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RESEARCH LETTER

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

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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).

TABLE 1 Updated clinical features of HHID patients

Patients	P1	P2	P3
Genetic defect	Unknown	**ARID1B**: c.5570_5573del (p.Lys1857Serfs*17)	**ARID1B**: c.4110G>A (p.His1339Ilefs*77)
Age at investigation	**25 y**	**26 y**	**19 y**
Growth parameters			
Height	156.3 cm (−1.6 SD)	155 cm (−1.8 SD)	154.5 cm (−1.8 SD)
OFC	55 cm (0 SD)	56.5 cm (+1 SD)	54.5 cm (−0.5 SD)
BMI	19.3	32	25.1
Menarche	9 y	13 y	15 y
Health			
Malformations	Thick and short corpus callosum	VSD, PDA, mild CoA. Cong. hip dislocation, midline supraumbilical hernia, cong. ptosis of right eye, no cerebral MRI	Thick and short corpus callosum
Vision	Strabism, myopia right, hyperopia left	Strabism, myopia	Myopia
General	Recurrent ear infections—tube insertion & adenotomy (5 y) enuresis up to 10 y	Recurrent ear infections—tube insertion & adenotomy (7 y) hemicrania	Severe atopic eczema
Ectodermal signs			
Hypertrichosis	Vanished	Vanished	Vanished
Hyperkeratotic skin plaques	Neck, shoulders, axillary area, between the breasts, and on the lower abdominal and dorsal areas	Middle of the back	Lower and upper limbs
Nails	Mild hypoplasia	Mild hypoplasia	Mild hypoplasia
Behaviour & development			
Walking	1 y 8 mo	2 y 4 mo	1 y 6 mo
Speech development (sentences)	2 y	4 y	5 y
Academic achievements	Reads, writes, counts	Reads, writes, counts	Reads, writes, counts
ID	Mild	Mild-moderate	Mild
Voice & speech behaviour	Voice hoarse, increasing inertia to speak	Voice hoarse, feeble; speech slurred, finally total refusal to speak	Voice high pitched; slurred speech, rapid change of pitch, diminishing use of speech
Sleeping problems	reverse sleeping rhythm	No	No
Behaviour/ personality	Withdrawn, stubborn, irritated, passive, temper tantrums, detests presence of others	Withdrawn, obstinate, passive, obsessive-compulsive, detests presence of others	Withdrawn, autistic, obsessive compulsive, detests presence of others
Cognitive regression	No (severe visuospatial and motor problems)	No	No

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.

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

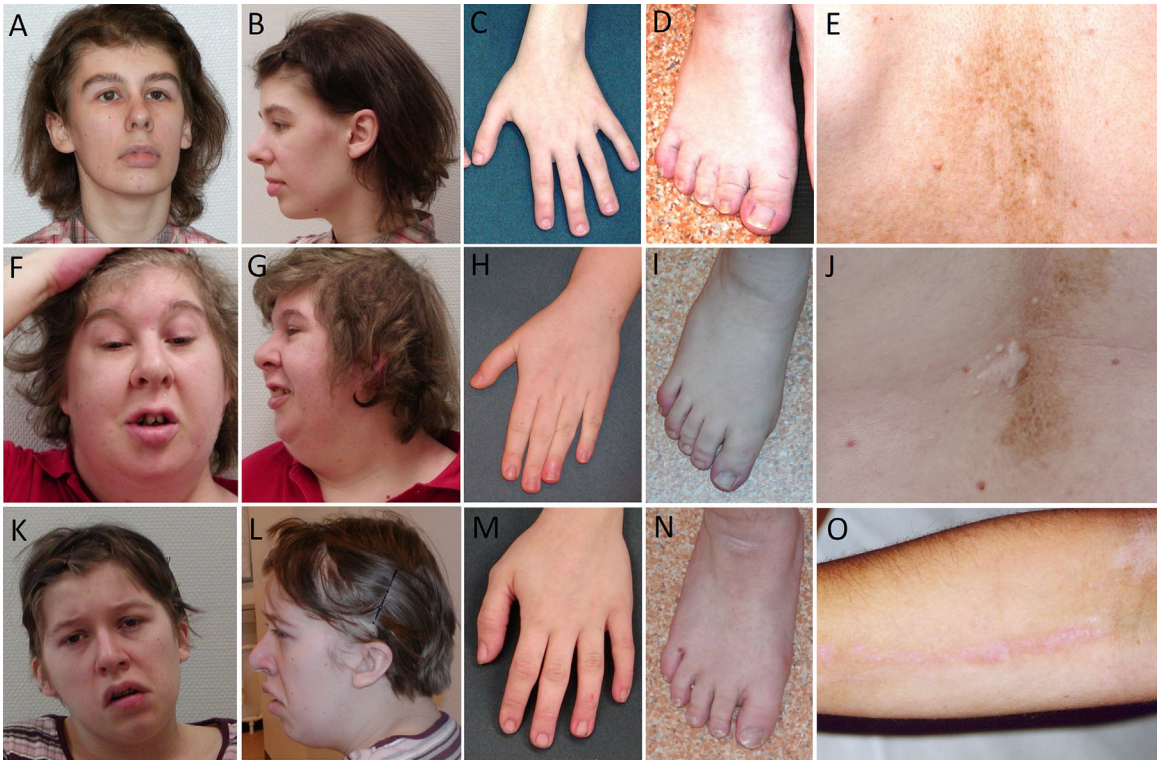

FIGURE 1 Phenotypes of patients with suspected HHID syndrome at clinical reinvestigation after about 10 years. Facial gestalt, hand and foot, and a location with hyperkeratotic plaques is shown for P1 at the age of 25 years (A-E), for P2 at the age of 26 years (F-J), and for P3 at the age of 19 years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

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

hyperkeratotic plaques, which may become only obvious with increasing age.

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