# Two *SMARCAD1* Variants Causing Basan Syndrome in a Canadian and a Dutch Family

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Basan syndrome is an autosomal dominant genodermatosis characterized by congenital adermatoglyphia, transient congenital facial milia, neonatal acral bullae, and absent or reduced sweating. Basan syndrome is rare and has been reported in only 10 kindreds worldwide. It is caused by variants in the skin-specific isoform of *SMARCAD1*, which starts with an alternative exon 1. All reported variants, except for one large deletion, are point mutations within the donor splice site of the alternative exon 1. In this paper, we report two families with Basan syndrome and describe two *SMARCAD1* variants. In one family, we have identified a complex structural variant (a deletion and a nontandem inverted duplication) using whole-genome optical mapping and whole-genome sequencing. Although this variant results in the removal of the first nine exons of *SMARCAD1* and exon 1 of the skin-specific isoform, it manifested in the typical Basan phenotype. This suggests that unlike the skin-specific isoform, a single copy of full-length *SMARCAD1* is sufficient for its respective function. In the second family, whole-exome sequencing revealed a deletion of 12 base pairs spanning the exon–intron junction of the alternative exon 1 of the skin-specific *SMARCAD1* isoform. In conclusion, we report two additional families with Basan syndrome and describe two *SMARCAD1* pathogenic variants.

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## INTRODUCTION

Basan syndrome (Online Mendelian Inheritance in Man #129200; also known as Basan-Baird syndrome) is a rare genodermatosis characterized by congenital adermatoglyphia (congenital absence of epidermal ridges and fingerprints), transient congenital facial milia, rapidly healing neonatal acral bullae, and absent or reduced sweating (Baird, 1964; Basan, 1965). It is an autosomal dominant disorder with high penetrance and variable expressivity. Variable features include palmoplantar keratoderma, syndactyly, clinodactyly, tapered fingers, hyperpigmented macules on the hands and feet, flexion contractures of the digits, nail dystrophy, and single transverse palmar crease (Baird, 1964; Basan, 1965; Límová et al., 1993). Since first described by Baird in 1964, the condition has been reported in only 10 kindreds worldwide (Table 1) (Baird, 1964; Basan, 1965; Chang et al., 2018; Gagey-Caron et al., 2009; Li et al., 2016; Límová et al., 1993; Luna and Larralde, 2012; Marks et al., 2014; Reed and Schreiner, 1983; Valentin et al., 2018).

Basan syndrome is caused by heterozygous variants in the skin-specific isoform of *SMARCAD1* (Online Mendelian Inheritance in Man #612761) (Marks et al., 2014; Li et al., 2016; Valentin et al., 2018). *SMARCAD1* encodes a highly conserved chromatin remodeler and a member of the SNF subfamily of helicase proteins (Adra et al., 2000). *SMARCAD1* comprises 24 exons and encodes two isoforms with different transcription start sites: a full-length isoform and a shorter skin-specific isoform (Figure 1a) (Nousbeck et al., 2011). The full-length SMARCAD1 (1,026 amino acids) is ubiquitously expressed in adult and fetal tissues and controls the expression of several transcription factors and histone modifiers (Costelloe et al., 2012; Okazaki et al., 2008). It is localized mainly in the nucleus and plays a critical role in chromatin remodeling, in homologous recombination repair of DNA double-strand breaks, and in genome stability (Adra et al., 2000; Costelloe et al., 2012; Okazaki et al., 2008). Mouse knock-out for the mouse homolog, *Smarcad1*, results in prenatal and perinatal lethality, reduced fertility, growth retardation, and skeletal abnormalities (Schoor et al., 1999).

The short isoform is encoded by an alternative exon 1, located in intron 9 of the long isoform, and exons 10–24 of full-length *SMARCAD1* (Nousbeck et al., 2011). It contains 596 amino acids (corresponding to amino acids 431–1,026 of the full length) and retains the helicase adenosine triphosphate–binding domain, helicase C-terminal domain, and the nuclear localization signal (Figure 1b). It is expressed predominantly in the skin and nails and, to a lesser extent, the esophagus (Nousbeck et al., 2011). However, little is known about its function(s) and mechanism of action. It is worth noting that there is no counterpart for the human skin-specific isoform in mouse *Smarcad1* (University of California Santa Cruz Genome Browser on Mouse, mm10).

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*Abbreviations: bp, base pair; kb, kilobase*

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**Table 1. Summary of Clinical Features of Basan Syndrome Described in Previous Literature**

| Phenotype and Genotype | Baird (1964) N = 13 | Basan (1965) N = 8 | Reed and Schreiner (1983) N = 4[1] | Límová et al. (1993) N = 3 | Gagey-Caron et al. (2009) N = 3 | Luna and Larralde (2012) N = 5 | Marks et al. (2014) and Adra et al. (2000) N = 7 | Li et al. (2016) N = 8 | Chang et al. (2018) N = 2[2] N = 4[3] | Valentin et al. (2018) N=1 | This study C: N = 12 D: N = 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Adermatoglyphia | + (13/13) | + (6/8) | + (4/4) | + (3/3) | + (3/3) | + (5/5) | + (7/7) | + (8/8) | [2] + (2/2) [3] + (3/4) | + (1/1) | C) + (12/12) D) + (3/3) |
| Hypohidrosis | + (13/13) | + (2/8) | + (4/4) | + (3/3) | + (3/3) | − (5/5) | + (2/7) | + (8/8) | n/a | n/a | C) + 12/12 D) + (3/3) |
| Absence of acrosyringia | + (1/13) | n/a | + (1/4) | + (1/3) 1 biopsy | n/a | − (5/5) 1 biopsy | n/a | n/a | n/a | n/a | n/a |
| Acral bullae | n/a | − (8/8) | + (2/4) | + (3/3) | + (2/3) | + (1/5) | + (4/7) | + (8/8) | [2] + (1/2) [3] + (4/4) | + (1/1) | C) + (12/12) D) − (3/3) |
| Congenital milia | + (13/13) | n/a | + (2/4) | − (3/3) | + (2/3) | + (2/5) | + (7/7) | + (8/8) | [2] + (1/2) [3] + (4/4) | + (1/1) | C) + (12/12) D) + (3/3) |
| Contractures of digits | + (7/13) | + (1/8) | − (4/4) | + (3/3) | − (3/3) | n/a | n/a | + (8/8) | [2] + (1/2) [3] + (3/4) | n/a | C) − (12/12) D) − (3/3) |
| Hyperkeratosis | + (1/13) 1 biopsy | + (2/8) | n/a | + (1/3) only 1 examined | + (1/3) | + (1/5) 1 biopsy | n/a | + (2/8) | n/a | + (1/1) | C) − (12/12) D) + (3/3) |
| Calluses | + (2/13) | + (4/8) | + (3/4) Leather like texture | n/a | n/a | + (4/5) | + (2/7) | + (1/8) leather like texture | n/a | n/a | C) − (12/12) D) + (3/3) |
| Nail involvement | − (13/13) | + Onychorrhexis with longitudinal ridges (3/8) Clubbing (3/8) | + Nail plate dystrophy (1/4) | n/a | − (3/3) | + rounded nails (1/5) | n/a | + Nail plate dystrophy (1/8) | n/a | + Onychorrhexis (1/1) | C) − (12/12) D) Onychorrhexis with deep longitudinal ridges + (3/3) Line of Beau + (3/3) Clubbing + (1/3) |
| Transverse palmar crease | − (13/13) | n/a | + (3/4) | n/a | − (3/3) | n/a | n/a | + (1/8) | n/a | n/a | C) − (12/12) D) − (3/3) |
| Additional symptoms | Sensitive to cold and hot weather. Bilateral webbing of the toes (5/13) Contractures of toes (9/13) | Syndactyly (5/8) Dot pattern warts (3/8) | Increased tolerance to heat (3/4) Acral sites get cold faster (3/4) Tapered fingertips (1/4) | Fine grasping difficulties (3/3) Tapered fingers (1/3) Contractures of toes (3/3) | Hypopigmented macules at the sites of previous blisters on hands and feet (2/3) | Bilateral syndactyly of fingers and toes (3/5) | n/a | Hyperpigmented macules (5/8) Knuckle pads (7/8) | [2]Bilateral syndactyly of the toes (1/2) [2/3]Clinodactyly of fifth digit (5/6) | Hyperpigmented macules (1/1) | C) Susceptibility to heat strokes (12/12) Webbing of fingers (4/12) D) Hypopigmented macules (3/3) Tapered fingertips (3/3) Knuckle pads (2/3) |
| *SMARCAD1* mutation | n/a | n/a | n/a | n/a | n/a | n/a | c.378+3A>T | c.378+1G>T | [2]Deletion 116 kb [3]c.378+5G>A | c.378+2T>G | C) complex rearrangement D) c.374_378+7del |

Abbreviations: C, Canadian; D, Dutch; del, deletion; kb, kilobase; n/a, not applicable.

[1]Family members available for examination.

[2]Descendants from the original Baird kindred.

[3]Second unrelated family.

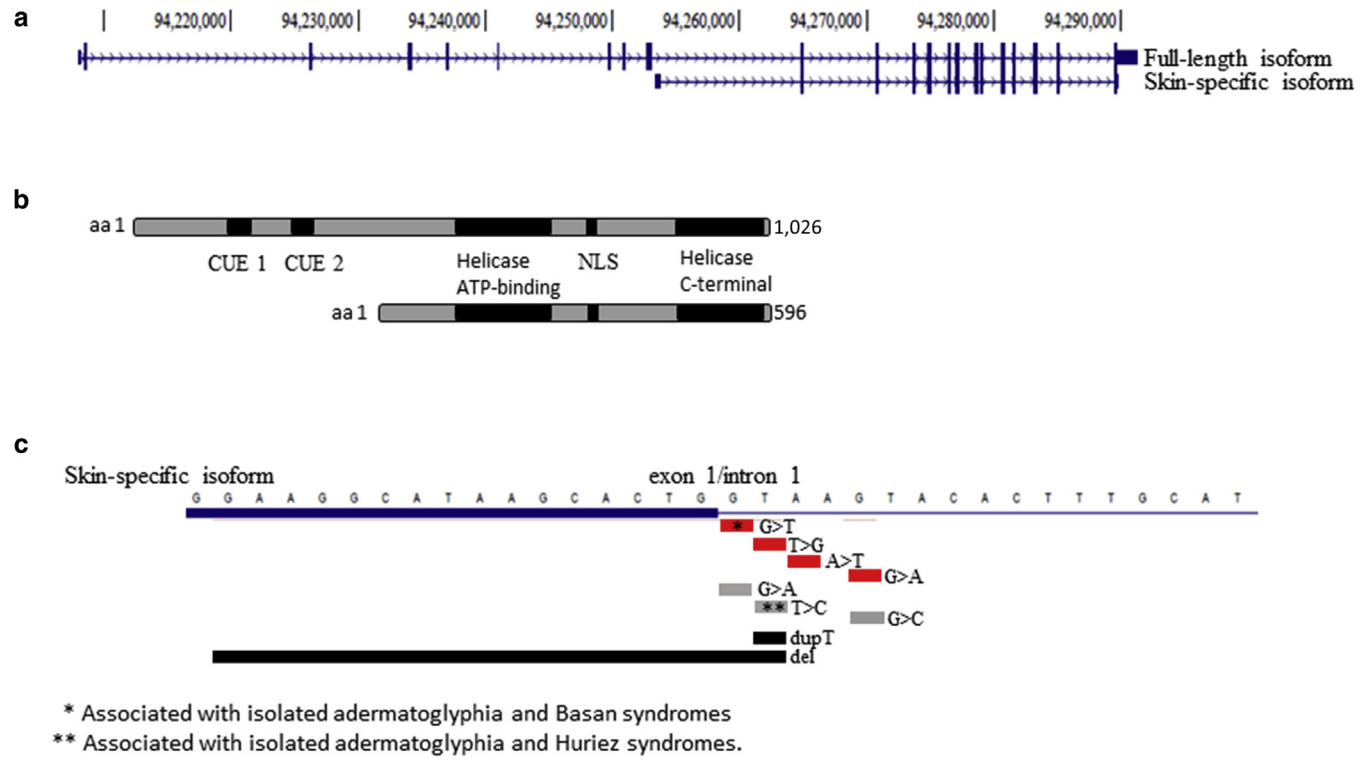


**Figure 1. *SMARCAD1* isoforms and mutational hotspot.** (**a**) The skin-specific isoform of *SMARCAD1,* encoded by an alternative exon 1, lacks exons 1−9 of the full-length isoform. (**b**) The skin-specific isoform protein (596 aa), starting at aa 431 of the full-length protein, lacks the two couplings of ubiquitin CUE domains but retains the two helicase domains and the NLS. (**c**) Previously reported mutations at the donor splice site of exon 1 of the skin-specific isoform associated with Basan (red), isolated adermatoglyphia (gray), and Huriez (black) syndromes. aa, amino acid; ATP, adenosine triphosphate; CUE, conjugation to endoplasmic reticulum degradation; del, deletion; dup, duplicate; NLS, nuclear localization signal.

Heterozygous variants in the skin-specific isoform are associated with three allelic autosomal dominant syndromes: Basan syndrome, isolated adermatoglyphia (Online Mendelian Inheritance in Man #136000), and Huriez syndrome (Online Mendelian Inheritance in Man #81600) (Burger et al., 2011; Lee et al., 2000; Marks et al., 2014; Nousbeck et al., 2011; Valentin et al., 2018). The three syndromes are characterized by adermatoglyphia and overlap in other clinical features (Günther et al., 2018). Huriez syndrome is characterized by a more severe phenotype, including congenital scleroatrophy of the hands and feet, palmoplantar keratoderma, nail changes, and an increased risk of cutaneous squamous cell carcinoma in affected areas of the skin (Günther et al., 2018; Lee et al., 2000). These data indicate a critical role for *SMARCAD1* skin isoform in the formation of dermatoglyphs. This also indicates that this isoform is expressed in early embryogenesis because dermatoglyphs are fully formed and become permanent by the 24th week of gestation (Babler, 1991).

To date, only five variants have been identified in patients with Basan syndrome. These variants involve the same conserved donor splice site at the 3′ end of exon 1 of the skin-specific isoform and result in haploinsufficiency for this isoform (Chang et al., 2018; Li et al., 2016; Luna and Larralde, 2012; Marks et al., 2014; Valentin et al., 2018). Four of the reported variants are point mutations located within the splice site consensus: c.378+1G>T, c.378+2T>G, c.378+3A>T, and c.378+5G>A (Figure 1c). The fifth variant is a large (116 kilobase [kb]) deletion spanning the same splice site (Chang et al., 2018).

In this study, we report two additional families with Basan syndrome: a Canadian and a Dutch family. We describe two *SMARCAD1* variants causing Basan phenotype in these families: a deletion of 12 base pairs (bps) affecting the skin-specific isoform and a complex rearrangement involving the full length and skin-specific isoforms.

## RESULTS

Two unrelated families—a Canadian family and a Dutch family—have been diagnosed with Basan syndrome (Figure 2). The probands of the Canadian family (V:2 and V:3) were dizygotic twin neonates and presented with congenital adermatoglyphia and multiple milia on the chin (Figure 3). Both developed blistering near the ankles at birth that healed within days. A five-generation detailed family history revealed >10 affected members from the maternal side (Figure 2a). In addition to adermatoglyphia, all affected members (n = 12) had transient milia on the face and blisters at birth and suffered from lack of sweat and susceptibility to heat strokes (Table 1). Four affected members (II:1, II:3, IV:2, IV:3) had webbing of the fingers. All affected individuals had normal nails, hair, teeth, and skin pigmentation.

The Dutch family consists of a mother and her two children (Figure 2b). In 2017, the mother, aged 39 years, presented at the dermatology clinic with palmoplantar adermatoglyphia and complaints of dry skin (Figure 4a). The patient also

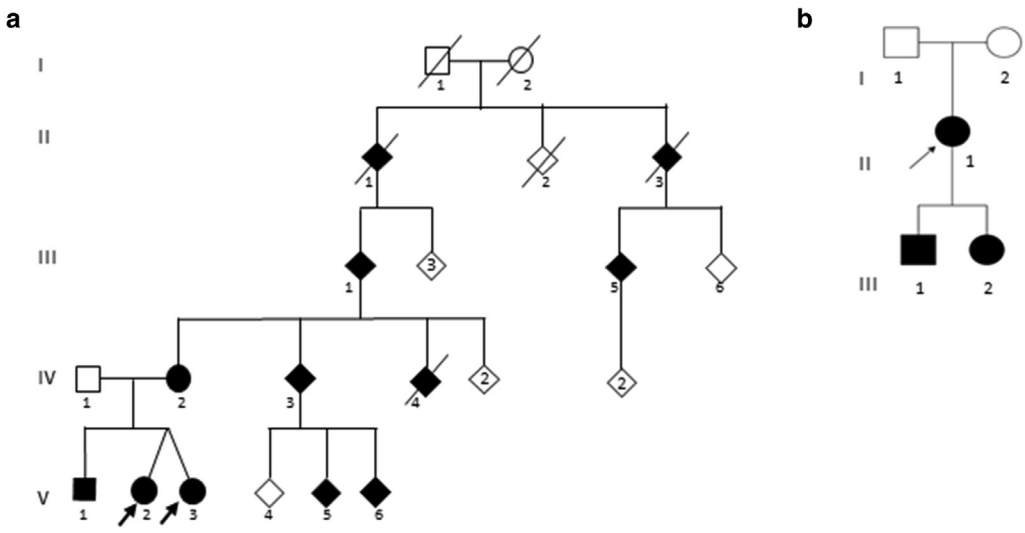


**Figure 2. Family pedigrees for a Canadian family and a Dutch family with Basan syndrome.** (**a**) Family history revealed a total of 12 (7 females and 5 males) affected members of the Canadian family. Sexes of the extended family members are not shown for confidentiality. (**b**) Three members were affected in the Dutch family. The probands are indicated by arrows.

noticed a frequent onion-like smell due to the dry skin. At birth, she had transient milia, which spontaneously disappeared in the first year of life, and hypopigmented macules that faded over the course of several years. In addition, painful palmoplantar punctate keratoderma and hyperkeratosis in combination with calluses have been (and still are) present since birth. She has never had acral bullae. Physical examination showed adermatoglyphia, hypohidrosis, tapered fingertips and palmar and plantar xerosis, and punctate hyperkeratosis. Onychorrhexis with deep longitudinal ridges and Beau lines were also seen. The fingernails showed clubbing on the second and fifth digit of the right hand. No

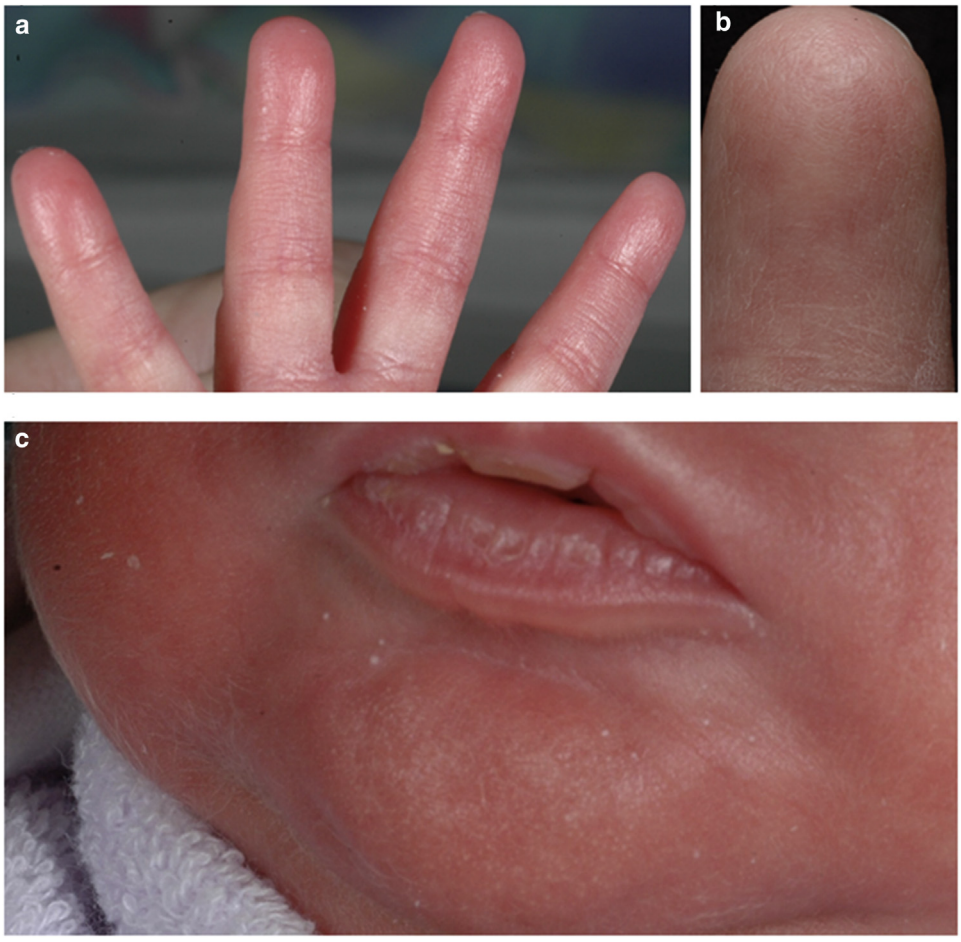


**Figure 3. The Canadian probands.** Dizygotic twins presented with (**a, b**) congenital adermatoglyphia and (**c**) multiple milia on the chin. Consent for the publication of these images was obtained from the proband's mother.

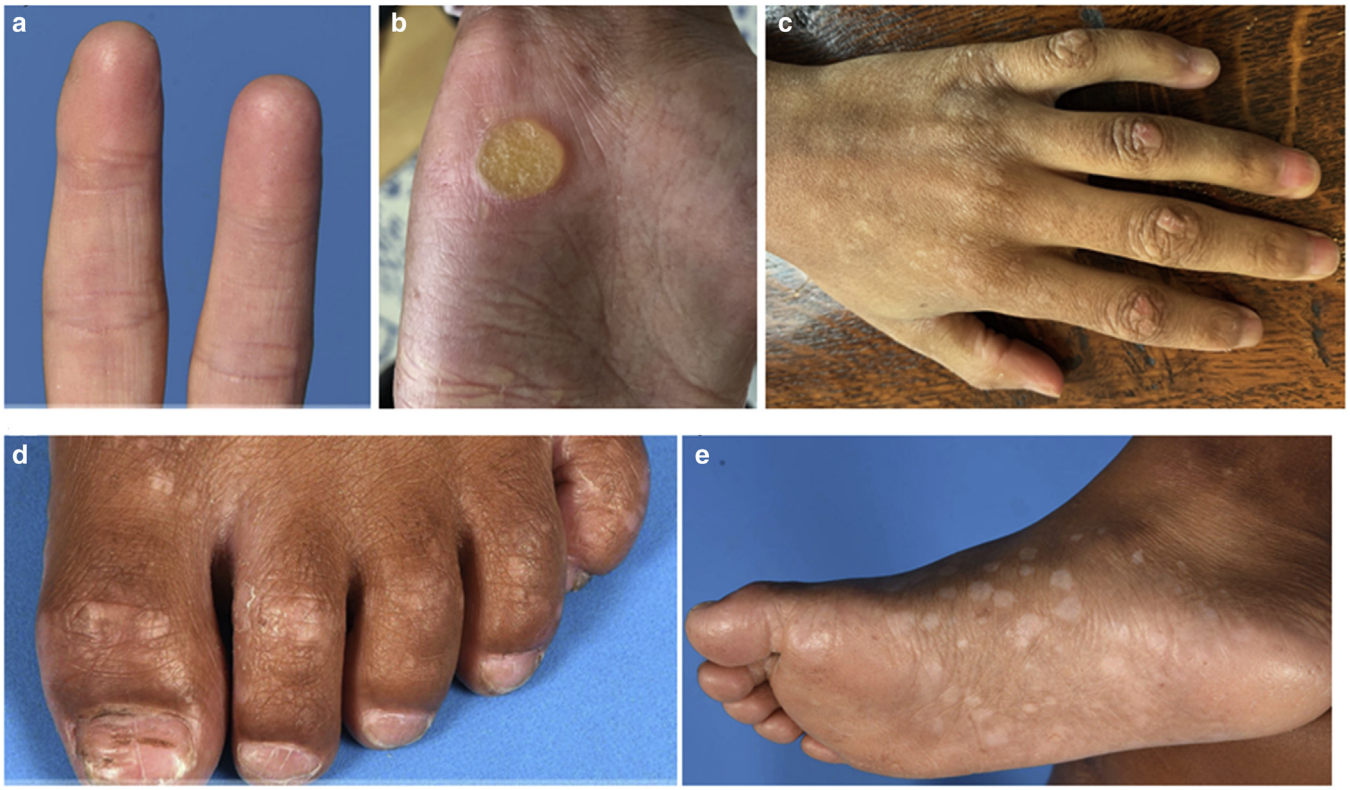


**Figure 4. Basan syndrome phenotypes in the Dutch family.** (**a**) Adermatoglyphia in the proband; (**b**) daughter's palm showing sharply demarcated hyperkeratotic plaque of 2 cm and dry scaly skin; (**c**) son's hand showing sharply-to-moderate demarcated skin to pink colored dry scaly soft papules on the dorsal side of the proximal interphalangeal joints (knuckle pads), sharply-to-moderate demarcated skin-colored flat soft papules on the dorsal side of the proximal interphalangeal phalanx and metacarpophalangeal joints, and moderate to poorly demarcated irregularly formed hypopigmented maculae on the dorsal side of the hand; (**d**) son's foot showing moderate to poorly demarcated hypopigmented maculae on the dorsal side of the toes and Beau's lines on toenail I; and (**e**) son's foot showing sharply-to-moderate demarcated regularly formed hypopigmented maculae on the medial side of the edge and sole and dry scaly skin and punctate hyperkeratosis on the toes and sole. Consent for the publication of these images was obtained from the proband.

transverse crease of the palm was observed. Her hair, nipples, mouth, and teeth revealed no abnormalities. The daughter and son, aged 10 and 7 years, respectively, were also affected and showed similar clinical features: adermatoglyphia; congenital milia; xerosis; punctate hyperkeratosis; hypopigmented macules on both hands, wrists, and feet; tapered fingertips; and the line of Beau on the toenails (Figure 4b–e). In addition, callosities were observed on their palms, wrists, and soles of the feet. Sharply-to-moderate demarcated skin to pink colored dry scaly soft papules were present on the dorsal side of the proximal interphalangeal joints (knuckle pads), and sharply-to-moderate demarcated skin-colored flat soft papules were present on the dorsal side of the proximal interphalangeal phalanx and metacarpophalangeal joints. They both have a Fitzpatrick skin type IV similar to their father, and no other abnormalities regarding their hair, mouth, or teeth were identified. No other family members were affected.

### Identification of two *SMARCAD1* variants

Whole-exome and whole-genome sequencing and structural variant analysis revealed two variants: a complex rearrangement in a Canadian family and a 12-bp deletion in a Dutch family. To our knowledge, both variants have not been previously reported.

### A complex *SMARCAD1* rearrangement causing Basan syndrome in the Canadian family

Targeted Sanger sequencing of the region spanning *SMARCAD1* hotspot, the donor splice site of exon 1 of *SMARCAD1* skin-specific isoform, was performed for one of the probands, and it revealed no variant. We then investigated other possible variants by performing a Trio Whole-Exome Sequencing (proband V:2, affected mother IV:2, and unaffected father IV:1). No candidate pathogenic variants were identified. This raised the possibility of a noncoding or a structural variant as the underlying cause of Basan phenotype in this family. To assess this, we performed Whole-Genome Sequencing and Whole-Genome Optical Mapping (BioNano Saphyr platform; Bionano Genomics, San Diego, CA) for one of the probands.

BioNano Optical Mapping data analysis predicted a heterozygous deletion of ~28.1 kb located within the region hg38 chr4:94,165,620-chr4:94,255,257 (Figure 5a). This region is mapped to the 5′ end of *SMARCAD1* and its upstream sequences. Further copy number variation analysis using genome sequencing data revealed a more complex structural rearrangement within this region (a deletion of ~50.9 kb and a duplication of ~23.4 kb) (Figure 5b). The predicted structural variants were confirmed first by PCR using primers specific for each of the predicted variants and then by Sanger sequencing to determine all the breakpoints (Figure 5c and

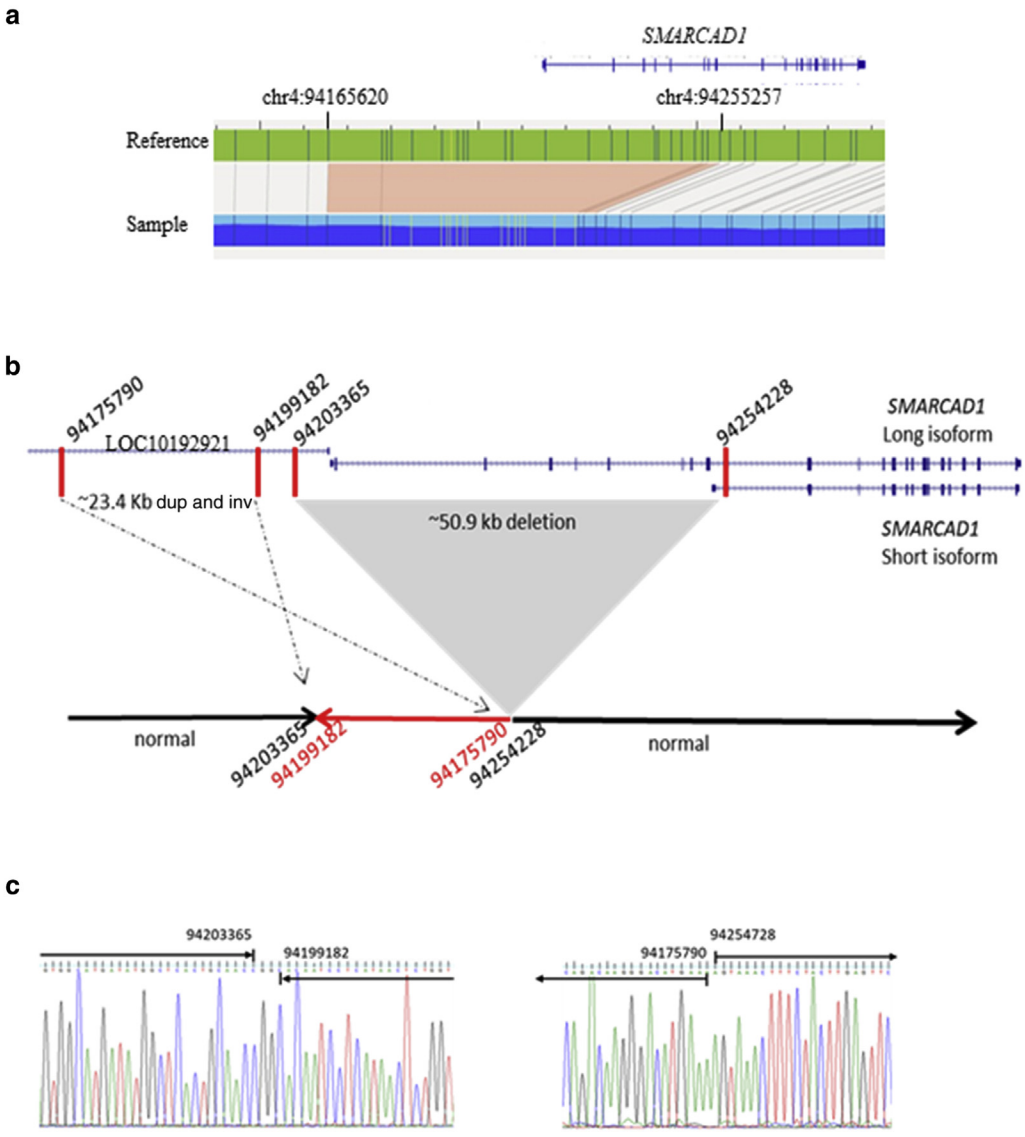


**Figure 5. A complex rearrangement involving *SMARCAD1* in the Canadian family.** (**a**) BioNano Optical Mapping for the Canadian probands' mother (IV:2). Assembled genome map (blue bar) is aligned to the reference (green bar). The location of *SMARCAD1* is shown (top). The gray lines indicate the alignment between the reference and the assembled sample map. The light red area indicates a deletion within the region (chr4:94165620-94255257). (**b**) The variant includes a deletion of ~50.9 kb and an inverted duplication of ~23.4 kb. The deletion encompasses exons 1–9 of *SMARCAD1* long isoform and exon 1 of the short isoform and includes the first exon of the long noncoding RNA (LOC101929210). (**c**) Sanger sequencing showing the rearrangement breakpoints. There was also an insertion of two nucleotides (GG) at the 5′ breakpoint. chr, chromosome; dup, duplicate; inv, inversion; kb, kilobase.

Table 2). The deletion comprises ~50.9-kb region (hg38 chr4:94,203365-94,254,728). It encompasses exons 1—9 of *SMARCAD1* long isoform and exon 1 of the short isoform and includes the known mutational hotspot at the donor splice site of the alternative exon 1. The deletion also includes the first exon of a long noncoding RNA (LOC101929210) located upstream of *SMARCAD1*. The duplication, comprising ~23.4-kb region, is located in intron 1 of the long noncoding RNA (hg38 chr4:94,175,790-94, 199182). The duplication is an inverted nontandem duplication. The inverted copy is inserted downstream at position chr4:94,203365, replacing the 50.1-kb deletion. The size of the duplication (~23.4 kb) may account for and explain the difference between the optical mapping predicted deletion (~28 kb) and the actual deletion size (~51 kb)

### A deletion in *SMARCAD1* short isoform causing Basan syndrome in the Dutch family

Whole-exome sequencing for the Dutch proband revealed a 12-bp deletion (c.374_378+7del) spanning the exon/intron junction of *SMARCAD1* short isoform (Figure 6). The deletion was confirmed by Sanger sequencing and includes the last five nucleotides of the exon and the first seven nucleotides of the intron, thus abolishing the donor splice site.

## DISCUSSION

Pathogenic variants in *SMARCAD1* skin-specific isoform are associated with three syndromes with overlapping features: isolated adermatoglyphia, Basan syndrome, and Huriez syndrome (Burger et al., 2011; Lee et al., 2000; Marks et al., 2014; Nousbeck et al., 2011; Valentin et al., 2018). All reported *SMARCAD1* skin-specific isoform variants involve the donor splice site of exon 1 and result in a complete loss of expression of the skin-specific isoform (Figure 1c) (Günther et al., 2018; Nousbeck et al., 2011). These data indicate that haploinsufficiency for the skin-specific isoform is the common underlying cause for isolated adermatoglyphia, Basan, and Huriez phenotypes. Interestingly, the same *SMARCAD1* variant may result in different syndromes in different families. For example, one variant, c.378+1G>T, has been reported in a family with Basan syndrome and in

**Table 2. Primers Used to Confirm and Define the Exact Breakpoints for *SMARCAD1* Variant in the Canadian Family**

| Primer | Sequence | Start | Strand | PCR Product |
|---|---|---|---|---|
| smrcd-5′Jun-F | GAGTCACAATCGTTTTCCCCA | 94202893 | + | 973 bp |
| smrcd 5′Jun-R | GGCCGGCAGATCACAAGA | 94198687 | + | — |
| smrcd 5′Jun-SeqR | TAGCAAAACTGGCAGATAGTTACC | 94199030 | + | — |
| smrcd-3′Jun-F | AGACAGGCCACTAGCTTAGA | 94176571 | − | 1,415 bp |
| smrcd-3′Jun-R | ACTTTATTCACGGGCTCAAGT | 94255319 | − | — |

Abbreviation: bp, base pair.
Primers' locations on the reference genome (hg38) and the variant-specific PCR product sizes are listed.

another with isolated adermatoglyphia (Li et al., 2016; Nousbeck et al., 2011). Another variant, c.378+2T>C, has been associated with isolated adermatoglyphia and with Huriez syndrome (Günther et al., 2018; Nousbeck et al., 2011). In addition, whereas the 12-bp deletion (c.374_378+7del) identified in this study is associated with Basan syndrome, an overlapping 18-bp deletion (c.363_378+2del) was previously reported in a family with Huriez syndrome (Günther et al., 2018). Recently, Valentin et al. (2018) suggested that adermatoglyphia and Basan syndrome are variable expressions of a single syndrome for which they proposed the name SMARCAD syndrome (SMARCAD1-associated, congenital facial milia, adermatoglyphia, reduced sweating, contractures, acral bullae, and dystrophy of the nails syndrome). We suggest that Huriez syndrome belongs to the same group and may represent the severe end of the same phenotypic spectrum.

The markedly different manifestations of *SMARCAD1* variants raise the possibility of a modifier polymorphism in *SMARCAD1* or in other genes. However, it is important to note that no single family has been reported with >1 of these syndromes, implying that the modifying factor cosegregates with the causative variant. We suggest that if modifier polymorphism(s) exist, they should therefore be located within the mutant *SMARCAD1* allele or in its linked flanking region.

The complex structural rearrangement identified in the Canadian family is intriguing. Although the loss of function affects both *SMARCAD1* isoforms as well as the adjacent long noncoding RNA (LOC101929210), the variant resulted in the typical Basan phenotype with no additional manifestations or increased severity. A similar finding was reported by Chang et al. (2018) where a large deletion involving both isoforms was associated with the typical Basan phenotype. Thus, unlike the skin-specific isoform, a single copy of *SMARCAD1* full length appears to be sufficient for its respective function.

*SMARCAD1* is located on chromosome 4 (4q22) within a common fragile site (FRA4F) (Rozier et al., 2004). Fragile sites are chromosomal loci where spontaneous rearrangements are common and have been associated with different diseases (Rozier et al., 2004). It is surprising that rearrangements in *SMARCAD1* have not been reported previously. One speculation is that many cases of isolated adermatoglyphia and Basan syndromes are not reported, given the benign nature of these syndromes. In addition, the structural variants that occur at the 5′ portion of *SMARCAD1* may be asymptomatic because the skin-specific isoform would be spared.

In conclusion, we report two new families with Basan syndrome and describe their clinical phenotypes. We have identified two *SMARCAD1*, to our knowledge, previously unreported variants associated with Basan syndrome. Most of the previously reported *SMARCAD1* variants are point mutations; in this study, we describe a complex structural variant (a deletion, a nontandem duplication, and an inversion) in a Canadian family and a 12-bp deletion overlapping the donor splice site of exon 1 of the skin-specific isoform in a Dutch family.

## MATERIALS AND METHODS

The study and research protocols were approved by the Dalhousie University (Halifax, Nova Scotia, Canada) Research Ethics Board. Family history was obtained from the probands' mother for the Canadian family and from the proband for the Dutch family. All participating members or their legal guardians signed informed written consent to perform the analysis and to publish the results, including family pedigrees. Consent for the publication of the images was obtained from the guardians. Saliva and/or blood samples were collected from eight affected and eight unaffected members of the Canadian family and from the proband of the Dutch family.

For the Canadian family, whole-exome and whole-genome sequencing were performed at Genewiz (South Plainfield, NJ). Data analysis was performed at the genomics core facility at Dalhousie University on the basis of GRCh38 and/or University of California Santa Cruz hg38 assembly and following the Best Practices workflow from the Broad Institute (Cambridge, MA) using Burrows-Wheeler Alignment, Picard, and the Genome Analysis Toolkit. Variants were annotated and filtered using a combination of snpEff and GEMINI. PCR and Sanger sequencing of *SMARCAD1* hotspot region, the donor splice site of exon 1 of the skin-specific isoform, was performed as previously described (Valentin et al., 2018). Primers used to define the exact junctions for *SMARCAD1* rearrangement in the Canadian family are shown in Table 2.

For the Dutch family, whole-exome sequencing was performed at GenomeScan (Leiden, The Netherlands), Agilent SureSelectXT Human all Exon, version 5 (Agilent Technologies, Santa Clara, CA), and Hiseq4000 (Illumina, San Diego, CA). Data analysis was performed at the Clinical Genetics department (Leiden University Medical Center, The Netherlands) using an in-house sequence analysis pipeline (Modular Genome Analysis Toolkit-Based Variant Calling Pipeline) on the basis of read alignment using Burrows-Wheeler Alignment, variant calling using Genome Analysis Toolkit, and

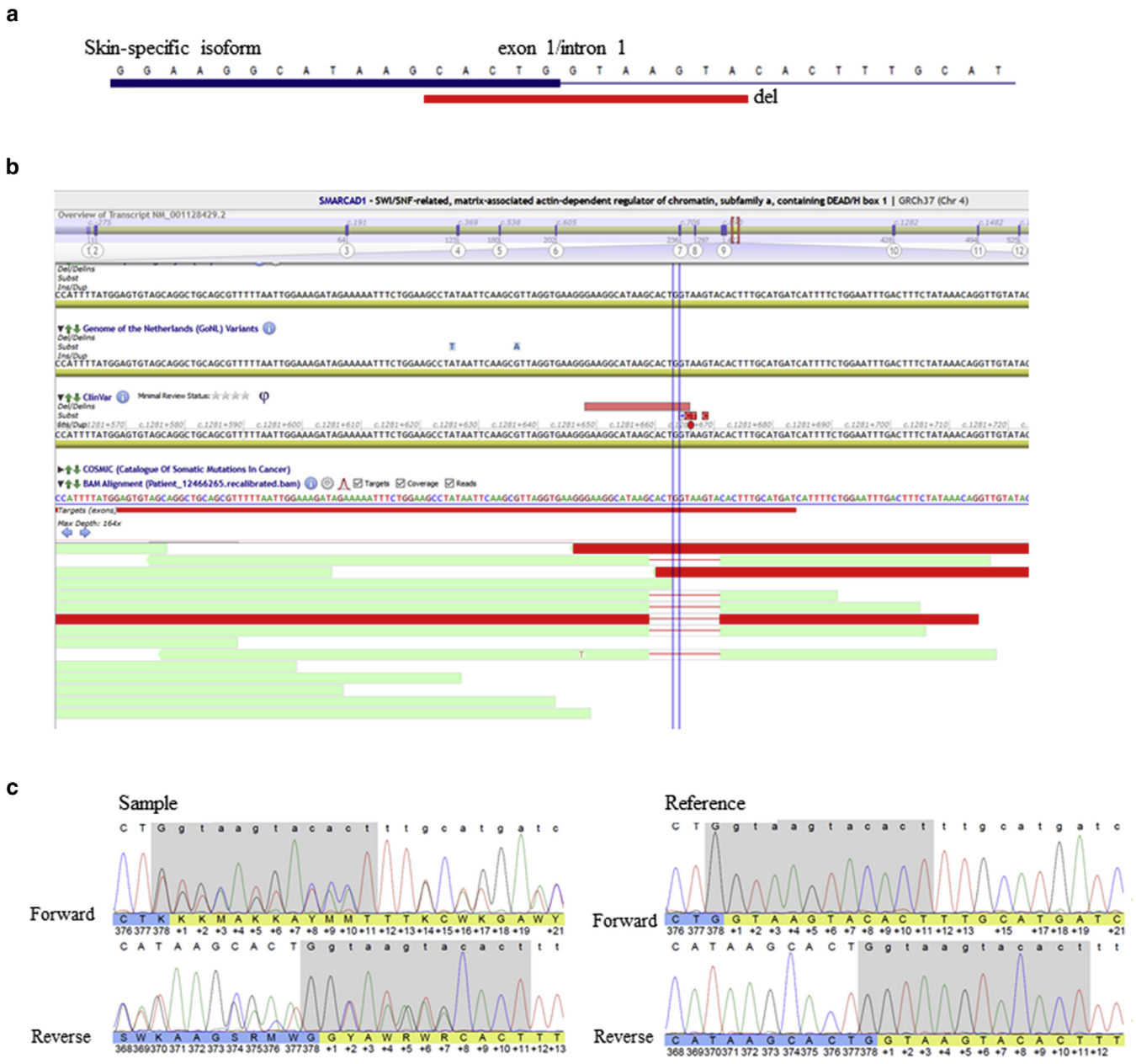


**Figure 6. A 12-bp del in *SMARCAD1* (c.374_378+7del) was identified in the Dutch family.** (**a**) The del (red) spans the exon–intron junction of exon 1 of *SMARCAD1* short isoform. (**b, c**) BAM file visualization using Alamut Visual software and Sanger sequencing confirmation of the del. bp, base pair; chr, chromosome; del, deletion.

variant annotation using the Variant Effect Predictor. LOVDplus (Leiden Genome Technology Center, Leiden University Medical Center) was used for filtering and interpretation of the variants.

Whole-genome optical mapping was performed at HistoGenetics LLC (Ossining, NY) using the BioNano Saphyr platform (Bionano Genomics). Optical mapping utilizes enzymes to label high molecular-weight DNA and generates high-resolution physical genome maps (Mantere et al., 2020[1]). Changes in patterning or spacing of the labels are detected to identify copy number variations, translocations, and inversions. To isolate a high molecular DNA, a fresh blood sample was collected from the Canadian probands' mother (IV:2, Figure 1a). The sample was immediately placed on ice and shipped to HistoGenetics LLC laboratory. Visualization and analysis of mapping data were performed with BioNano Access software (Bionano Genomics).

## Data availability statement

Datasets related to this article can be found at https://www.ncbi.nlm.nih.gov/sra/?term=PRJNA698009 hosted at the National Center for Biotechnology Information for the Canadian variant and at https://www.deciphergenomics.org/patient/429056 for the Dutch variant.

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## CONFLICT OF INTEREST

The authors state no conflict of interest.

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