RESEARCH LETTER

The HHID syndrome of hypertrichosis, hyperkeratosis, abnormal corpus callosum, intellectual disability, and minor anomalies is caused by mutations in ARID1B

Markus Zweier | Maarit M. Peippo | Minna Pöyhönen | Helena Kääriäinen | Anaïs Begemann | Pascal Joset | Beatrice Oneda | Anita Rauch

1 Institute of Medical Genetics, University of Zurich, Schlieren-Zurich, Switzerland
2 Mehiläinen Clinic, Vantaa, Finland
3 Department of Clinical Genetics, Helsinki University Central Hospital and Department of Medical Genetics, University of Helsinki, Helsinki, Finland
4 National Institute for Health and Welfare, Helsinki, Finland
5 Rare Disease Initiative Zurich, Clinical Research Priority Program for Rare Diseases, University of Zurich, Zurich, Switzerland
6 Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland
7 Neuroscience Center Zurich, University of Zurich and ETH Zurich, Zurich, Switzerland

Correspondence
Anita Rauch, Institute of Medical Genetics, University of Zurich, Wagistrasse 12, 8592 Schlieren-Zurich, Switzerland.
Email: anita.rauch@medgen.uzh.ch

KEYWORDS
abnormal corpus callosum, ARID1B, Coffin-Siris syndrome, HHID, hyperkeratosis, hypertrichosis, intellectual disability, minor anomalies

TO THE EDITOR:

In 2004, Pöyhönen et al. reported on three unrelated patients with hypertrichosis, hyperkeratosis, abnormal corpus callosum, intellectual disability (ID), and minor anomalies including low anterior hairline, thick arched eyebrows, broad nasal tip, columella below alae nasi, short philtrum, thick-everted lower lip, simple posteriorly angulated ears, and broad feet and finger tips (Pöyhönen et al., 2004). This observation was recognized as an OMIM entity (OMIM 609943), hereafter referred to as HHID syndrome. In 2009, Dalal and Mehrotra (2009) reported a further patient with HHID syndrome who additionally presented with short stature, short 4th and 5th toes, mild dilatation of the supratentorial ventricular system and nephrolithiasis. No further individual with suspected HHID has been published and the cause of their condition remained elusive. We now used whole exome sequencing (WES) in the three patients published by Pöyhönen et al. (2004) and discuss the updated phenotype in the light of today’s clinical knowledge and our genetic findings.

The detailed initial clinical description of patient 1 (P1, at age of 16 years), patient 2 (P2, at age of 17 years), and patient 3 (P3, at age of 10 years), all born to non-consanguineous parents from different parts of Finland, is provided in the original article by Pöyhönen et al. (2004). Clinical reassessment of the three patients after about 10 years revealed the previously described phenotype, except for hypertrichosis, which now resembled normal variation. Additionally, behavior anomalies such as severe obsessive-compulsive and autistic behavior and a hoarse or high pitched voice were noted (Table 1, Figure 1).

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Results of conventional karyotyping, subtelomeric FISH studies and targeted testing of CREBBP were normal. We then performed high resolution chromosomal microarray testing which did not reveal any apparent pathologic variant followed by WES in P1 and trio-WES in P2 and P3 and their healthy parents. The study was approved by the ethical committee of the canton of Zurich. Filtering for rare, non-synonymous exonic, and splice site variants in 821 known and 424 candidate ID genes (based on the SysID database, [Kochinke et al., 2016]), considering both dominant and recessive modes of inheritance, revealed pathogenic de novo loss of function mutations in ARID1B in P2 and P3. In P2, we identified a heterozygous deletion of 4 bp (NM_020732.3:c.5570_5573del) in the last coding exon of ARID1B, which causes a frameshift resulting in a premature truncation after 16 amino acids and thereafter a

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Updated clinical features of HHID patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>P1</td>
</tr>
<tr>
<td>Genetic defect</td>
<td>Unknown</td>
</tr>
<tr>
<td>Age at investigation</td>
<td>25 y</td>
</tr>
<tr>
<td>Growth parameters</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>156.3 cm (−1.6 SD)</td>
</tr>
<tr>
<td>OFC</td>
<td>55 cm (0 SD)</td>
</tr>
<tr>
<td>BMI</td>
<td>19.3</td>
</tr>
<tr>
<td>Menarche</td>
<td>9 y</td>
</tr>
<tr>
<td>Health</td>
<td></td>
</tr>
<tr>
<td>Malformations</td>
<td>Thick and short corpus callosum</td>
</tr>
<tr>
<td>Vision</td>
<td>Strabismus, myopia right, hyperopia left</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Ectodermal signs</td>
<td></td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>Vanished</td>
</tr>
<tr>
<td>Hyperkeratotic skin plaques</td>
<td>Neck, shoulders, axillary area, between the breasts, and on the lower abdominal and dorsal areas</td>
</tr>
<tr>
<td>Nails</td>
<td>Mild hypoplasia</td>
</tr>
<tr>
<td>Behaviour &amp; development</td>
<td></td>
</tr>
<tr>
<td>Walking</td>
<td>1 y 8 mo</td>
</tr>
<tr>
<td>Speech development (sentences)</td>
<td>2 y</td>
</tr>
<tr>
<td>Academic achievements</td>
<td>Reads, writes, counts</td>
</tr>
<tr>
<td>ID</td>
<td>Mild</td>
</tr>
<tr>
<td>Voice &amp; speech behaviour</td>
<td>Voice hoarse, increasing inertia to speak</td>
</tr>
<tr>
<td>Sleeping problems</td>
<td>reverse sleeping rhythm</td>
</tr>
<tr>
<td>Behaviour/personality</td>
<td>Withdrawn, stubborn, irritated, passive, temper tantrums, detests presence of others</td>
</tr>
<tr>
<td>Cognitive regression</td>
<td>No (severe visuospatial and motor problems)</td>
</tr>
</tbody>
</table>

y, years; mo, month; OFC, occipito-frontal circumference; BMI, body mass index; SD, standard deviation score; MRI, magnetic resonance imaging; VSD, ventricular septal defect; PDA, patent ductus arteriosus; CoA, coaxial; Cong., congenital; ID, intellectual disability.
significantly truncated protein (p.Lys1857Serfs*17). This mutation
has not been reported before and de novo occurrence was
confirmed by Sanger sequencing in the patient and her parents.
WES in P3 and her parents revealed a heterozygous de novo
mutation of the last coding basepair of exon 17 (NM_020732.3:
c.4110G>A), which was predicted to be synonymous, but located in
the conserved consensus splice donor site. This mutation had been
reported previously in a patient with nonspecific ID and results in
skipping of exon 17 in RNA from patient lymphocytes (Hoyer et al.,
2012). Therefore, it was predicted to cause a frameshift resulting in
a premature translational termination (p.His1339Ilefs*77); and thus,
possibly in nonsense-mediated mRNA-decay. In P1, no obvious
pathogenic or likely pathogenic loss of function mutation in a known
ID gene could be detected, although the whole coding region of
ARID1B was covered at least 20-fold and MLPA analysis showed
normal dosage for all exons. Of note, additional mutation screening
of all variants in related ID genes (ARID1B, SMARCA4, SMARCB1,
SMARCE1, SMARCA2, TBC1D24, SOX11, PHF6, TBC1D24, ADNP, and
KMT2A) revealed no obvious pathogenic variant, either. However,
interpretation of missense variants in other genes and analysis of
novel candidate genes were hampered by the fact that the father
was not available and a trio approach therefore not feasible.

Our findings establish mutations in ARID1B as the underlying
genetic defect in the HHID syndrome in two of three patients.
The underlying genetic defect in P1 remains currently elusive,
however, an undetected non-coding mutation of ARID1B cannot be
excluded.

Haploinsufficiency of ARID1B was recently implicated in both,
nonsyndromic ID and Coffin-Siris Syndrome (CSS, OMIM #135900)
(Hoyer et al., 2012; Santen et al., 2012; Tsurusaki et al., 2012). There is
accumulating evidence that ARID1B is one of the most commonly
mutated genes in ID and is associated with a broad phenotypic range
(Deciphering Developmental Disorders, 2015; Hoyer et al., 2012;
Santen & Clayton-Smith, 2014). The core phenotype of ARID1B
mutated patients, present in almost all patients with a prior CSS
diagnosis, comprises ID (100%), speech delay (100%), "coarse facies"
(95%), and hypertrichosis (95%). Common further anomalies were
small 5th finger or toe nails (81%), short fifth finger (73%), feeding
difficulties (65%), agenesis of the corpus callosum (35%), seizures
(23%), myopia (20%), and growth delay (19% height <−2.5 SDS, 71%
height <0 SDS) (Santen & Clayton-Smith, 2014). Retrospectively, the
HHID patients’ phenotypes fit well into the published ARID1B-
associated clinical spectrum including the key features of ID,
hypertrichosis, abnormal corpus callosum, and coarse face. However,
our patients show only mildly diminished nail size and demonstrate
that the key feature of hypertrichosis vanishes to levels of normal
variation during adolescence. Moreover, the most distinctive feature
shared by all patients with suspected HHID (Dalal & Mehrotra, 2009;
Pöyhönen et al., 2004) is the ectodermal sign of hyperkeratotic
plaques which has not yet been reported in any patient with CSS or
ARID1B-associated nonspecific ID. This might therefore constitute
either an underreported or an infrequent but distinct novel feature of
ARID1B-associated phenotypes. However, reevaluation of patients
with ARID1B mutations is needed to assess the true incidence of

FIGURE 1 Phenotypes of patients with suspected HHID syndrome at clinical reinvestigation after about 10 years. Facial gestalt, hand and
foot, and a location with hyperkeratotic plaques is shown for P1 at the age of 25 years (A-E), for P2 at the age of 26 years (F-J), and for P3 at
the age of 19 years (K-N). Of note, the picture with hyperkeratotic plaques for P3 (O) was taken at the age of 16 years.
hyperkeratotic plaques, which may become only obvious with increasing age.

REFERENCES


