Uncombable hair syndrome due to maternal uniparental disomy of chromosome 1

Breet, Hanna; Vos, Yvonne J.; Dijkhuizen, Trijnie; Voorbij-Vierstra, Carlijn L.; Bolling, Maria C.; van den Akker, Peter C.

Published in:
American Journal of Medical Genetics, Part A

DOI:
10.1002/ajmg.a.63086

Received: 6 September 2022 | Revised: 11 November 2022 | Accepted: 3 December 2022

DOI: 10.1002/ajmg.a.63086

CLINICAL ROUNDS

AMERICAN JOURNAL OF medical genetics PART A WILEY

Uncombable hair syndrome due to maternal uniparental disomy of chromosome 1

Hanna Breet[1] | Yvonne J. Vos[1] | Trijnie Dijkhuizen[1] | Carlijn L. Voorbij-Vierstra[2] | Maria C. Bolling[2] | Dr Peter C. van den Akker MD PhD[1,2]

[1]Department of Genetics, Expertise Center for Genodermatoses, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[2]Department of Dermatology, Expertise Center for Genodermatoses, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Correspondence
Peter C. van den Akker, Department of Genetics, Expertise Center for Genodermatoses, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
Email: p.c.van.den.akker@umcg.nl

Abstract

Uncombable hair syndrome is a hair shaft condition in which the hair is frizzy, light in color (silver to light brown), and cannot be combed flat. Autosomal dominant (with complete or incomplete penetrance), autosomal recessive, and sporadic cases have been reported. In 2016 causative mutations in three genes were identified for uncombable hair syndrome, all with an autosomal recessive inheritance pattern: *PADI3*, *TGM3*, and *TCHH*. In many cases, however, there is still no molecular diagnosis. Here, we describe a case of autosomal recessive uncombable hair syndrome resulting from maternal uniparental disomy of chromosome 1.

KEYWORDS
chromosomal aberrations, clinical genetics, genodermatosis, trisomy rescue, uncombable hair syndrome, uniparental disomy

1 | INTRODUCTION

Dupré et al., and Stroud and Mehregan described the first cases of "cheveux incoiffables" or "spun glass hair" in 1973 (Dupre et al., 1973; Stroud & Mehregan, 1973). Nowadays, over 200 cases of uncombable hair syndrome (UHS) [MIM: 191480] have been described. UHS is a hair shaft condition in which the hair is frizzy, light in color (silver to light brown), and cannot be combed flat. Electron microscopy shows highly specific features of longitudinal grooves and triangular shape of the hair shaft. The condition is usually diagnosed in early childhood and often improves around puberty. There is no therapy for UHS. Sometimes biotin supplementation is advised as biotin should improve hair strength and combability (Calderon et al., 2009).

Autosomal dominant (with complete or incomplete penetrance), autosomal recessive, and sporadic cases of UHS have been reported. In 2016, Basmanav et al. identified causative mutations in three genes for UHS, all with an autosomal recessive inheritance pattern; *PADI3* [MIM: 606755], *TGM3* [MIM: 600238], and *TCHH* [MIM: 190370] (Basmanav et al., 2016). Recently, Basmanav et al. confirmed UHS to be an autosomal recessive condition, because they identified biallelic pathogenic variants in *PADI3*, *TGM3* or *TCHH* in 80 of 107 patients with UHS (Basmanav et al., 2022). In 27 cases there was no molecular diagnosis. Here, we describe a case of UHS caused by a homozygous *PADI3* variant due to maternal uniparental disomy (UPD) of chromosome 1.

2 | REPORT

Our patient is a 23 months old girl with a hair dysplasia since the age of 4 months. Neonatal hair was unremarkable. The mother reported her daughter's nails did not need cutting. The family history was negative for hair or nail abnormalities and other skin conditions. On clinical examination, the hair was frizzy, light blonde colored, and could not be managed (Figure 1a–c). Hair pull test was negative. Eyebrows and eyelashes were short and body hair was sparse and frizzy. The nails of both hands and feet were short but appeared otherwise normal. There

FIGURE 1 (a–d) Clinical photographs of the patient showing frizzy, light blonde colored, unmanageable hair, and short toe nails. (e–g) Scanning electron microscopy of normal hair (e) and the hair of our patient showing longitudinal grooves and a triangular shape ("heart-shaped"), ultrastructural features typical for UHS. Scale bars = 100 µm. g: Detail of f (scale bar = 20 µm).

were no additional abnormalities of the skin, nails, or teeth. The parents' hair was normal.

Using scanning electron microscopy, her scalp hair appeared heart-shaped, due to longitudinal grooves, which confirmed the diagnosis UHS (Figure 1f,g). Simultaneously, whole exome sequencing (WES, Agilent SureSelect Human All Exome V6_S07604514) was performed and the three genes associated with UHS were analyzed. This revealed homozygosity for the likely pathogenic variant NM_016233.2:c.335T>A, p.(Leu112His) in *PADI3*. This variant has been described in other patients with UHS (Basmanav et al., 2016; Basmanav et al., 2022). Hence, the parents were informed that the diagnosis UHS was confirmed molecularly and that there is no increased risk of other clinical symptoms. It is likely that the manageability of the hair will improve during puberty.

Subsequent carrier testing of the parents showed that only the mother carried the *PADI3* variant. There were several possible explanations for this, the most likely being a large chromosomal deletion including *PADI3* on the paternal allele, maternal UPD of chromosome 1, mix-up of samples, and non-paternity. Therefore, we performed a SNP-array (Illumina Infinium® Global Screening Array), which excluded a large deletion of the paternal allele. However, chromosome 1 showed four large homozygous regions. One of these homozygous regions included the *PADI3* gene.

Large homozygous regions, restricted to only one chromosome, are indicative of UPD. UPD refers to a situation where someone inherited both chromosomes of a particular pair from one parent, while no chromosome from the other parent. To further study the origin of chromosome 1, the SNP-array data of both parents were analyzed with in-house software based on the publicly available SNPduo-tool (http://pevsnerlab.kennedykrieger.org/SNPduo). The results showed that both chromosomes 1 were inherited from her mother (Figure S1). Parts of chromosome 1 showed both maternal alleles, while other parts, including the *PADI3* region, showed one duplicated maternal allele. Hence, the UHS in our patient occurred through the rare event of UPD.

3 | DISCUSSION

There are several mechanisms that can lead to a UPD of a complete chromosome. Considering the frequency of the UPD mechanisms,

trisomy rescue was the most likely mechanism having led to UPD in this case (Figure S2). Trisomy rescue is a mechanism where one of the trisomic chromosomes is being discarded after a trisomic zygote has formed due to meiotic non-disjunction in one of the two gametes. In case of a UPD, the discarded chromosome is the one that came from the normal gamete. In our case, since the centromeric region is homozygous, there is an isodisomy, caused by maternal meiotic II non-disjunction with heterodisomic segments due to crossing-over during prophase 1. UPD is usually sporadic with no increased recurrence risk.

UHS is usually isolated, but sometimes other conditions are reported to co-occur (Calderon et al., 2009). The most common association is with ectodermal dysplasia (ED), so it is important to screen for associated symptoms. On clinical examination, we found no symptoms of ED other than the slowly growing nails. To exclude a concomitant ED causing a combination of hair abnormalities with slow-growing nails, 66 genes associated with common and rare EDs and isolated ectodermal abnormalities were analyzed (Table S1). This did not show any pathogenic or likely pathogenic variants, which decreased the possibility of a concomitant ED. The frizzy, light blonde colored and unmanageable hair is a typical manifestation of UHS due to biallelic pathogenic *PADI3* variants (Basmanav et al., 2022). Nail abnormalities have not been reported in other UHS cases, including those with *PADI3* variants, except for one patient with concomitant *PADI3* and *RSPO4* variants (Hsu et al., 2017). Whether the slowly growing nails in our patient are part of the UHS-spectrum due to *PADI3* variants or an unrelated symptom remains unclear at this stage.

Maternal UPD of chromosome 1 may have of itself no effect, but the four large homozygous regions on chromosome 1 pose an increased risk of a second autosomal recessive disorder. Although no features of other recessive disorders were noted, we further reduced the possibility of a concomitant, second recessive disorder by screening all genes in these homozygous regions. This did not disclose other pathogenic variants.

In conclusion, we report a 23 months old girl with typical clinical and electron microscopy features of UHS. The homozygous variant that was identified in *PADI3* was due to maternal isodisomic UPD after meiotic II non-disjunction and trisomy rescue. The recurrence risk is therefore low. UPD should always be considered in case of homozygous recessive diseases like UHS.

AUTHOR CONTRIBUTIONS

Hanna Breet conducted the research, collected data, and drafted the manuscript. Yvonne J. Vos and Trijnie Dijkhuizen performed genome diagnostics. Carlijn L. Voorbij-Vierstra collected data. Maria C. Bolling provided clinical supervision. Peter C. van den Akker provided concept, clinical, and manuscript supervision. All authors approved the final version of the manuscript and its submission to American Journal of Medical Genetics – Part A.

ACKNOWLEDGMENTS

We would like to thank the patient and her parents for their participation in the study. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST

Maria C. Bolling is a member of the data safety monitoring board of a Rigosertib study by Paracelsus Medical University, Salzburg, Austria and chair of the Dutch Working Group on Genodermatoses.

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.

ORCID

Hanna Breet https://orcid.org/0000-0002-4901-5831
Peter C. van den Akker https://orcid.org/0000-0002-3734-753X

REFERENCES

Basmanav, F. B., Cesarato, N., Kumar, S., Borisov, O., Kokordelis, P., Ralser, D. J., Wehner, M., Axt, D., Xiong, X., Thiele, H., Dolgin, V., Gossmann, Y., Fricker, N., Dewenter, M. K., Weller, K., Suri, M., Reichenbach, H., Oji, V., Addor, M. C., … Betz, R. C. (2022). Assessment of the genetic spectrum of uncombable hair syndrome in a cohort of 107 individuals. *JAMA Dermatology*, *31*, e222319.

Basmanav, Ü., Cau, L., Tafazzoli, A., Méchin, M. C., Wolf, S., Romano, M. T., Valentin, F., Wiegmann, H., Huchenq, A., Kandil, R., Garcia Bartels, N., Kilic, A., George, S., Ralser, D. J., Bergner, S., Ferguson, D. J. P., Oprisoreanu, A. M., Wehner, M., Thiele, H., … Betz, R. C. (2016). Mutations in three genes encoding proteins involved in hair shaft formation cause uncombable hair syndrome. *American Journal of Human Genetics*, *99*(6), 1292–1304.

Calderon, P., Otberg, N., & Shapiro, J. (2009). Uncombable hair syndrome. *Journal of the American Academy of Dermatology*, *61*(3), 512–515.

Dupre, A., Rochiccioli, P., & Bonafe, J. L. (1973). "Cheveux incoiffables": anomalie congenitale des cheveux. *Bulletin de la Societe Francaise de Dermatologie et Syphiligraphie*, *80*, 111–112.

Hsu, C. K., Romano, M. T., Nanda, A., Rashidghamat, E., Lee, J. Y. W., Huang, H. Y., Songsantiphap, C., Lee, J. Y., Al-Ajmi, H., Betz, R. C., Simpson, M. A., McGrath, J. A., & Tziotzios, C. (2017 May). Congenital anonychia and uncombable hair syndrome: Coinheritance of homozygous mutations in RSPO4 and PADI3. *The Journal of Investigative Dermatology*, *137*(5), 1176–1179.

Stroud, J. D., & Mehregan, A. H. (1973). *The first human hair symposium*. Medcom Press.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Breet, H., Vos, Y. J., Dijkhuizen, T., Voorbij-Vierstra, C. L., Bolling, M. C., & van den Akker, P. C. (2022). Uncombable hair syndrome due to maternal uniparental disomy of chromosome 1. *American Journal of Medical Genetics Part A*, 1–3. https://doi.org/10.1002/ajmg.a.63086