Heterozygous Deletion Impacting *SMARCAD1* in the Original Kindred with Absent Dermatoglyphs and Associated Features (Baird, 1964)

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In 1964, Baird described a family with adermatoglyphia, facial milia, and skin fragility. Using whole exome sequencing, genotyping, and Sanger sequencing, we identified a 116-kb heterozygous deletion involving exons 1-9 of SMARCAD1 in descendants of this kindred. This contrasts with point mutations within exon 9 in all other reported families. *(J Pediatr 2017;■■:■■-■■).*

Individuals lacking fingerprints are rare and often come to attention owing to problems with travel or immigration.[1] There are a few hereditary skin disorders with adermatoglyphia (ADG), all with an autosomal-dominant inheritance: isolated ADG (OMIM #136000); Basan-Baird syndrome (BBS, also known as Basan syndrome, OMIM #129200) with ADG, skin fragility, contractures, and transient milia; and Naegeli-Franceschetti-Jadassohn syndrome (OMIM #16100) with ADG, diminished sweating, reticular hyperpigmentation of skin, and hyperkeratosis of the palms and soles.[2-5] *KRT14* mutations have been identified in Naegeli-Franceschetti-Jadassohn syndrome, and *SMARCAD1* mutations are reported in both isolated ADG and BBS.

In 1964, Baird described in *The Journal*[6] a Philadelphia area Irish-American family in which 13 members in 3 generations showed absent dermal ridges. Some affected family members showed partial flexion contractures of the fingers and toes, and some showed webbing of the toes. Affected persons all had transient milia on the face and blistering on their palms and soles at birth. Skin fragility continued through childhood for some. Hair, teeth, and nails were normal. The same features were identified in a different family by Basan in 1965,[7] leading to the name BBS, with fewer than 10 families reported since then. Members of Baird's original family came to clinical attention again in 1995[8] and now, as we identify a large heterozygous deletion in *SMARCAD1*. We additionally describe a previously unreported 3-generation kindred with BBS.

Methods

A 13-day-old girl presented with blisters on hands and feet, ADG, facial milia, bilateral syndactyly of the toes, and fifth digit clinodactyly (**Figure 1**, A and B; **Figure 1**, D, subject V-1). Her father (**Figure 1**, D, subject IV-3) also has ADG, clinodactyly, and finger contractures (**Figure 1**, C). A detailed family history revealed that additional members of the father's family were affected, and the father identified his aunt as individual III-5 in Baird's 1964 study (**Figure 1**, D) from her photograph.[6]

A second unrelated family with a nearly identical phenotype presented with a 1-week-old boy with extensive blistering of the hands, feet, and knees as well as facial milia (**Figure 2**, A and B; available at www.jpeds.com). His mother, older brother, and grandfather had similar blistering and milia at birth and ADG, flexion contractures of the hands, and fifth digit clinodactyly (**Figure 2**, C-E).

Whole exome sequencing using Agilent SureSelect Human All Exon Kit (Agilent Technologies, Santa Clara, California) was performed. Hiseq2000 platform (Illumina, San Diego, California) started paired-end sequencing with read lengths of 90 bp. Illumina base-calling software V.1.7 was applied to process raw image files for base calling.

Sequencing reads were aligned to the human reference genome (UCSC hg19) with Burrows–Wheeler Aligner (BWA, version 0.7.13, Massachusetts Institute of Technology, Cambridge, MA).[9] Local realignment of reads containing indel sites and base quality score recalibration were performed with the Genome Analysis Tool Kit (GATK, version 3.5, Broad Institute, Cambridge MA).[10] Single nucleotide variation and small indels were called with a GATK UnifiedGenotyper. Read depth were called with GATK DepthOfCoverage.

Copy number variations (CNVs) are structural genome variations including deletions or duplications. CNV was predicted by using the exome hidden Markov model (XHMM, Yokohama City University School of Medicine, Yokohama, Japan) software.[11] To generate CNVs with high confidence, the whole exome sequence data of the original BBS trio and 387

ADG	Adermatoglyphia
BBS	Basan-Baird syndrome
lncRNA	Long noncoding RNA
PCR	Polymerase chain reaction
TSS	Transcription start site

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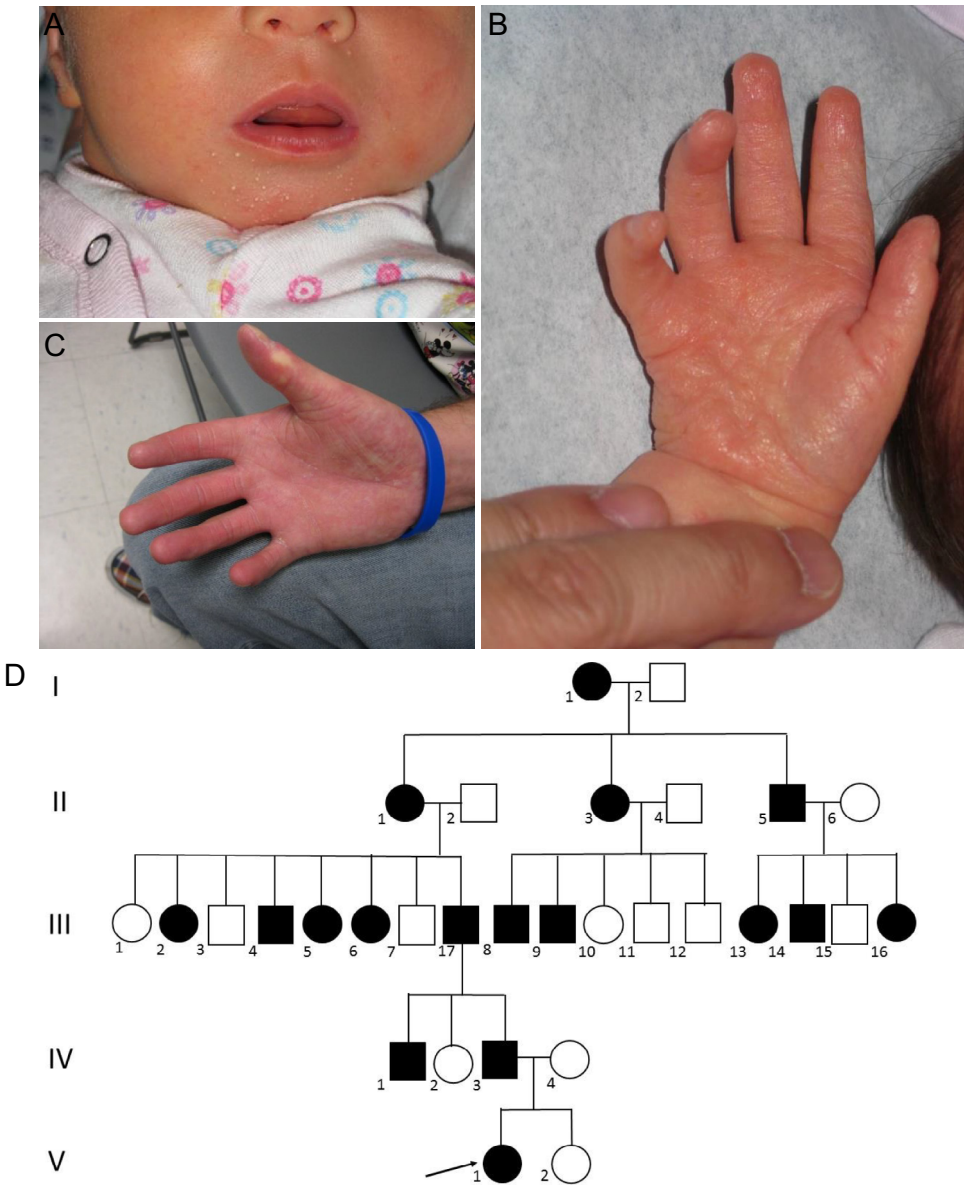

Figure 1. Descendants of the original Baird kindred. Photographs of index patient with **A,** facial milia, **B,** absent dermatoglyphs and fifth digit clinodactyly. **C,** Photograph of index patient's father with adermatogylphia and contractures of his fingers. **D,** Pedigree of family with arrow head on index patient.

other unrelated individuals were analyzed by XHMM. Target regions with extreme GC content (<10% or >90%) and low complexity regions were filtered out from further analysis.

Universal Probe Library probes (Roche, Indianapolis, Indiana) and corresponding primers were selected using the ProbeFinder v2.49 software (Roche). Hemizygous deletions were determined when quantitative polymerase chain reaction (PCR) relative copy number value for a specific sample normalized to the reference sample was less than 0.75 (**Table**; available at www.jpeds.com). To map the exact deletion breakpoint, primers approximately 118 kb apart flanking the candidate deletion (**Table**) were used to amplify and sequence from family 1 affected subject DNA. Primers flanking the mutation hotspot were used to amplify and sequence from family 2 affected subjects' DNA.

Results

Whole exome sequencing in patient V-1 and her affected father IV-3 did not reveal any candidate single nucleotide variants or small short indels (insertions/deletions), but CNV analysis detected an approximately 45-kb heterozygous deletion (chr4:95,129,542-95,174,582) in the *SMARCAD1* gene (**Figure 3**, A, green bar in **Figure 3**, B; available at www.jpeds.com),

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