regina C. Betz and Ming Li
Email: regina.betz@uni-bonn.de
and liming01@xinhuamed.com.cn

C.P., A.H. and L.Z. contributed equally.

References

1 Betz RC, Cabral RM, Christiano AM *et al*. Unveiling the roots of monogenic genodermatoses: genotrichoses as a paradigm. *J Invest Dermatol* 2012; **132**:906–14.
2 Chen T, Zhang B, Ziegenhals T, *et al*. A missense mutation in SNRPE linked to non-syndromal microcephaly interferes with U snRNP assembly and pre-mRNA splicing. *PLOS Genet* 2019; **15**: e1008460.
3 Pasternack SM, Refke M, Paknia E *et al*. Mutations in *SNRPE*, which encodes a core protein of the spliceosome, cause autosomal-dominant hypotrichosis simplex. *Am J Hum Genet* 2013; **92**:81–7.

Funding sources: This work was supported by grants from the National Nature Science Foundation of China (81874239 and 82073422); the ShanghaiHealth System Excellent Academic Leader Training Project (2018BR22); and the Pujiang Talents Program (18PJ1407300). The work was also supported by a grant from the German–Israeli Foundation (R.C.B.), and by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under the auspices of the German Excellence Strategy – EXC2151 – 390873048 (R.C.B.).

Conflicts of interest: The authors declare they have no conflicts of interest.