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Congenital generalized hypertrichosis terminalis: a proposed classification and a plea to avoid the ambiguous term "Ambras syndrome"

Congenital generalized hypertrichosis terminalis (CGHT) is a heterogenous group of diseases with continuing excessive growth of terminal hair. "Ambras syndrome" was first coined by Baumeister in 1993 to describe a case of nonsyndromic CGHT which was erroneously analogized to the portrait paintings of Petrus Gonzales and his children, exhibited in Ambras Castle near Innsbruck, Austria. This family probably, a syndromic type with abnormal dentition, inherited as an autosomal dominant trait. CGHT associated with gingival hyperplasia is probably a particular entity typified by the historical cases of Julia Pastrana and her son. An X-linked type of CGHT has likewise been categorized as "Ambras syndrome". Moreover, some reports have mistakenly classified "Ambras syndrome" as an example of hypertrichosis lanuginosa. Potential gene loci identified so far may include 8q22, 17q24.2-q24.3 and Xq24-q27.1. The designation "Ambras syndrome" has thus been applied to various types of congenital hypertrichosis that differ to such degree that the name "Ambras" has no specific meaning, neither in the past nor in the future. Hence, this misleading term should now be jettisoned.

Key words: Ambras syndrome, congenital hypertrichosis, hypertrichosis lanuginosa, terminal hair

Congenital generalized hypertrichosis (CGH) is a conspicuous rarity in human history. Its incidence has been estimated to be one in a billion but is probably much higher, given the number of descriptions of at least nine genetic disorders with this feature [1, 2]. More or less well documented cases can be found in portraits and literature since the 16th century. Considerable obscurity prevails in the literature concerning the classification and nomenclature of CGH, with several terms being used interchangeably and confusingly, such as hypertrichosis universalis, hypertrichosis lanuginosa, congenital hypertrichosis lanuginosa, Ambras syndrome and hypertrichosis universalis lanuginosa [2, 3].

The three crucial factors defining a precise nosology of CGH are (1) the hair type, (2) an association with extracutaneous abnormalities and (3) the pattern of inheritance [4]. The hair type description and the denomination of hair as lanugo hair in several reports are not in accordance with the current delineation of hair types based on structure, diameter and pigmentation of hair shafts. Lanugo hair is fine, soft, unmedullated and usually unpigmented hair, usually shed *in utero* during the eighth or ninth month of gestation. Postnatal hair can be divided into vellus hair and terminal hair, with the former being soft, unmedullated, occasionally pigmented and seldom more than 2 cm long, whereas the latter is longer, coarser and often medullated and pigmented [4]. A conversion of vellus hair to terminal hair occurs during puberty in the androgen-dependent areas of the skin. For generalized hypertrichosis, both autosomal dominant and X-linked patterns of transmission have been reported, whereas other cases have been described as "sporadic". The spectrum of the extent of coverage and the density of hypertrichosis varies, even within the same disease. Syndromic cases can be associated with facial dysmorphism or other extracutaneous abnormalities [2]. However, the degree and extent of facial deformity varies and the judgment of abnormality, such as "triangular" or "coarse" face, hypertelorism, "nasal contour" or "short stature", should take into account the ethnicity and developmental stage of the affected individuals.

The name "Ambras syndrome" was first proposed by Baumeister *et al*. in 1993 to define patients with congenital onset of diffuse, continually growing "vellus hair" (which was actually terminal hair) especially on the forehead, eyelids, nose, cheeks and preauricular region, typically involving the external auditory canal [5]. In 2003, a reexamination of the then three-year-old Greek girl originally described by Baumeister *et al.* showed persistent excessive hair growth without remarkable physical, psychomotor, mental or laboratory findings at the age of 14 (Dr. Christian Andres and Pr. Johannes Ring, Munich, Germany). Genetic studies later identified a structural chromosome abnormality involving 8q22 with a pericentric inversion, which was later shown to exert a positional effect on the phenotype [5]. A subsequent study indicated that this long-range positional effect might downregulate expression of *TRPS1*, the gene of trichorhinophalangeal syndrome 1, leading to hypertrichosis ("Ambras syndrome") in humans and the Koa phenotype in mice [6-8].

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Table 1. Different types of congenital geneneralized hypertrichosis terminalis (CGHT) with continuously and vigorously growing terminal hair remaining in adulthod.

	Examples and references	Extracutaneous defects	Remarks
Nonsyndromic sporadic CGHT	Historical cases: Barbara Urselerin (Augsburg, Germany), Stephan Bibrowski (Lionel the Lion-faced Man, Poland) Media reports: Supatra Sasuphan (Thailand), Prithviraj Patil (India) Medical reports: Baumeister FA *et al.* (Greece) [5]; Sun M *et al.* (China) [10]; Goel N *et al.* (India) [3]; DeStefano GM *et al.* (patient from Mexico) [11]	No	• Potential gene locus: 8q22 [5], 17q24.2-q24.3 [10, 11] • Possibility of heritability cannot be excluded as most of these patients did not have offspring.
Syndromic autosomal dominant CGHT	Historical cases: The family of Ambras (Tenerife, Canary islands?), The hairy Burmese family (Myanmar)	Dental anomalies	
	Historical cases: Julia Pastrana (Mexico) Medical reports (sporadic cases): Ray AK (India) [14]; Winter GB *et al.* (London, England) [15], Guevara-Sanginés E *et al.* (Mexico) [16]; Canún S *et al.* (Mexico) [17], Sun *et al.* (China, patient KK) [10], DeStefano GM *et al.* (patient from Yemen) [11]	Gingival hyperplasia, short stature	• Potential gene locus: 17q24.2-q24.3 [10] • The inheritance in sporadic cases remains undetermined.
X-linked CGHT, nonsyndromic	Medical reports: Macías-Flores MA *et al.* (Mexico) [18]	No	• Males were consistently more severely affected than females • Potential gene locus: Xq24-q27.1
X-linked CGHT, syndromic	Medical reports: Tadin-Strapps M *et al.* (Mexico) [21]	Deafness, dental anomalies	• Potential gene locus: Xq24-q27.1.
	Zhu H *et al.*, (China) [23]	Scoliosis and spina bifida (in one case)	• Potential gene locus: Xq27.1

(Origin of the patient reported); [references]

The terminology of "Ambras syndrome" as proposed by Baumeister *et al.* was based on the CGH terminalis (CGHT) demonstrated in the portraits of Petrus Gonzales and his children (the family of Ambras), exhibited in Ambras Castle, located near Innsbruck, Austria [5]. In our view, the current use of "Ambras syndrome" to describe continuous vigorous growth of thick terminal hair includes three different major groups of patients with CGHT *(table 1):*

Group 1: Nonsyndromic sporadic CGHT

This type often occurs sporadically. The case described by Baumeister can be reclassified as belonging to this group, based on our follow-up observation. Other possible cases include historical reports on Barbara Urselerin from Augsburg, Germany, Stephan Bibrowski from Poland (better known as "Lionel the Lion-faced Man") and some recent case reports [3, 9], as well as media reports (a girl named Supatra Sasuphan from Thailand and a boy named Prithviraj Patil from India). The three families recently described by Sun *et al*. from China can also be phenotypically ascribed to this group, because, except for a somewhat coarse facial contour, the affected individuals had no extracutaneous anomalies such as dental anomalies, gingival overgrowth or mental deficiency [10]. Genetic studies showed autosomal dominant inheritance with pathogenic copy-number mutations on 17q24.2-q24.3. None of these cases showed extracutaneous defects. Another recent study using whole genome sequencing in an unrelated sporadic case from Mexico identified a 1.3 Mb cryptic deletion of 17q24.2-q24.3 encompassing the ATP-binding cassette transporter *ABCA5*, a cholesterol transporter gene, with dramatic reduction of ABCA5 protein levels throughout the patient's hair follicles [11].

Group 2: Syndromic autosomal dominant CGHT

This type is exemplified by "the family of Ambras" with Petrus Gonzales and his three children as well as at least one of their descendants in the third generation [5, 12]. The hairy Burmese family in the nineteenth century was another example, beginning with Shwe-Maong, his daughter,

Table 2. Examples of autosomal dominant diseases showing less dense and extensive CGHT with multiple congenital abnormalities of greater severity and compromised life expectancy

	Main clinical features	Hypertrichosis	Gene/Locus MIM No.
Cantú syndrome (OMIM 239850)	• Facial dysmorphism (macrocephaly, broad nasal bridge, epicanthal folds, wide mouth, and full lips) • Neonatal macrosomia • Psychomotor retardation • Osteochondrodysplasia • Cardiomegaly	Forehead, arms and legs, and part of the trunk	12p12.1/ABCC9/601439
Cornelia de Lange syndrome-1 (OMIM 122470)	• Facial dysmorphism (microcephaly, arched eyebrows, synophrys, ptosis, anteverted nares, maxillary prognathism, long philtrum, thin lips, and 'carp' mouth) • Prenatal and postnatal growth retardation • Psychomotor retardation • Short arms and fingers • Gastroesophageal reflux disease	Forehead, back and extremities	5p13.2/NIPBL/608667
Barber-Say syndrome (OMIM 209885)	• Facial dysmorphism (macrostomia, sparce eyebrows, ocular telecanthus, bilateral ectropion, abnormal and low-set ears, bulbous nasal tip with hypoplastic alae nasi, and low frontal hairline) • Nipple hypoplasia or absence • Hyperlaxity and redundancy of skin, • Anomalous external genitalia	Back and neck	Unknown
Schinzel-Giedion syndrome (OMIM 269150)	• Facial dysmorphism (midface hypoplasia, high protruding forehead) • Severe mental retardation • Skeletal abnormalities • Genitourinary and renal malformations • Cardiac defects • Neuroepithelial neoplasia	Generalized but sparing the face. Can recede during infancy	18q12.3/ SETBP1/611060
Zimmermann-Laband syndrome (OMIM 135500)	• Gingival fibromatosis, abnormalities of the cartilage of the nose and/or ears • Dysplastic or absent nails • Hypoplasia of the distal phalanges • Scoliosis • Hepatosplenomegaly	Generalized but sparing the face	3p14.3/unknown

Mahphoon, and one of two grandsons, Moung-Phoset, and great-grand-daughter, Mah-Mé [13]. An X-linked transmission is highly unlikely because males and females were affected to the same degree. These two families have been described as having deficient dentition but they were of normal stature as compared to their ethnicity. The early designation as "congenital hypertrichosis lanuginosa" was incorrect.

CGHT with gingival hyperplasia (gingival fibromatosis) may be considered as a particular subtype of this group. A typical example is Julia Pastrana (1834-1860) and her son [2]. Sporadic cases have been described in several reports [10, 14-17]. All these patients were of rather short stature, but had a normal number of teeth and unremarkable psychomotor development. Another patient from Yemen with gingival hyperplasia and epilepsy was born into a consanguineous family, indicating an autosomal recessive trait. A splice mutation in *ABCA5* was found to cause a decrease in protein levels throughout the patient's hair follicles [11].

Group 3: X-linked CGHT

A nonsyndromic X-linked type, originally described by Macias-Flores *et al*. in a Mexican five-generation family with 19 affected individuals, is characterized by excessive

Table 3. Examples of autosomal recessive diseases with very early onset of severe insulin resistance showing acanthosis nigricans and mild to moderate generalized hirsutism

	Main clinical features	Skin manifestations	Gene/Locus MIM No.
Rabson-Mendenhall syndrome (OMIM 262190)	Growth retardation Pineal hypertrophy Dental abnormalies Phallic enlargement/precocious puberty Insulin resistant diabetes mellitus Early death (5-15 years)	Acanthosis nigricans Hirsutism	19p13.2/INSR(compound heterozygosity)/147670
Donohue syndrome (OMIM 246200)	Elfin faces Growth retardation Gingival hyperplasia Phallic enlargement/precocious puberty Lipodystrophy Insulin resistant diabetes mellitus Death in early infancy	Acanthosis nigricans Hirsutism	19p13.2/ INSR(homozygosity)/147670
Berardinelli-Seip syndrome (OMIM 269700)	Congenital generalized lipodystrophy Extreme insulin resistance/hypertriglyceridemia Hepatosplenomegaly/hepatic steatosis Hypertrophic cardiomyopathy	Acanthosis nigricans Hirsutism	11q12.3/ BSCL2/606158

hair growth present at birth, which increases during the first year of life, sparing the palms, soles and mucosae [18]. There was no gingival hypertrophy or any other systemic abnormality. Males were consistently more severely affected than females, with the latter showing a patchy or checkerboard pattern of excessive hair distribution, reflecting functional X-chromosome mosaicism. The gene locus was mapped to Xq24-q27.1 [19, 20].

Moreover, syndromic X-linked forms have also been described. Tadin-Strapps *et al*. observed a large Mexican kindred characterized by a combination of CGHT, deafness and abnormal shape and position of teeth, inherited as an X-linked trait [21]. Males were more severely affected than females, who exhibited only mild hypertrichosis without deafness or dental anomalies. Haplotype analysis in this pedigree revealed linkage to a 13-cM region on Xq24-q27.1. A position effect on fibroblast growth factor 13 was recently found to be associated with this phenotype [22]. In another study of a five-generation Chinese family by Zhu *et al*, interchromosomal insertions at the same Xq27.1 site mediated by a human specific palindrome near *SOX3* was identified [23]. From 11 affected individuals, all of the four examined males had severe hypertrichosis associated with scoliosis (plus spina bifida in one case only), whereas all affected females had only mild hypertrichosis.

Another group of patients with less dense and extensive CGHT show mostly multiple congenital abnormalities of greater severity and compromised life expectancy [1, 24-30]. These may include autosomal dominant diseases, such as Cantú syndrome, Cornelia de Lange syndrome, Barber-Say syndrome, Schinzel-Giedion syndrome and Zimmermann-Laband syndrome *(table 2),* and autosomal recessive diseases with a very early onset of severe insulin resistance and acanthosis nigricans, such as Rabson-Mendenhall syndrome, Donohue syndrome and Berardinelli-Seip syndrome *(table 3).* By contrast, most of the patients in our analysis tended to maintain continuously and strongly growing terminal hair in adulthood, indicating a peculiar category of hypertrichosis, probably with a different pathogenesis *(table 1).*

In conclusion, "Ambras syndrome" appears to be a useless term because it deludes one into believing that a nosologically uniform entity with this name may exist. In fact, this designation never had a specific meaning. It was interchangeably applied to various types of hypertrichosis that differ from each other both clinically and genetically. Hence, the name "Ambras syndrome" should no longer be used to delineate any of the different types of congenital hypertrichosis. ■

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