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Unmasking of a Recessive *SCARF2* Mutation by a 22q11.12 de novo Deletion in a Patient with Van den Ende-Gupta Syndrome

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Key Words
Arachnocamptodactyly · Blepharophimosis · Congenital contractures · *SCARF2* · Van den Ende-Gupta syndrome

Abstract
Van den Ende-Gupta syndrome (VDEGS) is a congenital condition characterized by craniofacial and skeletal manifestations, specifically blepharophimosis, malar and maxillary hypoplasia, distinctive nose, arachnocamptodactyly, and long slender bones of the hands and feet. To date, only 24 patients have been described. It is generally thought that the syndrome is transmitted by an autosomal recessive mode of inheritance, although evidence for genetic heterogeneity has recently been presented. We report on a girl followed from birth up to 3 years of life with a set of peculiar minor anomalies, arachnocamptodactyly of hands and feet, characteristic of VDEGS in association with a 22q11.12 deletion. Recently, the VDEGS gene was mapped to the DiGeorge syndrome region on 22q11.2, and homozygous mutations in the *SCARF2* gene were identified. We now report the first patient with VDEGS due to compound heterozygosity for the common 22q11.2 microdeletion and a hemizygous *SCARF2* splice site mutation.

Van den Ende-Gupta syndrome (VDEGS; MIM 600920) is a very rare autosomal recessive disease characterized by distinct craniofacial and skeletal anomalies such as blepharophimosis, down-slanted eyes, a flat and wide nasal bridge, malar and/or maxillary hypoplasia, prominent ears, a narrow and beaked nose, an everted lower lip, palatal abnormalities, camptodactyly, arachnodactyly, long thumbs, hallux valgus, flexion contractures, slender ribs, hooked clavicles, and bowed long bones [van den Ende et al., 1992; Bistritzer et al., 1993; Gupta et al., 1995; Phadke et al., 1998; Schweitzer et al., 2003; Guerra et al., 2005; Carr et al., 2007; Leal and Silva, 2009]. In 1992, van den Ende and colleagues first reported a 10-year-old girl, born to consanguineous Brazilian parents, with characteristic features. She had normal intelligence, blepharophimosis, malar hypoplasia, a beaked nose, an everted lower lip, and arachnocamptodactyly of fingers and toes. The authors suggested a 'new' autosomal recessive Marden-Walker-like syndrome. Gupta et al. [1995] reported a 3-year-old girl with similar features whose parents were first cousins. X-ray showed maxillary hypoplasia with a small anterior cranial fossa, slender ribs with lateral ends hooked to the clavicles, an absent glenoid fossa, bowed humeri, ulnae and femora, and rela-

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tively long fibulae. The bones of the hands and feet were relatively long, with the exception of the terminal phalanges which were shortened.

Following these initial observations, Phadke et al. [1998] reported 2 unrelated Indian girls with some features of the condition. Bistritzer et al. [1993] reported 2 double second cousins from an inbred pedigree suspected to have VDEGS. Cardiac examination and general development were normal. One female infant had a prominent clitoris and fused labia. Schweitzer et al. [2003] reported 2 Hispanic brothers born to unrelated parents, who both had distinctive cerebellar enlargement, a new finding for this disorder. Ali et al. [2010] observed cutaneous syndactyly of toes 2 and 3 as a consistent feature in their patients. Further patients with this constellation of anomalies have been reported, reinforcing the hypothesis of an autosomal recessive mode of inheritance [Bistritzer et al., 1993; Schweitzer et al., 2003; Carr et al., 2007; Ali et al., 2010]. Only one report by Leal and Silva [2009] suggested genetic heterogeneity and an autosomal dominant trait based on the observation of 3 affected individuals, 2 brothers and their half-sister, assuming gonadal mosaicism.

The patients affected by VDEGS had a normal karyotype, and FISH for specific 22q11.12 abnormalities performed in 3 cases was normal [Gupta et al., 1995; Schweitzer et al., 2003; Carr et al., 2007]. Recently, Anastasio et al. [2010] mapped VDEGS to the DiGeorge syndrome region on 22q11.2 and identified homozygous mutations in the *SCARF2* gene as the underlying cause in 4 patients from 3 highly inbred Bedouin families. We now report the first patient with VDEGS due to compound heterozygosity for the common 22q11.2 microdeletion and a hemizygous *SCARF2* splice site mutation.

Clinical Report

The female proband is the first child born to a 30-year-old mother and a 32-year-old father. Both parents were healthy and non-consanguineous, and no drugs had been taken during the gestational period. Pregnancy was uneventful except for bilateral clubfeet, mild bilateral pyelectasis, and lack of visualization of opening-closing hand movements observed at 21+6 weeks of gestation by prenatal ultrasound scan. Growth parameters were: biparietal diameter 52 mm (25th–50th centile), head circumference 193 mm (25th–50th centile), abdominal circumference 160 mm (25th–50th centile), femur length 38 mm (50th centile). Cytogenetic analysis performed on a chorionic villous sample was normal female (46,XX).

The girl was delivered by caesarean section at 38 weeks of gestation with an APGAR score of 7–9 at the first and fifth minute. Birth weight was 2,450 g (3rd–10th centile), length 50 cm (50th centile), and head circumference 34 cm (10th centile). At birth, minor facial anomalies were evident including hypertelorism, blepharophimosis, unilateral microphtalmia, corneal opacity, broad nasal bridge, narrow nose, malar hypoplasia, long philtrum, low set and posterior angulated ears, thin vermillion of the lips, microretrognathia, and microstomia. Camptodactyly and arachnodactyly of fingers and toes, proximally set thumb, bilateral clubfeet (most marked on right foot), and cutaneous syndactyly of 2nd/3rd toes bilaterally were also present. In addition, hypo-extensibility of the proximal interphalangeal joints between the second and fifth fingers and self-limiting joint contractures without stiffness at knee and elbow level were observed (fig. 1a, b).

At day 2 of life, she had a transient episode of hypocalcemia (7.8 mg/dl). Cerebral and abdominal ultrasound scans were performed and were both normal. No anomalies were evident in the brainstem auditory evoked response. An ophthalmological examination showed blepharophimosis, right sclerocornea, bilateral microcornea and cataracts. Fundus oculi was normal. A total-body skeletal X-ray survey was performed and revealed mild dolichocephaly, long and thin phalanges and metatarsals, 11 pairs of thin ribs, and a bilateral clavicle hook (fig. 2).

On follow-up at 1 year and at 2 years 9 months, her growth and development were normal. At the latter examination she measured: height 87 cm (10th centile), weight 11.9 kg (10th centile), and head circumference 48.3 cm (10th centile).

The same minor facial anomalies were evident, as was arachnodactyly of hands and feet, but camptodactyly and bilateral clubfeet had improved (fig. 3, 4). A cardiac ultrasound scan was performed and showed an ostium secundum atrial septal defect. The child had a mild motor developmental delay that improved progressively with physiotherapy. The major motor milestones were sitting at 8 months and walking at 22 months. Speech development was normal.

Molecular Analysis

Array-comparative genomic hybridization (array-CGH) analysis was performed using commercially available oligonucleotide microarrays containing about 99,000 60-mer probes with an estimated median spatial resolution of nearly 10 kb and a functional resolution close to 35 kb (Human Genome CGH Microarray 105A Kit, Agilent Technologies). Labeling and hybridization were performed following the protocols provided by the manufacturer (Agilent Technologies according to the Agilent protocol Oligonucleotide Array-Based CGH for Genomic DNA Analysis v 2.0). Slides were dried and then scanned using an Agilent G2565BA DNA microarray scanner.

Image analysis was performed by CGH Analytics software v. 3.4.40 with default settings. The software automatically determines the fluorescence intensities of the spots for both fluorochromes, performs background subtraction and data normalization, and compiles the data into a spreadsheet that links the fluorescent signal of every oligo on the array to the oligo name, its position on the array, and its position in the genome. The linear order of the oligos is reconstituted in the ratio plots consistent with an ideogram. The ratio plot is arbitrarily assigned such that gains and losses in DNA copy number at a particular locus are

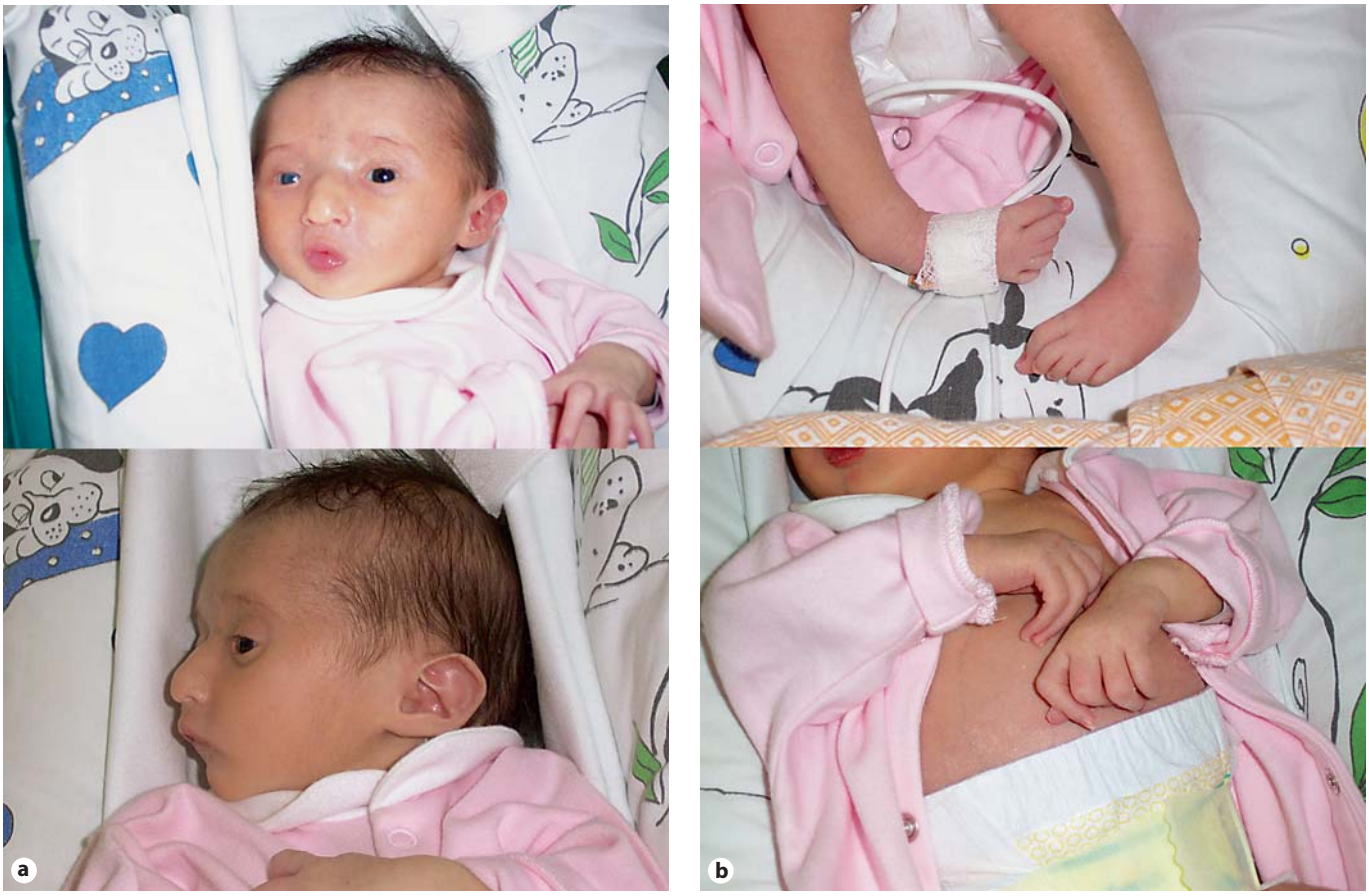

Fig. 1. Clinical features of the proband include **a** blepharophimosis, flat wide nasal bridge, malar hypoplasia, and prominent ears, and **b** arachnocamptodactyly of fingers and toes, proximally set thumb, and bilateral clubfeet.

observed as a deviation of the ratio plot from a modal value of 1.0. DNA sequence information is taken from the public UCSC database (Human Genome Browser, http://genome.ucsc.edu, March 2006 assembly).

Mutational analysis of the *SCARF2* gene in the patient was performed by Sanger sequencing using an ABI 3730 capillary sequencer after PCR amplification with intronic primers for the 11 coding exons. In addition, both parents were sequenced for exon 4 and flanking intronic regions.

Results

A 22q11.1–q11.21 microdeletion was identified with the proximal breakpoint in 22q11.1 located between 17.08 and 17.27 Mb (last oligonucleotide present and first deleted, respectively) and the distal breakpoint between 19.83 and 19.89 Mb in 22q11.21 (last oligonucleotide de-

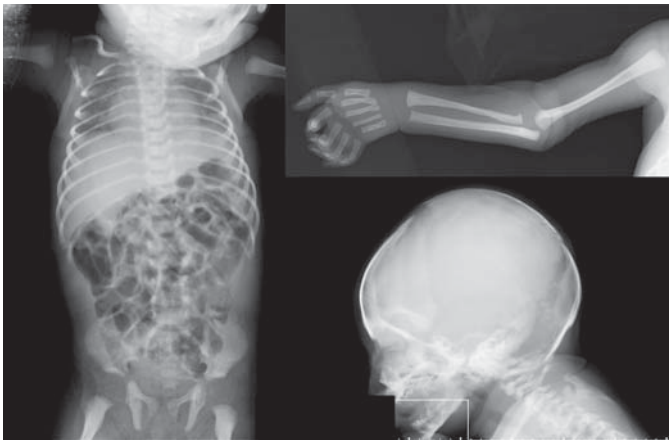

Fig. 2. Radiographs of the patient showing hooked clavicles, slender ribs, and long bones.

Fig. 3. Proband at 1 year of age and at 2 years 9 months.

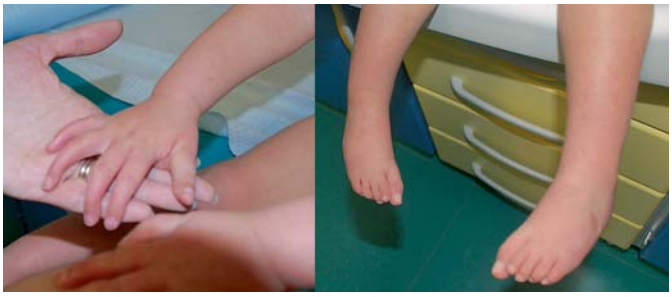

Fig. 4. Hands and feet of the proband at 2 years 9 months.

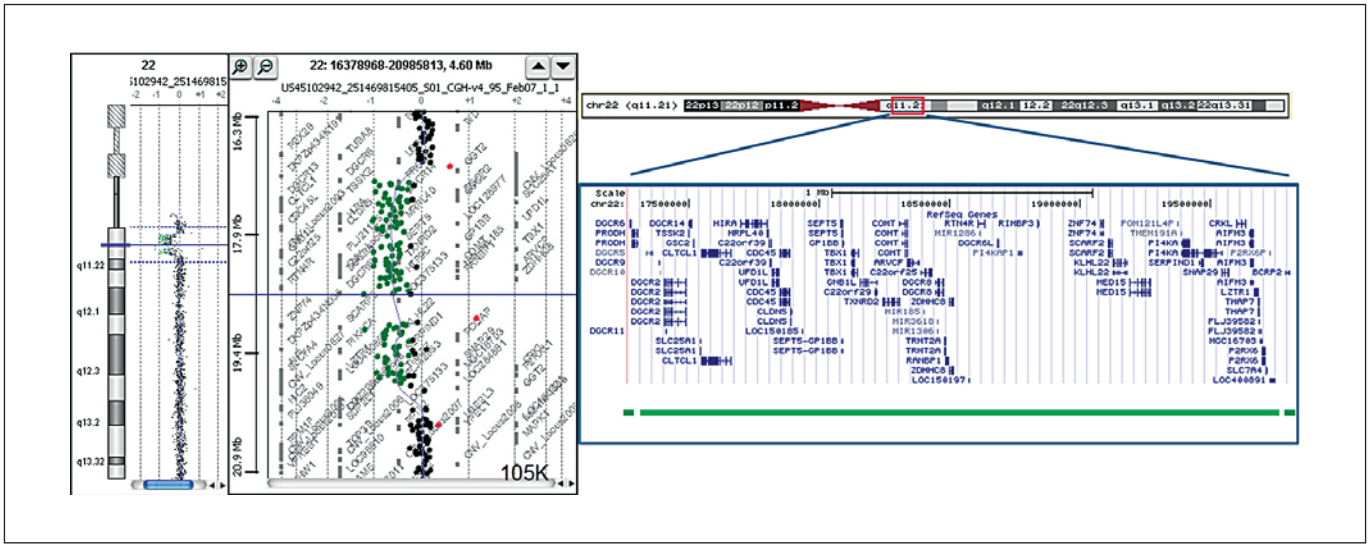

Fig. 5. Results of array-CGH. On the left the chromosome 22 ideogram is shown indicating the 22q11.21 microdeletion in the ratio profile. On the right, the deletion indicated by the array-CGH experiment is mapped against the corresponding genomic region in the UCSC genome browser build 36.1 (2006). In the lower part, the extent of the deletion in the patient described in this report, which represents the common '3-Mb' deletion size, is indicated (green line).

leted and first present, respectively, referring to hg18). Thus the deletion corresponds to the common DiGeorge/VCFS '3-Mb' deletion between low copy repeats LCR-A (LCR22–2′) and LCR-D (LCR22–4′) [Rauch et al., 2005; Guo et al., 2011]. To confirm the array data, a second array-CGH experiment was performed in the patient and parents. The deletion was confirmed in the patient, while the parents showed a normal result. Analysis of the deleted region suggested the absence of at least 39 known genes (fig. 5).

Sanger sequencing of the *SCARF2* gene revealed the c.854 + 1G>T (intron 4) splice acceptor mutation hemizygous in the patient and heterozygous in the healthy mother, while the father showed the wild-type sequence (fig. 6). Online bioinformatics tools such as 'Mutation taster' and 'Human splicing finder' both indicated loss of the splicing site.

Discussion

The facial phenotype of our case and the pattern of congenital anomalies are similar to that of patients previously reported by van den Ende et al. [1992] and Gupta et al. [1995]. Since the VDEGS was considered an autosomal recessive condition, detection of a heterozygous 22q11.2

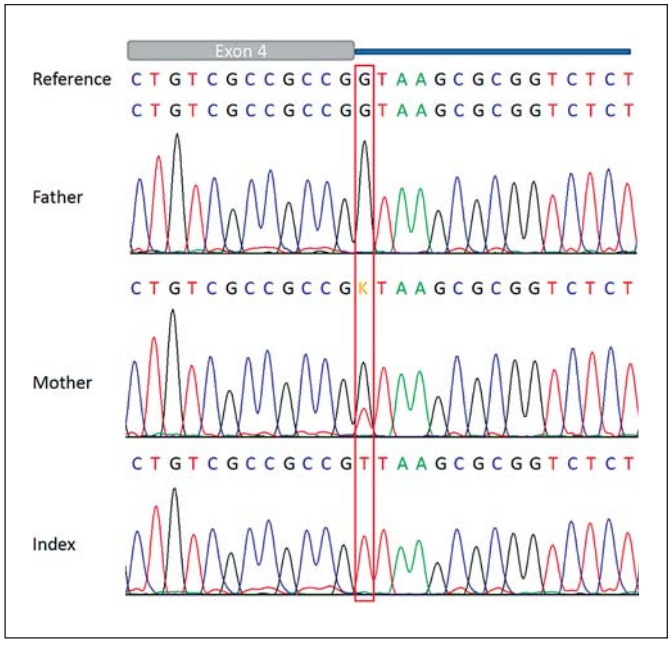

Fig. 6. Electropherograms showing the *SCARF2* c.854 + 1G>T (intron 4) splice acceptor mutation hemizygous in the patient (index) and heterozygous in the healthy mother. The relatively small mutation versus wild-type peak in the mother may be caused by preferential amplification of the wild-type allele or by mosaicism for the mutation.

deletion in our patient was surprising. The recent identification of homozygous mutations in the *SCARF2* gene in inbred families with VDEGS [Anastasio et al., 2010] suggested unmasking of a recessive mutation of *SCARF2,* which is located within the 22q11.2 common deletion region. Subsequent sequencing of *SCARF2* in our patient revealed indeed a maternally inherited splice site mutation in addition to the 22q11.2 microdeletion and hence absence of a functional *SCARF2* gene. *SCARF2* contains putative epidermal growth factor-like domains in its extracellular domain, along with a number of positively charged residues in its intracellular domain, indicating that it may be involved in intracellular signaling. *Scarf2* is expressed in mouse branchial or pharyngeal arches and mandibular maxillary and urogenital ridge tissues [Anastasio et al., 2010].

Comparison of the clinical findings of our case with clinical characteristics of 24 patients described with this condition (table 1) [van den Ende et al., 1992; Bistritzer et al., 1993; Gupta et al., 1995; Phadke et al., 1998; Schweitzer et al., 2003; Guerra et al., 2005; Carr et al., 2007; Leal and Silva 2009; Ali et al., 2010; Anastasio et al., 2010] confirms considerable overlap of our case with the published patients with VDEGS, particularly the facial appearance and the arachnocamptodactyly. The most common anomalies are indeed arachnodactyly, camptodactyly, an unusual facial appearance with blepharophimosis, beaked nose, malar hypoplasia, everted lips, and prominent ears. Growth and intelligence are normal in all cases. The finger contractures usually gradually improve and do not cause functional limitations. In all cases, radiographic features showed slender long bones, metacarpals, metatarsal, and phalanges. Further investigation is warranted concerning the relevance of cerebellar enlargement and learning difficulties reported by Schweitzer et al. [2003].

In addition, the patient reported here had sclerocornea and cataracts never described previously in VDEGS. Instead, ocular findings such as sclerocornea, microphtalmia, and cataract have been described in the 22q11 deletion syndrome [Binenbaum et al., 2008; Casteels et al., 2008]. The patient here reported presented with a 2.56–2.8 Mb deletion that represents the typical 3-Mb deletion at 22q11.2 that is usually observed. In addition to the ocular anomalies, she showed some typical clinical features of the 22q deletion phenotype such as ostium secundum atrial septal defect and transient neonatal hypocalcemia [McDonald-McGinn and Sullivan, 2011]. The facial features such as small mouth, prominent nose, hypertelorism, and narrow palpebral fissures, although overlapping with the 22q11 deletion syndrome, were clearly dominated by the characteristics of VDEGS. She had no other 22q11.2 deletion features, in particular no velopharyngeal insufficiency, no thymic hypoplasia, and no evidence of immunodeficiency.

Limb anomalies are uncommon in 22q11.2 deletion patients. A few studies reported patients with a 22q11.2 deletion and polydactyly, ectrodactyly, thumb anomalies, minor upper/lower limb skeletal anomalies, synostosis, and contractures, but neither arachnodactyly nor hypo-extensibility of fingers are described so far [Kokitsu-Nakata et al., 2008]. On the contrary, arachnocamptodactyly is the most characteristic clinical feature of VDEGS.

To our knowledge, no published patient with a 22q11.2 deletion showed clinical features similar to a VDEGS phenotype. On the other hand, cases with VDEGS had a normal karyotype, and FISH for specific 22q11.2 abnormalities performed in 3 cases was normal [Gupta et al., 1995; Schweitzer et al., 2003; Carr et al., 2007].

VDEGS has been generally considered to be an autosomal recessive entity, given that 3 affected individuals

Table 1. Clinical features in VDEGS

	van den Ende et al. 1992	Bistritzer et al., 1993		Gupta et al. 1995	Phadke et al. 1998		Schweitzer et al., 2003		Guerra et al. 2005	Carr et al. 2007		Leal and Silva, 2009			Anastasio et al., 2010				Ali et al., 2010						22q11 deletion	Our case
		Case			Case		Case			Case		Case			Case				Case							
		1	2		1	2	1	2		1	2	1	2	3	1	2	3	4	1	2	3	4	5	6		
Craniofacial findings																										
Blepharophimosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Flat wide nasal bridge	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
Malar hypoplasia	+	?	?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Large ears	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	–	–	–	+	+	+	+	+	+	–	+
Small squared ears	+	–	–	–	–	–	–	–	–	–	+	–	–	–	+	+	–	–	–	–	–	–	–	–	+	–
Narrow nose	–	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	–	+
Everted lower lip	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Bulbous nasal tip	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–
Small mouth		–	–	+	–	–	–	–	–	–	–	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+
Palatal anomalies	C	?	?	S	H	H	H	H	S	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H/C	H
Downslanting eyebrows	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–
Sclerocornea cataracts	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Skeletal findings																										
Aracnodactyly	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
2,3 skin syndactyly															+	+	+	+	+	+	+	+	+	+	–	+
Hypoextensibility	+	+	+	+	+	+	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	–	+
Hypoplastic distal digital creases	?	+	+	?	?	?	+	+	+	–	?	+	–	–	+	+	+	+	–	–	–	–	–	–	–	–
Elongated thumbs/halluces	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Knee contractures	–	+	+	+	–	–	+	+	–	+	+	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–
Clubfeet	+	–	–	–	–	–	+	–	+	–	mild	+	–	–	–	–	–	–	–	–	–	–	–		–	+
Hallux valgus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
Radiological findings																										
Long slender metacarpals/phalanges	+	?	?	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
Small anterior cranial fossa	–	?	?	+	?	?	–	–	+	+	?	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
Malar hypoplasia	+	?	?	+	?	?	–	–	+	–	?	+	?	–	–	+	+	+	+	+	+	+	+	+	+	+
Slender ribs	?	?	?	+	+	+	+	+	+	–	?	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hooked clavicles	?	?	?	+	?	?	+	+	+	+	?	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
Hypoplastic glenoid fossa	?	?	?	+	–	–	+	+	+	+	?	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
Dislocated radial head	–	?	?	+	+	+	–	–	+	–	+	+	–	–	–	–	–	–								
Overtubulated long bones	?	?	?	+	+	+	+	+	+	+	+	+	+	+	–											
Bowed long bones	–	?	?	+	+	+	–	?	+	+	–	+	+	–	–											
SCARF2 analysis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	+	+	+	N	N	N	N	N	N		+

C = Cleft; H = high; N = not performed; S = short.

from different families were born to normal and consanguineous parents [van den Ende et al., 1992; Bistritzer et al., 1993; Gupta et al., 1995]. The identification of homozygous mutations in the *SCARF2* gene as the underlying cause reported by Anastasio et al. [2010] in VDEGS patients from 3 consanguineous families further supports the conclusion that VDEGS is an autosomal recessive entity. Our case, though, demonstrates that sequencing alone might falsely indicate a homozygous mutation and that the recurrence risk is not necessarily 25% in all cases. After exclusion of a compensating deletion/duplication event by FISH in the parents [Alkalay et al., 2011], we would assume an approximately 1% recurrence risk for the 22q11.2 deletion with reference to the possibility of a germ line mosaicism. Accordingly, recurrence risk for VDEGS would be approximately 0.5%.

Recently, because 3 affected individuals, 2 brothers and their half-sister, were reported, Leal and Silva [2009]

hypothesized an autosomal dominant transmission and gonadal mosaicism, suggesting genetic heterogeneity. However, we consider it more likely, that all 3 half-siblings are by change carriers of recessive mutations, a hypothesis that could now be proven.

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