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A new form of hypertrichosis inherited as an X-linked dominant trait

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Summary. A family with a distinct form of congenital generalized hypertrichosis was studied. Males were more severely affected than females, who exhibited asymmetric hair distribution. This finding was attributed to lyonization, since genealogical studies indicated an X-linked pattern of inheritance. A back mutation is postulated as the origin of this new phenotype.

Introduction

Hypertrichosis is a rare condition which nonetheless has aroused man's curiosity through history, as can be inferred from its depiction in paintings since the Middle Ages and literature since the sixteenth century. Felgenhauer (1969) reviewed the ancient literature, and found seven families with 21 members affected with total hypertrichosis. Five of these families showed a definite autosomal dominant pattern of inheritance. So far, the familial forms have been described as autosomal dominant congenital hypertrichosis lanuginosa (Danforth 1925; Beighton 1970; Freire-Maia et al. 1976; McKusick 1983), hypertrichosis with associated gingival hyperplasia and autosomal dominant transmission (Byars and Sarnat 1944; McKusick 1983) and a new form associated with a mild osteochondrodysplasia and probable autosomal recessive inheritance (Cantú et al. 1982). The purpose of this report is to describe a family with a severe form of hypertrichosis inherited in an X-linked pattern of inheritance.

Case report

The propositus (V-8 in Fig. 1), aged 6 years, was the product of a first full-term uncomplicated pregnancy and normal delivery.

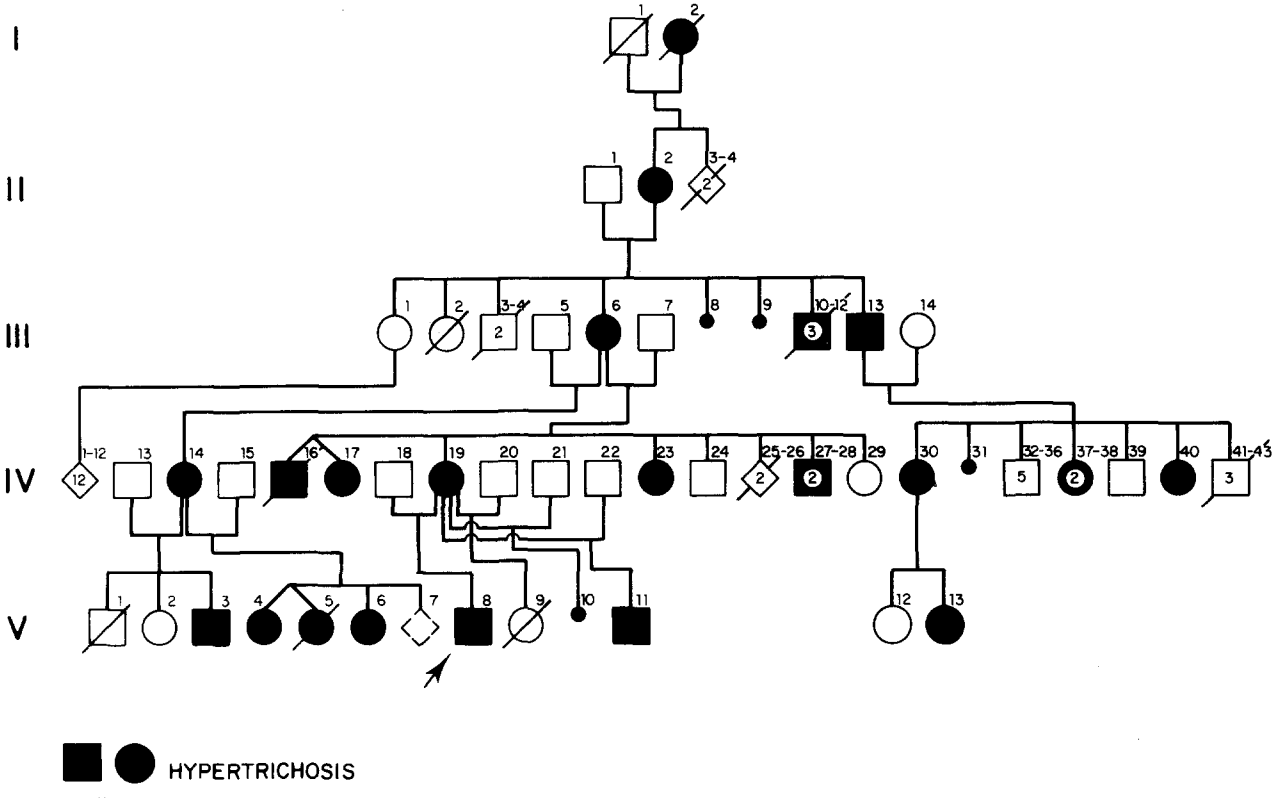

Fig. 1. Pedigree

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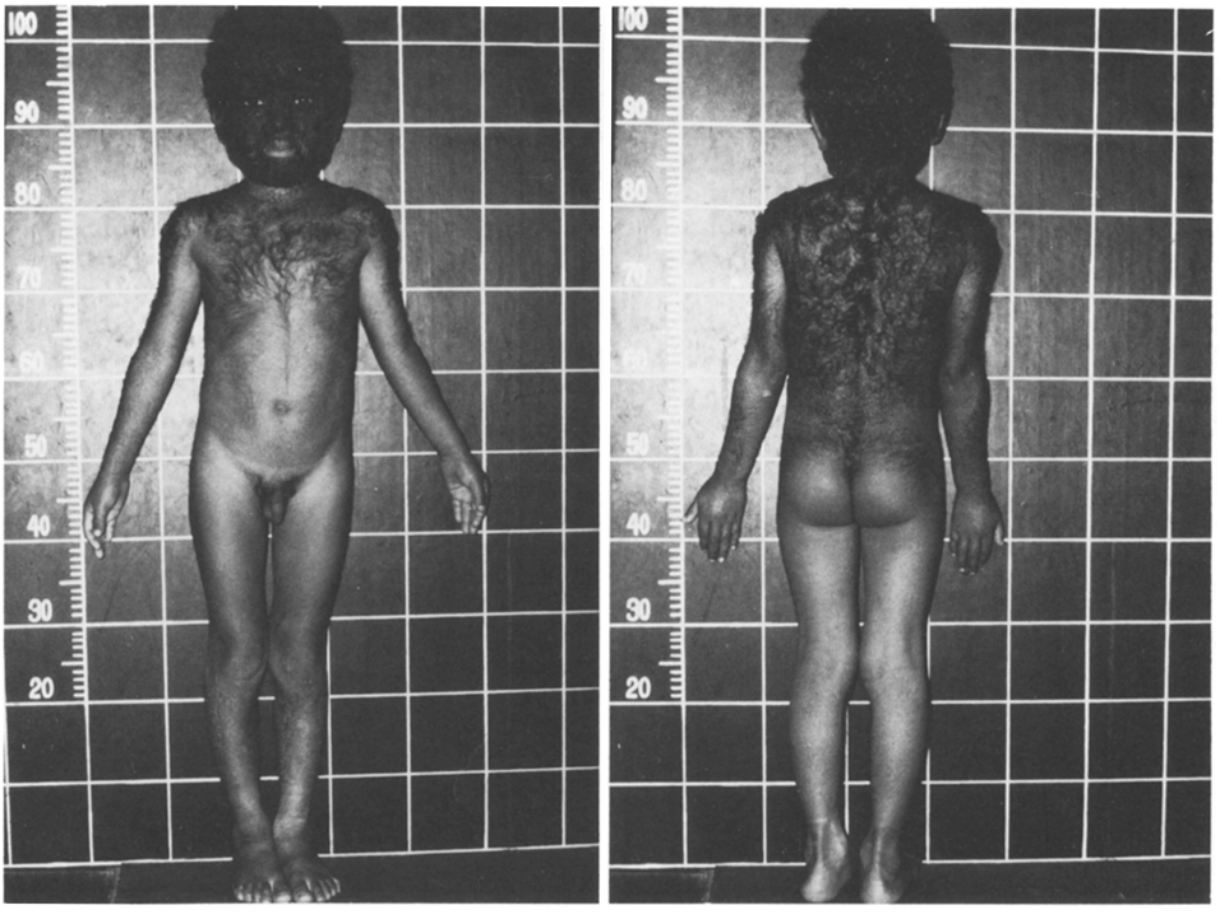

Fig. 2. The propositus. Note the excessive hair on face, trunk and genital region, the normal sized genitalia and the mildly affected legs

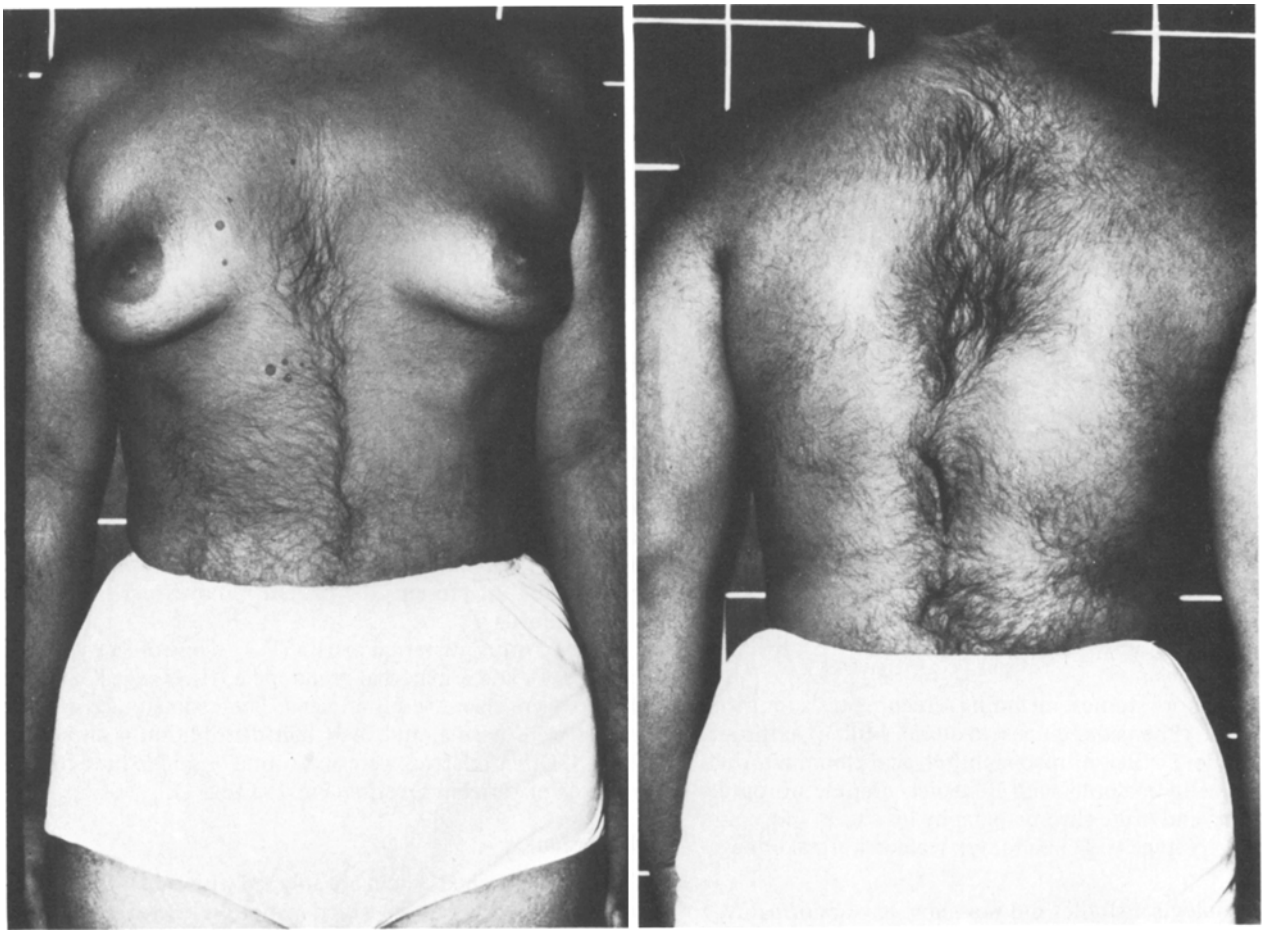

Fig. 3. The propositus' mother exhibiting a lesser degree of hairiness than her son. Observe the asymmetric hair distribution

Table 1. Distribution and severity of hairiness in the affected members[a]

	Propositus										
	V-8	V-3	V-6	V-11	V-13	IV-14	IV-19	IV-23	IV-30	III-6	III-13
Face											
Long eyelashes	3	4	3	4	2	1	2	1	1	1	3
Forehead	4	4	2	4	1	1	2	5	1	0	3
Cheeks	4	3	2	3	1	1	2	5	2	0	4
Chin	4	4	1	2	0	1	2	0	1	0	4
Neck											
Anterior	2	2	1	1	0	1	0	0	1	0	2
Posterior	2	3	1	2	0	2	2	2	2	1	4
Trunk											
Anterior	3	2	1	1	0	0	2	2	1	2	3
Posterior	3	3	2L1R	2	0	1	3	3	1	3	3
Abdomen											
Anterior	2	1	0	1	0	1	2	2	1	1	3
Midline	3	2	1	2	0	2	2	2	2	2	4
Genital region	3	1	1	3	0	3	3	3	0	3	3
Limbs											
Arms	3	2	2	3	1	0	2	2R3L	1	1	3
Forearms	2	2	1	2	1	1	2	3	2	2	2
Thighs	3	1	1	1	1	0	2	2	1	0	1
Legs	2	1	1	2	0	0	2	2	1	1	1
Hands (dorsal face)	1	1	1	2	1	1	1	1	1	1	1
Feet (dorsal face)	1	1	1	1	0	1	0	0	1	0	0
Gluteal region	3	1									3

Arabic numbers = degree of affection in a progressive 1–4 scale
R = right; L = left
[a] Personally examined

Birthweight was not recorded. From birth, excessive lanugo was noted. During the 1st year of life, the hair became more dense and, except for palms and soles, the hairiness covered practically all the body, although it was less evident on the lower limbs. The somatometric parameters were within the normal range. Clinical examination (Fig. 2) revealed excessive hair on the face, to such a degree that the eyebrows could not easily be distinguished (Table 1); the external ears were also covered by hair, as was the neck and thorax, although less severely. The abdomen and extremities were mildly affected, except for the pubic region where the hair was abundant. The face showed a slightly hypoplastic nasal lobule and alae nasi, mild anteverted nostrils, thick lips, moderate prognathism and normal teeth; the neck was short and the external genitalia normal for age.

The laboratory studies, including screening tests for metabolic defects (Phenistix, glucose oxidase, Millon, anthrone, ferric chloride, DNPH, nitrosonaphthol, acid albumin turbidity, CTA, methylmalonic acid, Benedict, cyanide nitroprusside), plasma and urine chromatography for sugars and amino acids, and karyotype (GTG banding), yielded normal or negative results.

The radiological studies did not show any abnormality.

Family data

The propositus' mother (IV-19) was aged 18 years at the propositus' birth. She was also affected by congenital generalized asymmetric hairiness, though to a lesser degree than her son (Fig. 3, Table 1). The excessive hairiness had been present since birth and was moderately distributed on the face, being heavier on cheeks, moustache and beard. On the body the hairiness was abundant inside the external ears, on the anterior and posterior trunk, abdomen, breasts, axillary region and lower limbs (see Table 1). During puberty (15–16 years of age) she noted a mild decrease of the hairiness, mainly on trunk and lower limbs. At present, the patient removes her facial hair every other day.

A propositus' maternal cousin (V-3), a boy of $8^{5}/_{12}$ years of age (Fig. 4), and a maternal granduncle (III-13) aged 38 years (Fig. 5), were also severely affected. Their somatometric parameters were normal and their hair distribution is shown in Table 1. Other relatives were also found or said to have hypertrichosis of variable severity (Fig. 1, Table 1).

Discussion

The cases described herein are affected with a distinct form of congenital hypertrichosis which is more severe in males than

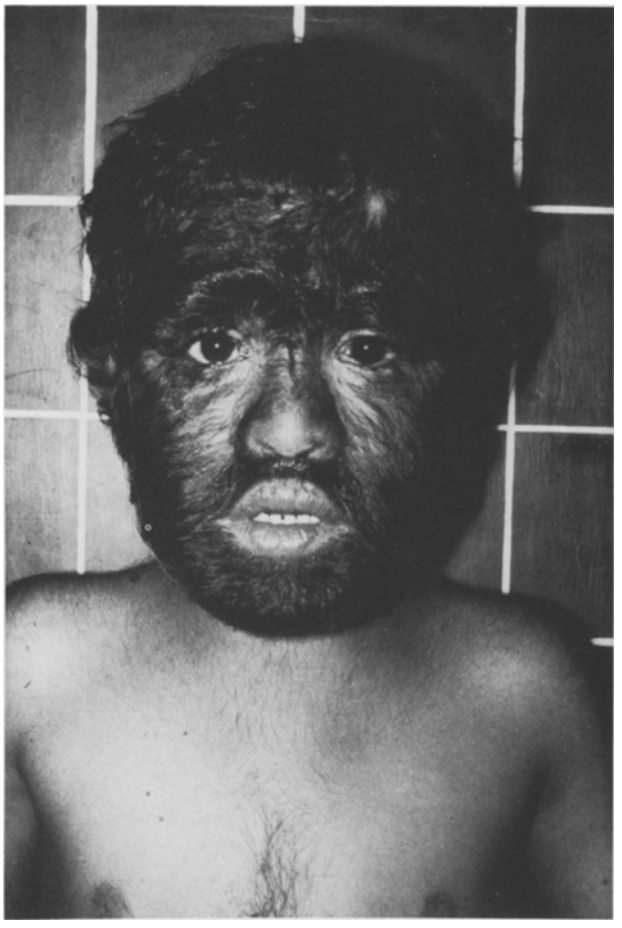

Fig. 4. Facial appearance of the propositus' maternal cousin (V-3). Note the dense hairiness, including the eyelids

in females. At present, three types of generalized hypertrichosis are known: The congenital hypertrichosis lanuginosa, also named universalis, in which the fetal hair is unchanged through post-natal stages (Beighton 1970); a form associated with gingival hyperplasia (Byars and Sarnat 1944); and a form associated with skeletal dysplasia (Cantú et al. 1982). The hypertrichosis in the patients described here does not correspond to any of these three entities, mainly because of the non-lanuginosa nature of the hair and the absence of gingival hyperplasia and of skeletal anomalies.

The species *Homo sapiens* has as many hairs, though shorter and thinner, as his ape cousins; the virtually naked skin appearance is due to the loss of thick hair, which probably happened at an early stage in the evolution of *Homo erectus* (Leakey 1977). Siebold (quoted by Felgenhauer 1969) and Virchow (quoted by Danforth 1925) considered hypertrichosis as a "normal" atavistic reversion (sic); likewise, Danforth (1925) stressed a phylogenetic significance, arguing that hypertrichosis is simply the manifestation of the normal primitive hairiness of the species. Beighton (1970) claimed that a simple genetic explanation is more plausible. Among other authors, Ecker (quoted by Felgenhauer 1969) considered hypertrichosis universalis as a persistence of the embryonic hair, resulting from a developmental arrest, and associated as a rule with dental anomalies.

In the present family, the facts that the affected females transmitted the trait to both their male and female offspring, that the only affected father passed on the mutant gene to all his daughters but to none of his sons, and the sex ratio of affected members (14 females and 7 males), strongly suggest an X-linked dominant pattern of inheritance. The milder degree of manifestation and the uneven hair distribution in females could be the result of lyonization.

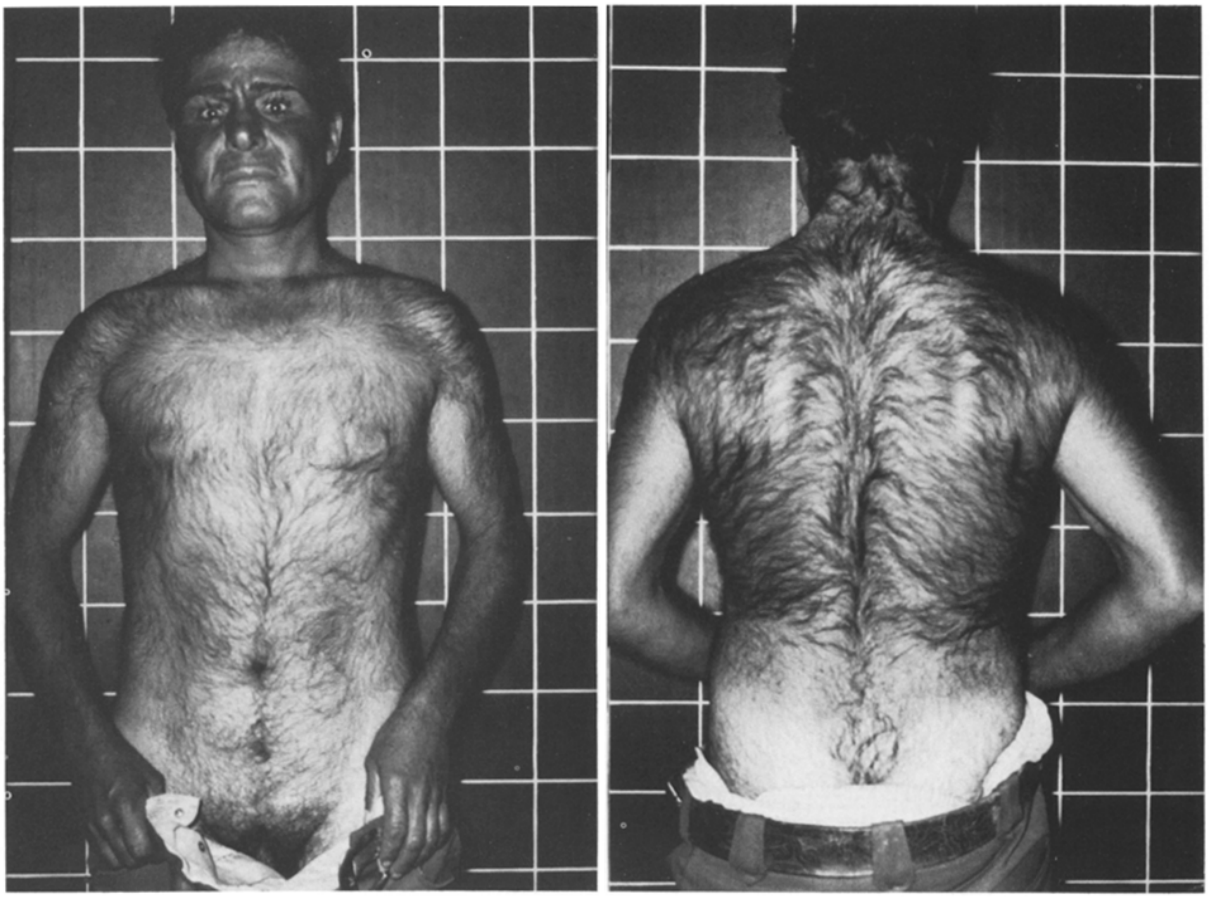

Fig. 5. Subject III-13. Note the generalized hypertrichosis (the face was entirely shaved)

To conclude, the present paper describes a new uncomplicated though severe form of congenital generalized hypertrichosis, inherited in an X-linked dominant fashion with a lyonization effect. Although there are some similar familial instances described in medical literature, autosomal dominant inheritance and no differences between sexes have been found (Beighton 1970; McKusick 1983). So, if cases with the X-linked hypertrichosis have been described previously, there is no evidence of it. The rarity of medical reports on this entity quite probably reflects an extremely low incidence in the general population (since such an apparent and spectacular disorder could hardly go unnoticed and unreported) and consequently, a very low mutation rate of the gene involved. Therefore, it is feasible to postulate that this trait is due to a back mutation which awakened a very old "sleeping" gene.

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