REVIEW ARTICLE
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A review of genetic syndromes associated with hypertrichosis

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INTRODUCTION

Hypertrichosis can be very troublesome for the affected patients and their families. This condition is characterized by an increase in hair growth beyond normal variation in areas that are not predominantly androgen-dependent, independent of age, race, or sex[1,2]. Hypertrichosis is classified according to the age of onset (congenital or acquired), the extent of distribution (generalized or localized), and whether it is isolated or associated with various abnormalities[2,3]. Further classification takes into consideration the type of follicle: lanugo, vellus, or terminal hair. Lanugo follicles are responsible for the growth of the first hairs, which are thin, soft, slightly pigmented, and nonmedullated, produced in the uterus, and are eliminated after birth. Lanugo hypertrichosis has been observed in adults with various forms of hypertrichosis. Vellus follicles are not medullated, thin, and poorly pigmented, and terminal hair is pigmented, medullated, and has a larger diameter compared with other types of hair[1,4].

The incidence of isolated hypertrichosis is unknown, and it is considered very rare. The incidence increases when it presents itself as a phenotype of several genetic syndromes[2]. Several causes of hypertrichosis have been described, including the use of drugs, infection, neoplasia, genetic diseases, and metabolic or nonendocrine disorders, but it is not caused by an excess of androgens[5]. This condition is often confused with hirsutism; however, the latter refers specifically to the growth of terminal hair in women or children, in androgen-dependent areas, and in places where there is normally no terminal hair, with a typical adult male distribution pattern[6].

There are several theories for the pathogenesis of hypertrichosis. First, it has been proposed to be caused by the conversion of intermediate or vellus hair to terminal hair, or from changes in the hair growth cycles, with follicles spending more time in the anagen phase and an increase in follicular density[1]. However, the triggers of these mechanisms are still not fully understood.

Hypertrichosis is not only a cutaneous sign but also an underlying rare complex disease that can affect multiple organ systems[1-3,7] and has previously been related to abnormalities in the head and neck, skeletal, nervous system, intellectual disability (ID), neoplasia, abdominal, genitourinary, cardiovascular, among others. However, there are only a few reviews in the literature. The aim of this study was to offer an overall survey of hypertrichosis-associated genetic diseases described in the literature and provide a summary of its clinical presentation.

METHODS

A search was performed from June 2020 to October 2020 in the online electronic database *Online Mendelian Inheritance in Man* (OMIM, https://www.omim.org), with associations of the terms "hypertrichosis" or "hirsutism." Nondependent disturbances to androgen metabolism or syndromes with overlapping features were included as hypertrichosis. Additional searches were performed in the electronic databases PubMed (https://pubmed.ncbi.nlm.nih.gov) and Orphanet (https://www.orpha.net/consor/cgi-bin/index.php) to complement the search for scientific articles, in the English language.

The clinical features of each disturbance were organized into categories by one collaborator, as provided in OMIM, and

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features of the head and neck, inheritance, skeletal, cardiovascular, ID, nervous system, neoplasia, genitourinary, abdominal, endocrine, respiratory, dental anomalies, and phenotypic and genetic characteristics were also evaluated. The data were entered into Excel for statistical analyses. The study collected public domain data, thus dispensing with the approval of the Ethics and Research Committee.

RESULTS

A total of 274 entries were found in OMIM. In 33 entries, both terms hypertrichosis and hirsutism were referring to the same disturbance. Notably, 121 genetic conditions associated with hypertrichosis were included in the research, as described in Chart 1. Description of genes and disturbances caused by hyperandrogenism or related conditions, such as polycystic ovarian syndrome, hyperprolactinemia, hyperthyroidism, congenital adrenal hyperplasia, androgen-secreting tumors, among others, were excluded. However, more than one OMIM entry can refer to the same syndrome. Disturbances with overlapping syndromes were also included. A few disturbances were not found in OMIM, but were found in PubMed (i.e., dysraphism, nevoid hypertrichosis, polythelia pilosa, primary multifocal hypertrichosis, and segmental odontomaxillary dysplasia). The distribution of the frequency of clinical involvement categories is described in Table 1.

The main inheritance pattern observed was autosomal recessive (44.62%). Nevertheless, some disturbances can occur with a mixed pattern. Autosomal dominance was observed in 36.36%, and other or unknown inheritance patterns were observed in 20.66% of genetic entities. The most affected categories observed were the head and neck features (80.16%), skeletal (78.51%), and the nervous system (73.55%).

Other highlighted categories were ID (52.06%), abdomen (42.97%), genitourinary (39.66%), dental anomalies (32.23%), cardiovascular (32.23%), respiratory (25.61%), and early death, until childhood (18.18%). Malignancies were of another concern, observed in 8.26% of cases, as described in Table 2, and endocrinopathies were identified in 14.04% of disturbances.

DISCUSSION

There has been a growing recognition that rare diseases are relevant medical and social problems[8-10]. In this study, 121 genetic disturbances associated with hypertrichosis were identified. The first documented case of hypertrichosis in the scientific literature was the case of Petruz Gonzales, born in the Canary Islands archipelago in 1556, at the Ambras Castle[2]. Other cases later became famous, including those of circus exhibitionists, such as the case of Julia Pastrana, a Mexican dancer of indigenous origin, and the Russian Theodoro Petrov[11,12]. Although more than 300 new Mendelian phenotypes are added to the OMIM each year[13], only a few cases of hypertrichosis-associated genetic disturbances have been reported.

The prevalence of congenital generalized hypertrichosis is very rare[2]. Nevertheless, no universally accepted definition for rare diseases has yet been established[10,14]. According to the World Health Organization (WHO) and the criterion adopted by the Ministry of Health of Brazil, a rare disease is a disease whose prevalence affects less than 65/100,000 individuals or 1.3/2,000 individuals[15,16]. All conditions described in this study are rare.

Hypertrichosis can be classified as being associated with other symptoms, or as an isolated feature, but there are only a few examples of hypertrichosis as a cardinal symptom[17]. The majority of diseases express hypertrichosis as a component of complex syndromes[18], as shown in this study. Another classification is based on the localization hypertrichosis; however, the literature is not always clear enough to discern between localized and generalized hypertrichosis.

Head and neck features were the most affected category, identified in more than two-thirds of the disturbances; this includes abnormalities in the head, face, ears, eyes, nose, mouth, neck, and teeth, which reveal the importance of a thorough physical exam. Teeth abnormalities were identified in 32.23% of genetic entities. Dental anomalies are excellent dysmorphic markers and may help in syndrome diagnosis[12,19].

Skeletal involvement was identified in 78.51% of disturbances. Genetic skeletal disorders account for most human skeletal dysplasia; however, the genotype–phenotype correlations remain an important challenge[20]. Mutations in the same gene may be associated with heterogeneous phenotypes, as the same phenotype can be caused by mutations in several genes, such as Coffin–Siris, which has a wide genetic heterogeneity[20].

The nervous system was affected in 73.55% of the genetic entities. ID is a prominent feature observed in 52.06% of cases, usually identified early in childhood, due to developmental delay[7]. Given the greater clinical severity of the disease, its incidence is much higher than the worldwide prevalence, estimated at 1% of the general population[21]. ID is diagnosed by IQ testing; however, its severity (i.e., mild, moderate, severe, and profound) can be highly variable, even in the same disorder, given the wide heterogeneous phenotype of genetic diseases[21].

Another major concern is the association between hypertrichosis and cancer development, observed in 8.26% of cases (Table 2). In this context, different genes are associated, the main inheritance pattern observed is autosomal dominant, and the prognosis is usually poor. No correlation was found between the genetic entity and a unique type of malignancy, as

Chart 1. Genetic syndromes associated with hypertrichosis.

Syndromes	
Achalasia–Microcephaly	Dental Anomalies And Short Stature
Adducted Thumbs Syndrome	Desanto–Shinawi Syndrome
Agenesis of corpus callosum, cardiac, ocular, and genital syndrome	Developmental and Epileptic Encephalopathy 57
Alazami–Yuan Syndrome	Developmental and Epileptic Encephalopathy 85 With or Without Midline Brain Defects
Amaurosis Congenita, Cone–Rod Type, With Congenital Hypertrichosis	Diabetes Mellitus, Insulin Resistant, With Acanthoses Nigricans Type A
Anemia, Congenital Hypoplastic, With Multiple Congenital Anomalies/Mental Retardation Syndrome	Diarrhea, chronic, with villous atrophy
Barber–Say Syndrome	Distichiais, Tristichiasis
Becker Nevus Syndrome	Donohue Syndrome
Beckwith–Wiedemann Syndrome	Dysraphism
Bloom Syndrome	Dyssegmental Dysplasia, Rolland–Desbuquois Type
Bohring–Opitz Syndrome	Ectodermal Dysplasia 14, Hair/Tooth Type with or Without Hypohidrosis
Cahmr Syndrome	Ehlers–Danlos Syndrome, Dermatosparaxis Type
Cantu Syndrome	Erythroderma, Ichthyosiform, Congenital, Reticular
Cerebellar Ataxia, Mental Retardation, And Dysequilibrium Syndrome 2	Erythrokeratodermia Variabilis Et Progressiva 2
Cerebellar, Ocular, Craniofacial, And Genital Syndrome	Facial Dysmorphism, Hypertrichosis, Epilepsy, Intellectual/ Developmental Delay, And Gingival Overgrowth Syndrome
Cerebral Malformation, Seizures, Hypertrichosis, And Overlapping Fingers	Facial Hypertrichosis
Cerebrooculofacioskeletal Syndrome 1	Fibromatosis, Gingival, With Hypertrichosis And Mental Retardation
Cervical Hypertrichosis with Underlying Kyphoscoliosis	Filippi Syndrome
Cervical Hypertrichosis, Anterior Cervical	Floating–Harbor Syndrome
Cervical Hypertrichosis, Congenital Anterior Cervical, with Peripheral Sensory and Motor Neuropathy	Fontaine Progeroid Syndrome
Chromosome 17q12 Deletion Syndrome	Frontometaphyseal Dysplasia 1 e 2
Chromosome 17q21.31 Duplication Syndrome	GM-1 – Gangliosidosis type I
Coffin–Siris Syndrome 1, 2, 3, 4, 8 ,9	Hairy Ears; Hairy Ears, Y-Linked
Congenital Disorder Of Glycosylation Iaa, Iq e Ile	Hairy Elbows
Cornelia De Lange Syndrome 1, 3, 4	Hairy Palms and Soles
Corpus Callosum, Agenesis Of, With Abnormal Genitalia	Hajdu–Cheney Syndrome
Cousin Syndrome	Hennekam Lymphangiectasia–Lymphedema Syndrome 1
Craniorhiny	Histiocytosis–Lymphadenopathy Plus Syndrome H Syndrome, Rosai–Dorfman Disease, Familial
Crouzon Syndrome	Hydronephrosis Congenital, With Cleft Palate, Characteristic Facies, Hypotonia, Mental Retardation
Curry–Jones Syndrome	Hypertrichosis lanuginosa; congenital; with/without gingival hyperplasia; Ambras

Continue...

Chart 1. Continuation.

Syndromes	
Hypomelanosis of Ito	Neurodevelopmental Disorder With Progressive Microcephaly, Spasticity, And Brain Anomalies
Intellectual developmental disorder with cardiac defects and dysmorphic facies	Nevoid Hypertrichosis
Imagawa–Matsumoto Syndrome	Oliver–Mcfarlane Syndrome
Immunodeficiency 49	Perching Syndrome
Joubert Syndrome 10	Polythelia Pilosa
Kabuki Syndrome 2	Pontocerebellar Hypoplasia Type 8
Leigh Syndrome	Porphyria Cutanea Tarda I, Ii,Porphyria, Congenital Erythropoietic Variegate Porphyria
Lethal Short-Limb Skeletal Dysplasia, Al Gazali Type	Primary Multifocal Localized Hypertrichosis
Leukodystrophy, Hypomyelinating, 17	Ramon Syndrome
Liang–Wang Syndrome	Rubinstein–Taybi Syndrome I, Ii
Lichtenstein Syndrome	Sandestig–Stefanova Syndrome
Light Fixation Seizure Syndrome	Schinzel–Giedion Midface Retraction Syndrome
Lipodystrophy, Congenital Generalized, Type 2 Berardinelli–Seip Syndrome	Schwartz–Jampel Syndrome, Type 1
Lissencephaly 7 With Cerebellar Hypoplasia	Seckel Syndrome 9
Lymphedema–Hypoparathyroidism Syndrome	Segmental Odontomaxillary Dysplasia
Mandibulofacial Dysostosis With Macroblepharon And Macrostomia	Sialuria
Mannosidosis, Alpha B, Lysosomal	Spastic Paraplegia 53, Autossomal Recessive
Marshall–Smith Syndrome	Specific Granule Deficiency 2
Meester–Loeys syndrome	Spinocerebellar Ataxia 42, Early-Onset, Severe, With Neurodevelopmental Deficits
Melanocytic Nevus Syndrome	Spinocerebellar Ataxia, Autosomal Recessive 20
Mental Retardation, Autosomal Dominant 57	Spondyloepimetaphyseal Dysplasia, Genevieve Type
Mental Retardation, Autosomal Recessive 35	Stocco Dos Santos X-Linked Mental Retardation Syndrome
Mental Retardation, Microcephaly, Epilepsy, And Coarse Face	Sweeney–Cox Syndrome
Mental Retardation, X-Linked 99, Syndromic, Female-Restricted	Tenorio Syndrome
Mental Retardation, X-Linked, Syndromic, Chudley–Schwartz Type	Trichohepatoneurodevelopmental Syndrome
Mental Retardation, X-Linked, Syndromic, Nascimento Type	Trichomegaly
Michelin Tire Baby Syndrome	Vissers–Bodmer Syndrome
Mitochondrial Complex I Deficiency, Nuclear Type 23	Warburg Micro Syndrome
Mucopolysaccharidosis, Type Ii, Iiic, Iiid, Vii	Wiedemann–Steiner Syndrome
Mullerian Derivatives, Persistence Of, With Lymphangiectasia And Postaxial Polydactyly	Zimmermann–Laband Syndrome 1
Multicentric Osteolysis, Nodulosis, And Arthropathy	

one condition can be associated with several types of malignancies, but some may occur more often than others. For example, melanocytic nevus syndrome is associated with melanoma, and Beckwith–Wiedemann is associated with Wilms tumor and hepatoblastoma[22,23]. Nevertheless, Bloom syndrome and Schinzel–Giedion syndrome are associated with multiple malignancies[24,25]. In other genetic diseases, such as the Bohring–Opitz syndrome and Rubinstein–Taybi syndrome, tumor predisposition has been observed in many case reports, but the risk cannot be established or fully dismissed because epidemiologic studies have not been conducted to demonstrate an increased risk of developing cancer[26,27].

Hypertrichosis is not caused by androgens but is often confused with hirsutism, which is usually associated with hyperandrogenism. In this study, 17 conditions were associated with endocrinopathies. The most common abnormalities were diabetes mellitus, insulin resistance, and thyroid dysfunction (hypothyroidism and thyroid lymphangiectasis). Diabetes mellitus, insulin resistance, acanthosis nigricans type A, and Donohue syndrome are caused by a mutation in the insulin receptor gene (INSR) and are associated with insulin resistance and hyperinsulinemia[28,29]. Another example is the Berardinelli–Seip syndrome, which is associated with polycystic ovary disease, diabetes mellitus, and the Beckwith–Wiedemann syndrome, which is associated with adrenocortical cytomegaly and pituitary hyperplasia[23,30]. However, the Donohue syndrome, Berardinelli–Seip syndrome, and Beckwith–Wiedemann syndrome are the major causes of hypertrichosis in the literature[1,2,18,23]. One probable reason why these genetic conditions are classified as

Table 1. Clinical features of hypertrichosis associated genetic syndromes.

	Syndromes n (%)
Head and neck	97 (80.16)
Skeletal	95 (78.51)
Nervous system	89 (73.55)
Intellectual disability	63 (52.06)
Autosomal recessive	54 (44.62)
Abdominal	52 (42.97)
Genitourinary	48 (39.66)
Autosomal dominant	44 (36.36)
Cardiovascular	39 (32.23)
Dental anomalies	39 (32.23)
Respiratory	31 (25.61)
Other or unknown inheritance pattern*	25 (20.66)
Early death (until childhood)	22 (18.18)
Endocrine	17 (14.04)
Neoplasia	10 (8.26)

*X-linked, Y-linked, somatic mosaicism, somatic mutation, and isolated cases.

Table 2. Genetic disturbances with hypertrichosis associated with neoplasia.

Syndrome	OMIM	Inheritance	Gene	Chromosome
Beckwith–Wiedemann	130650	AD	H19; ICR1; KCNQ10T1; CDKN1C	11p15.5 11p15.4
Bloom	210900	AR	RECQL3	15q26.1
Bohring–Opitz	605039	AD	ASXL1	20q11.21
Curry–Jones	611707	Somatic mosaicism	SMO	7q32.1
Donohue	246200	AR	INSR	19p13.2
Melanocytic nevus	137550	Somatic mutation	NRAS	1p13.2
Polythelia pilosa	–	–	–	–
Porphyria Cutanea tarda I, II Congenital erythropoietic porphyria Variegate porphyria	176090 176100 263700 176200	AD–AR AR AD	UROD UROS PPOX	1p34.1 10q26.2 1q23.3
Rubinstein–Taybi I, II	180849 613684	AD AD	CREBBP EP300	16p13.3 22q13.2
Schinzel–Giedion midface retraction syndrome	269150	AD	SETBP1	18q12.3

AD: autosomal dominant; AR: autosomal recessive; OMIM: Online Mendelian Inheritance in Man.

hypertrichosis is that hyperandrogenism may aggravate the problem, as hypertrichosis has also been described in adult males, not only in androgen-dependent areas[1,2,18].

Hypertrichosis can cause significant emotional distress for affected patients and their families[1,18]. Patients may experience difficulty in accessing the qualified health system, as the clinical characteristics are heterogeneous and can lead to diagnosis delays[15]. Early diagnosis of these conditions helps guide early intervention, screening, and genetic counseling of patients and their family members. The development of clinical protocols helps health professionals, patients, and families to make decisions regarding the most appropriate alternatives for their healthcare.

There is a limitation in the interpretation of data from case reports, with a small number of patients, an inherent characteristic of rare disease studies. The literature is not always clear enough to elucidate the type of hair disorder, whether hypertrichosis or hirsutism. In fact, it is common for both terms to be used in case reports of the same genetic disorder. It was imperative to deepen the knowledge to perform the necessary discernment to conduct the work and exclude what was not the object of investigation of the study.

CONCLUSIONS

This study shows that hypertrichosis may be more common than estimated, especially when we consider it to be a phenotype of several diseases. The research also suggested that cutaneous manifestations may also hide an underlying disease that requires investigation. Multiple organ systems can be affected, and the study highlights the most affected ones. These aspects reinforce the need for further studies to support protocols for public organizations and policies, facilitate decision-making, and promote ongoing health training for the management of hypertrichosis and its underlying potential disorders.

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AUTHORS' CONTRIBUTIONS

VFC: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review and editing. **MCB:** Conceptualization, Data curation, Formal analysis, Writing – original draft. **DRBM:** Conceptualization, Writing – review and editing. **MJBA:** Formal analysis, Writing – review and editing. **PRB:** Formal analysis, Writing – review and editing. **HMJ:** Conceptualization, Data curation, Formal analysis, Writing – review and editing.

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