

Keratosis Pilaris and Ulerythema Ophryogenes Associated With an 18p Deletion Caused by a Y/18 Translocation

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We present a patient with partial monosomy of the short arm of chromosome 18 caused by de novo translocation t(Y;18) and a generalized form of keratosis pilaris (keratosis pilaris affecting the skin follicles of the trunk, limbs and face—ulerythema ophryogenes). Two-color FISH with centromere-specific Y and 18 DNA probes identified the derivative chromosome 18 as a dicentric with breakpoints in p11.2 on both involved chromosomes. The patient had another normal Y chromosome. This is a third report the presence of a chromosome 18p deletion (and first case of a translocation involving 18p and a sex chromosome) with this genodermatosis. Our data suggest that the short arm of chromosome 18 is a candidate region for a gene causing keratosis pilaris. Unmasking of a recessive mutation at the disease locus by deletion of the wild type allele could be the cause of the recessive genodermatosis. *Am. J. Med. Genet.* 85:179–182, 1999.

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KEY WORDS: keratosis pilaris; ulerythema ophryogenes; monosomy 18p; translocation Y/18

INTRODUCTION

Monosomy of the short arm of chromosome 18 is one of the most common autosomal deletions, with a variable clinical picture, with more than 100 cases reported to date [reviewed by Schinzel et al., 1974; Aksu et al., 1976; de Grouchy and Turleau, 1984]. In approximately 15% of the patients, the monosomy 18p is the result of a chromosomal translocation with another

chromosome, mainly acrocentrics [Aksu et al., 1976; Fryns et al., 1986]. Translocations between 18p and the sex chromosomes are rare. Recently, the occurrence of an 18p deletion in patients with keratosis pilaris was reported [Zouboulis et al., 1994; Horsley et al., 1998]. Here we present the third case of 18p deletion (due to a translocation between 18p and a sex chromosome), with the above-mentioned genodermatosis.

CLINICAL REPORT

The 18-year-old patient (Fig. 1) was the first child of healthy, nonconsanguineous parents, who were 20 years old of the time of his birth. The pregnancy was complicated by vaginal spotting of a few days duration in the first and third trimesters. The child was delivered at term with a birthweight of 2,850 g and length 50 cm. During the neonatal period, transient lymphedema of the lower limbs, a heart murmur, and inguinal hernia were detected. At age 1 year, retarded psychomotor development was noted. During childhood the patient had recurrent respiratory infections. At 6 years scoliosis was noticed, as well as umbilical hernia and astigmatism of both eyes, with evidence of severe physical and mental retardation. At 18 years his height was 159 cm ($\leq$ 5th centile), weight 48 kg (5th centile), and head circumference 55 cm (50th centile). He was mentally retarded, with muscular hypotonia, mild conductive unilateral hearing impairment, speech defects, tremor, scoliosis, hyperopia, astigmatism, mitral valve prolapse, and tricuspid regurgitation, genua valga. He had a triangular face with coarse hair, high forehead, prominent ear helices with “floppy” earlobes, moderate bitemporal constriction, broad-based long nose with beaked nasal tip, short philtrum, wide mouth with protruding upper lip, high-arched palate, and abnormally shaped teeth. The neck, chest, back, arms, shoulders, and thighs showed multiple small follicular, partially inflammatory, keratotic papules 1–3 mm in diameter (Figs. 2, 3). The skin changes did not involve scalp, palms, or soles. The patient also had erythema with follicular papules symmetrically present on eyebrows, cheeks, and, to a lesser extent, chin and forehead (ulerythema ophryogenes). Histological examination of

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Fig. 1. The propositus' face with erythematous areas and disseminated, follicular, keratotic papules on the cheeks and eyebrows (ulerythema ophryogenes).

skin from the eyebrow showed hyperkeratosis, follicular plugging, atrophy of the epidermis, and mild non-specific inflammatory infiltrates. Fibrotic changes were seen around the follicles. These findings were consistent with the diagnosis of ulerythema ophryogenes. Skin involvement began in childhood and initially was diagnosed as atopic dermatitis. The patient's parents had no skin lesions or other pertinent findings.

CYTOGENETIC AND MOLECULAR CYTOGENETIC RESULTS

The patient's karyotype was obtained by the standard analysis of GTG-banded chromosomes from peripheral blood lymphocytes. Two-color FISH was performed according to standard protocols [Lichter and Cremer, 1992]. DNA probes were purchased from Oncor (Gaithersburg, MD). The probe specific for the centromeric region of chromosome Y was labeled with biotin and detected by an avidin-FITC (fluorescein isothiocyanate) system; the probe specific for chromosome 18 was digoxigenated and detected by anti-digoxigenin-



Fig. 2. Keratosis pilaris on the patient's back.

rhodamine. The chromosomes were counterstained with propidium iodide and DAPI. Fluorescent signals were analyzed on a Zeiss Axioskop fluorescence microscope. Digital images were captured using an imaging system and software from PSI (League City, TX).

Chromosomal study of the patient showed a 46,XY,18p+ karyotype. A derivative chromosome 18 was present as a metacentric chromosome in all metaphases examined (Fig. 4). Additional cytogenetic methods (C-banding and DA/DAPI analysis) identified the variant 18p+ as a possible translocation t(Y;18). FISH analysis with the mixture of DNA probes pYZ3 and pYZ1 specific for centromeric and heterochromatic Yq12 regions gave positive signals on the short arm of the aberrant chromosome 18. The patient also had another normal chromosome Y (Fig. 5a).

Two-color FISH with two centromere-specific probes for chromosomes 18 (p18Z1) and Y (pYZ3) showed two close signals on the aberrant chromosome 18 (Fig. 5b). Thus, chromosome 18p+ was in fact a dicentric chromosome with partial loss of material of the short arms of chromosome 18 and Y as the result of de novo translocation between these two chromosomes with breakpoints at p11.2 in both. Therefore, the karyotype of the



Fig. 3. Keratosis pilaris on the patient's thigh.

patient was interpreted as 46,XY,der(18)t(Y;18).ish dic(Y;18)(p11.2;p11.2) (DYZ3+,D18Z1+), with monosomy for 18p11.2→pter and duplication of Yp11.2→qter. The patient's parents had normal chromosomes.

DISCUSSION

Classical and molecular cytogenetic methods showed that our patient had the 18p- syndrome resulting from

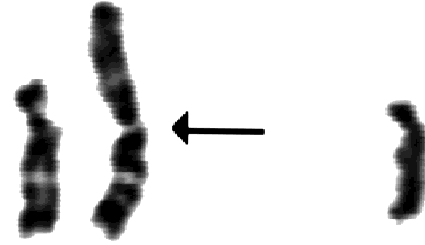


Fig. 4. Partial G banded karyotype of the proband's chromosomes 18 and Y. The der(Y;18) is indicated by an arrow.

a de novo Y;18 translocation. The additional presence of one normal chromosome Y maintained normal male sexual differentiation. The second Y chromosome may have originated from nondisjunction of sister chromatids during paternal meiosis II, resulting in a YY-sperm. As to the origin of Y;18 translocation, the break could have arisen during paternal meiosis or after the fertilization of a normal ovum by a YY-sperm. Only five patients with 18p- syndrome and a variable clinical picture caused by Y;18 translocation have been described [Lau et al., 1985; Maserati et al., 1986; el Kalla et al., 1992; Kakinuma et al., 1994; Gimelli et al., 1996]. However, in these cases the translocations have not been associated with an extra Y chromosome.

The clinical characteristics of our patient are, in general, similar to those typical of the 18p- syndrome, including mental and developmental delay, muscular hypotonia, umbilical and inguinal hernias, high forehead, protruding ears, broad-based nose, wide mouth with protruding upper lip, dental anomalies, heart malformations, and cubitus valgus. He also had IgA deficiency. On the other hand, keratosis pilaris and ulerythema ophryogenes are not a manifestation of the 18p- syndrome.

Keratosis pilaris defines a group of cutaneous disor-

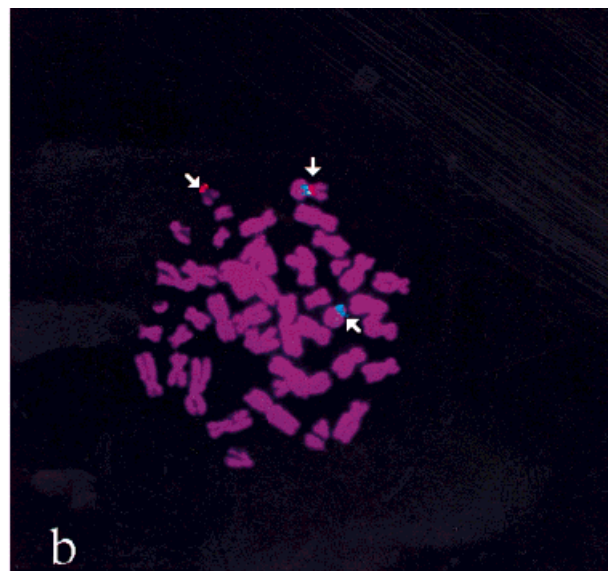
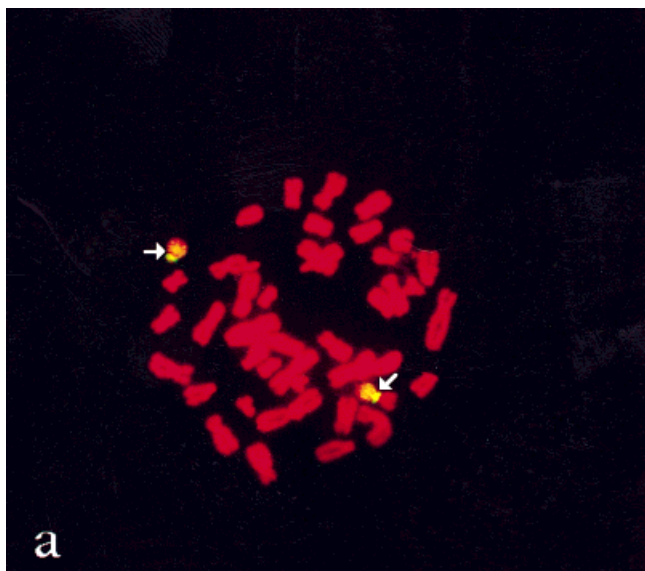


Fig. 5. (a) FISH analysis with the mixture of DNA probes pYZ3 and pYZ1 specific for centromeric and heterochromatic Yq12 regions showing the normal Y chromosome and the der(Y;18). (b) Two-color FISH analysis with centromere-specific DNA probes for chromosomes 18 (blue) and Y (red), showing two nearly located signals at the der(Y;18).

ders of ectodermal origin characterized by follicular hyperkeratosis and frequently occurring with ichthyosis or atopy. Ulerythema ophryogenes is classified as one of the types of this genodermatosis [Azambuja et al., 1987]. Combinations of these disorders have also been reported [Azambuja et al., 1987; Zouboulis et al., 1994]. The pathogenesis of these diseases may be a disorder of the keratinocyte, which is responsible for inducing both hyperkeratosis and inflammatory changes [Baden and Byers, 1994]. Oranje et al. [1994] distinguished four distinct clinical entities that show keratosis pilaris followed by atrophy (keratosis pilaris atrophicans): 1) *keratosis pilaris atrophicans faciei*, a probable autosomal dominant trait, 2) *atrophoderma vermiculata*, a probable autosomal recessive trait; 3) *keratosis follicularis spinulosa decalvans* with X-linked inheritance; 4) *folliculitis spinulosa decalvans*, a probable autosomal trait.

Zouboulis et al. [1994] described a 13-year-old boy with monosomy 18p and follicular, partially inflammatory, keratotic papules of eyebrows, foreskin, and cheeks (ulerythema ophryogenes) in combination with keratosis pilaris affecting shoulders, upper back, upper arms, and thighs. Our patient has a very similar clinical picture of widespread keratosis pilaris. Recently, Horsley et al. [1998] described a 37-year-old woman with del(18p) which was in fact a cryptic 2;18 translocation and keratosis pilaris affecting only the distal extensor aspect of her arms. All three patients are monosomic for 18p11.2-pter. This suggests that the short arm of chromosome 18 is a candidate region for a gene causing widespread keratosis pilaris (skin lesions affecting the skin follicles of trunk and limbs in combination with *keratosis pilaris atrophicans faciei*, i.e., ulerythema ophryogenes) and the local keratosis pilaris (lesions affecting the skin follicles of separate skin areas). Since most patients with 18p- syndrome have neither keratosis pilaris nor ulerythema ophryogenes, one may surmise that the manifestation of keratosis pilaris involves the unmasking of a recessive mutation by loss of the wild-type allele in the deleted part of 18p. Although our patient also has a duplication of Yp11.2→qter, it is unlikely that his skin disorder results from this abnormality.

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REFERENCES

- Aksu F, Mietens C, Scholz W. 1976. Numerische und strukturelle aberrationen des Chromosoms Nr.18. *Klin Paediatr* 188:220–232.
- Azambuja R, Proenca NG, Cardoso WV. 1987. Ulerythema ophryogenes and folliculitis ulerythematosus reticulata. *Hautarzt* 38:411–413.
- Baden HP, Byers HR. 1994. Clinical findings, cutaneous pathology, and response to therapy in 21 patients with keratosis pilaris atrophicans. *Arch Dermatol* 130:469–475.
- de Grouchy J, Turleau C. 1984. *Clinical atlas of human chromosomes*. New York: John Wiley. p 308–313.
- el Kalla S, Mathews AR, Menon NS. 1992. del(18p) syndrome with complex tetralogy of Fallot in an infant with 45,X,t(Y;18)(q12;q11.2). *Am J Med Genet* 42:665–666.
- Fryns JP, Kleczkowska A, Vinken L, Geutjens J, Smeets E, van den Berghe H. 1986. Acrocentric/18p translocation in two mentally retarded males. *Ann Genet* 29:107–111.
- Gimelli G, Cinti R, Varone P, Naselli A, Di Battista E, Pezzolo A. 1996. The phenotype of a 45,X male with a Y/18 translocation. *Clin Genet* 49:37–41.
- Horsley SW, Knight SJJ, Nixon J, Huson S, Fitchett M, Boone RA, Hilton-Jones D, Flint J, Kearney L. 1998. Del(18p) shown to be a cryptic translocation using a multiprobe FISH assay for subtelomeric chromosome rearrangements. *J Med Genet* 35:722–726.
- Kakinuma S, Sasabe F, Negoro K, Nogaki H, Morimatsu M. 1994. 18p-syndrome with bilateral pyramidal tract signs, dystonia of the lower extremities and concentric visual field defect. *Rinsho Shinkeigaku* 34:474–478.
- Lau YF, Ying KL, Donnell GN. 1985. Identification of a case of Y:18 translocation using a Y-specific repetitive DNA probe. *Hum Genet* 69:102–105.
- Lichter P, Cremer T. 1992. Chromosome analysis by non-isotopic in situ hybridization. In: Rooney DE, Czepulkowski BH, editors. *Human cytogenetics. A practical approach*. New York: Oxford University Press, V.1. p 157–192.
- Maserati E, Waibel F, Weber B, Fraccaro M, Gal A, Pasquali F, Schempp W, Scherer G, Vaccaro R, Weissenbach J. 1986. A 45,X male with a Yp/18 translocation. *Hum Genet* 74:126–132.
- Oranje AP, Loes DM, Oosterwijk JC. 1994. Keratosis pilaris atrophicans. One heterogeneous disease or a symptom in different clinical entities? *Arch Dermatol* 130:500–502.
- Schinzel A, Schmid W, Lüscher U, Nater M, Brook C, Steinmann B. 1974. Structural aberrations of chromosome 18. I. The 18p-syndrome. *Arch Genet* 47:1–15.
- Zouboulis CC, Stratakis CA, Rinck G, Wegner RD, Gollnick H, Orfanos CE. 1994. Ulerythema ophryogenes and keratosis pilaris in a child with monosomy 18p. *Pediatr Dermatol* 11:172–175.