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Hypertrichosis associated with genetic conditions with head and neck alterations

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Abstract

INTRODUCTION: Hypertrichosis is a rare disorder in which there is an exaggerated growth of body hair in places that are not necessarily androgen-dependent, a particular feature of hirsutism. Its etiology is still questionable, with an increased incidence when associated with syndromes. This genetic association leads to numerous significant systemic and craniofacial changes, which should be recognized and considered by the dentist.

OBJECTIVE: To assess, in databases, the presence of congenital hypertrichosis associated with genetic syndromes and conditions affecting the head and neck.

METHODS: The search was conducted in PubMed-NCBI databases; genetic conditions along with their characteristics were available in Online Mendelian Inheritance in Man (OMIM) and in Protein®.

RESULTS: The analysis was performed on 63 articles and all diseases were considered as rare. In the syndromes, prevalence of autosomal dominant inheritance was observed in 48.64%, followed by autosomal recessive in 45.9%, 1 X-linked recessive case, and 1 arising from defective mitochondrial energy generation. Among the 63 genetic conditions, 44 showed neurodevelopmental changes. Besides the craniofacial involvement itself, there is a high prevalence of alterations of the oral structures involving 47 of all conditions, including mainly dental abnormalities, palatal and gingival changes.

CONCLUSION: The association of hypertrichosis with genetic components is strongly associated with major craniofacial changes. Therefore, the knowledge of the dental surgeon about the conditions that can affect the oral cavity is impressive because it is related to a correct treatment and better quality of life for the patient.

KEYWORDS: Craniofacial Abnormalities; Dermatology; Genetic Disorders; Hirsutism; Hypertrichosis

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Introduction

Hypertrichosis *[#307150 (WMO)*)] is a rare disorder in which the body hair grows longer than is considered normal when compared to people of the same age, sex, race, and for a particular area of the body [1-3]. It usually occurs in regions where hair follicles are present that are not necessarily androgen-dependent, except for those locations such as the lips, palms of the hands, and soles of the feet that are normally hairless [1,3].

One condition that can occasionally lead to a misdiagnosis of hypertrichosis is hirsutism [4]. This variation affects especially females, resulting in abnormal hair growth and giving them a male phenotype, since in these cases hair growth is androgen-dependent, thus distinguishing it from hypertrichosis [1,4-8].

The clinical features of hypertrichosis vary according to the type of hair and there are three variations that can

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eventually manifest themselves [4,5]. Lanugo is the hair that covers the fetal skin and is lost in the first weeks of the baby's life, being thin and non-pigmented. The vellus replaces the lanugo and corresponds to most of the postnatal body hair, not being androgen- dependent, besides being lightly pigmented, thin and short. The terminal hairs, on the other hand, are thicker, more pigmented, and their length varies according to their location due to androgen dependence [1,4,5,9-11].

One of the mechanisms that occurs in congenital hypertrichosis is the conversion of vellus hair to terminal hair in regions where terminal hair would not normally develop, but this change is not well understood [4]. Another is based on changes in the hair growth cycle. Hair follicles go through three stages - anagen, catagen, and telogen [11,12]. A systemic influence will lead to changes in this pattern, so that the follicles persist longer in the anagen phase, the active phase of growth, resulting in the characteristic phenotype [4].

In its idiopathic form, atavism is an assumption that would explain the typical physical appearance. The ancestral gene responsible for hair growth would remain latent during its evolution and by an erroneous reactivation in them, the hypertrichotic [1] profile would result. Its classification is based on the etiology and location and may be related to a congenital or acquired form, with a localized or generalized pattern, and according to the type of hair [2,4,13].

For the most part, hypertrichosis is considered an aesthetic problem, but often it may signal an underlying systemic alteration, since the incidence increases when it is associated with genetic syndromes or conditions [1,4,14]. Some syndromes with associated hypertrichosis have been mentioned featuring specific molecular defects, such as Fontaine Progeroid Syndrome with involvement of the *SLC25A24* gene; Coffin-Siris Syndrome affecting the genes of the *BAF* complex and Wiedeman-Steiner Syndrome involving the *KMT2A* gene [1,15-17].

Systemic conditions such as kidney, heart and bone problems may be associated with the presence of congenital hypertrichosis [1]. Moreover, craniofacial dysmorphisms with hypertelorism, eyebrow abnormalities, prominent mouth philtrum, dental anomalies with oligodontia, microcephaly, short neck, high and arched palate and gingival hyperplasia are signs commonly found in these carriers [1,18]. The recognition of these alterations in these individuals by the dentist is essential, since it will provide a differential diagnosis and a better clinical outcome for the dental abnormalities [19].

Therefore, this paper presents a review of the literature on syndromes and genetic conditions associated with the presence of congenital hypertrichosis with head and neck involvement.

Material and Methods

The present study consists of a qualitative exploratory research work. An extensive search of the PubMed-NCBI databases for scientific papers was performed in a limited period from July to September 2020, with no limits set as to the date they were published. The scope of this project is the investigation of genetic conditions that appear concomitantly with the clinical picture of hypertrichosis with craniofacial changes. Syndromes and polymorphisms based on these features were available in *Online Mendelian Inheritance in Man* (OMIM) and *Protein*, which were considered sufficient for this manuscript taking into account the inclusion and exclusion criteria [19,20].

Papers that did not associate hypertrichosis as a characteristic were excluded, as well as those considered extremely rare with not very relevant craniofacial features, those associated with acquired hypertrichosis, and those citing isolated hirsutism not associated with hypertrichosis. All cases that presented clinical conditions of hypertrichosis with craniofacial comorbidities and those rarely associated with hypertrichosis, but with relevant head and neck alterations, were included. The

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descriptor used for the search was "hypertrichosis" limited to the English language. Occasionally, an extension of the search to complement the study was performed by PubMed-NCBI [20].

Results

After a rigorous search in the English language literature, a total of 143 genetic conditions were found, and of these, 63 were included in the research. The studies were analyzed individually and, in all of them, where hypertrichosis appeared associated with some genetic component, a great reflection on the head and neck structures was noticed, as well as a great oral and dental involvement.

These genetic disorders were tabulated so that, in summary, they described the most commonly encountered general and craniofacial features (Charts 1 and 2), and those conditions that rarely had the hypertrichotic condition but with relevant head and neck changes (Chart 3) [19].

Discussion

The syndromes identified that presented hypertrichosis as a common feature were those in which this cutaneous finding manifested itself in a generalized manner; in these cases, the phenotype was consistent with craniofacial involvement. These include Cahmr, Cantu, and Gingival Overgrowth Syndrome [21-23]. In addition to the syndromes, hypertrichosis as a consiste feature has been cited in polymorphisms such as Hypertrichosis Lanuginosa Congenita, Hypertrichosis Congenita Generalized, A atp Linkage Cassette subfamily A member 5 and Hypertrichosis Congenita Generalized, with or without gingival hyperplasia [24-26].

In syndromes associated with hypertrichosis, it is noteworthy that the mode of inheritance commonly found is autosomal dominant (AD), with an involvement of 48.64% (18). In addition, the remainder showed to be autosomal recessive (AR) in 45.94% (17), 1 case arising from defective mitochondrial energy generation (Mi) and 1 X-linked recessive [19,20].

An analysis of the general characteristics of the disorders showed a significant prevalence of neurodevelopmental changes, with an involvement in 29 out of 37 of the syndromes identified, and polymorphisms bringing an involvement in 15 out of 26. Embryologically, the nervous system and the skin derive from the ectoderm, so the presence of these congenital skin conditions are highly associated with neurological changes [27]. Traits such as intellectual and cognitive impairment, delayed psychomotor development, limb ataxia, spasticities, cerebellar atrophy, and some psychiatric behavioral manifestations have been cited.

Furthermore, it can be seen that all the genetic disorders selected in the study presented head and neck alterations, but some features were more commonly found than others. These included those showing nasal changes (39 of 63), dental abnormalities including changes in shape, size, quantity, and delayed eruption (26 of 63), ear dysmorphisms (24 of 63), with palate changes (19 of 63), gingival involvement (17 of 63), showing microcephaly (16 of 63), and traits of micrognathia (14 of 63).

It was observed during the selection of genetic conditions, 01 study in which there was disagreement regarding the classification of the diagnosis of the skin condition, not making clear the distinction between true hypertrichosis or hirsutism, in which the term used in the clinical synopsis of the study did not match the term that appeared described in the text [28]. According to Wendelin et al., (2003), there are reports in the literature that hypertrichosis is erroneously referred to as hirsutism [4]. According to Mofid A. et al. (2007), a differential diagnosis must be made because these are two different [29] conditions. Hirsutism is excessive hair growth in women in androgen-dependent areas including facial beards and moustaches, and body hair in the pubic area and inner thighs, while hypertrichosis is excessive hair growth in androgen-independent areas and gender [4-8].

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In view of the research carried out at *OMIM*, we noticed that all syndromes and polymorphisms associated with congenital hypertrichosis are considered rare diseases, since there are few case reports described in the literature [5]. The definition of being rare is based on the prevalence of affected individuals, but this definition varies in different countries, since some consider the total number of affected individuals and not the proportion of the affected population [30,31].

According to Mukherjee K. (2019), in the United States a rare condition is defined as one that affects fewer than 200,000 patients, in the European Union fewer than 250,000, and in Japan fewer than 50,000 patients. According to the World Health Organization- WHO (2016), in which was also adopted by the Ministry of Health in Brazil, define rare diseases those that affect up to 65 people in every 100,000 individuals [31,32].

It is evident that systemic capillary pathology associated with a genetic component is accompanied by several changes in the head and neck, both in its morphology and physiology, as shown in the researched literature [1]. It is possible to observe some of these morphophysiological changes in Coffin-Siris syndrome 3, which include microcephaly, visual and hearing impairment, anteverted nostrils, and trichomegaly, as described in charts 1.

Dysmorphisms of the facial bones have been widely reported, including micrognathia, prognathism and hypoplasia of the malar bones as shown in Bloom syndrome, Autosomal Recessive Mental Retardation 35, Congenital Disorder of Glycosylation Type IIe, Barber-Say and Progeroid Fontaine syndromes. Furthermore, oral and dental involvement is quite prevalent, and in certain genetic diseases accompanied by hypertrichosis, dental involvement is quite characteristic of the systemic condition carried as shown in Congenital Erythropoietic Porphyria (chart 2), since erythrodoontia is the most typical dental alteration. According to Gomes (2020), calcified tissues show high susceptibility in pigment deposition and porphyrins have a higher affinity for phosphate and calcium, explaining a greater deposition of them during osteogenesis and odontogenesis, thus conferring a reddish coloration both in bones and teeth [33].

The research carried out shows significant gingival involvement in those with congenital hypertrichosis, highlighting hyperplasias, hypoplasias, hypertrophies, and fibromatoses. Gingival fibromatosis is described as an excessive and benign enlargement of the free and attached gingiva [34] and, according to Chacon-Camacho, its etiological basis may be isolated or as part of a genetic condition. It is considered rare, but its incidence increases when it is associated with a genetic disease, commonly those characterized by hypertrichosis, and gingival fibromatosis is largely considered an important diagnostic component of these diseases [35].

Hypertrichosis as characteristics of genetic syndromes involve a series of head and neck alterations, as mentioned before, and must be taken into consideration by health professionals, especially dentists. In view of the results, it can be stated that hypertrichosis, when associated with a genetic component, whether a disease or a syndrome, reflects major changes in the head and neck region, besides the face itself, secondarily affecting the oral structures, including changes in the quantity and morphology of the teeth, gingival structures, tongue and palate. The relevance of knowledge of congenital hypertrichosis accompanied by craniofacial dysmorphisms by oral health professionals can be seen, since the dental surgeon routinely practices clinical evaluation of the maxillomandibular complex, not limited only to the evaluation of the oral cavity, but also being made a careful observation of the head and neck region [19,20].

Although rare, it is advisable that these professionals have an understanding of this genetic picture since it will influence the clinical conduct of the patient. In cases of suspicion, medical follow-up should be done and, when associated with dental interventions, will result in better oral clinical outcomes.

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Therefore, this paper provides a study that will help to contribute to the expansion of knowledge by oral health professionals about these conditions with head and neck involvement, helping in the differential diagnosis and multiprofessional work.

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Chart 1: Genetic syndromes reported with hypertrichosis: features

SYNDROMES	MOI	Chromosome	OMIM	FEATURES
Cahmr	AR	N/A	211770	General: Congenital lamellar cataract, generalized hypertrichosis, and mental retardation. H&N: Highly arched palate, microdontia, and depressed nasal bridge.
Ramon	AR	N/A	266270	General: Low weight, kyphosis, scoliosis, hypertrichosis,mental retardation, and seizures. H&N: Kerubism, gum fibromatosis,papillomatosis, and delayed tooth eruption.
Barber-Say	AD	2q37	#209885	General: Generalized hypertrichosis and mental retardation. H&N: Mandibular prognathism, Micrognathia, dysmorphic ears, Hypertelorism, Macrostomia, High arched palate, and Delayed eruption.
Progeroid Fontaine	AD	1p36	#612289	General: Hair abnormalities, aged appearance, and hypertrichosis. H&N: Microcephaly, progeroid appearance, micrognathia, retrognathia, dysmorphic ears, hypertelorism, microstomia, high arched palate, and oligodontia.
Coffin Siris 1	AD	6q25	#135900	General: Intellectual disability, hypertrichosis, poor growth. H&N: Facial hypertrichosis, dysmorphicears, strabismus, long eyelashes, wide nasal tip, macrostomia, and delayed dentition.
Histiocytosis-Lymphadenopathy Plus	AR	10q22	#602782	General: Short stature, splenomegaly, camptodactyly, hypogonadism and hypertrichosis. H&N: Submandibular lymphadenopathy, orbital and nasal mass due to histiocytosis, exophthalmos, retropharyngeal lymphadenopathy, and cervical lymphadenopathy.
Zimmermann-Laband 3	AD	1q21	#618658	General: Hypoplasia or aplasia of phalanges, hypertrichosis, jointhyperextensibility and hepatosplenomegaly. H&N: Facial hypertrichosis, thick eyebrows, long eyelashes, triangular nostrils, gingival hyperplasia, high and arched palate, and a bifid uvula.
Wiedemann-Steiner	AD	11q23	#605130	General: Hypertrichosis cubitalis, intellectual disability and short stature. H&N: Dysmorphic ears, hypertelorism, strabismus, thick eyebrows, long eyelashes, high arched palate, and abnormal dentition.
Cantu	AD	12p12	#239850	General: Generalized congenital hypertrichosis, osteochondrodysplasia,cardiomegaly and lymphedema. H&N: Macrocephaly, coarse facies, prominent forehead, long eyelashes, wide and flat nasal bridge, gingival hypertrophy, and short neck.

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Zimmermann-Laband 1	AD	1q32	#135500	General: Hypertrichosis, joint hyperextensibility, and intellectual disability. H&N: Prognathism, dysmorphic ears, thick eyebrows, gingival fibromatosis, gingival hyperplasia, higharched palate, and delayed tooth eruption.
Schinzel-Giedion Midface Retraction	AD	18q12	#269150	General: Hypertrichosis, mental retardation, skeletal abnormalities,genitourinary, renal and cardiac malformations. H&N: Coarse facies, midface hypoplasia, facial hemangioma, shallow orbits, proptosis, hypertelorism, macroglossia, and short neck.
Leigh	AR, Mi	N/A	#256000	General: Hypertrichosis, psychomotor retardation, hypotonia, ataxia, and dysphagia. H&N: Ophthalmoplegia, optic atrophy, nystagmus, strabismus, ptosis,and pigmentary retinopathy.
Seckel Syndrome 9	AR	3p21	#616777	General: Growth retardation, microcephaly, mental retardation and hypertrichosis. H&N: Microcephaly, scaphocephaly,micrognathia, and pointy nose.
Lymphedema-Hypoparathyroidism	AR	N/A	247410	General: Lung disease, nephropathy, brachydactyly, and hypoparathyroidism. H&N: Cataracts, ptosis, telecanthus, wide nasal bridge, and hypertrichosis.
Zimmermann-Laband 2	AD	8p21	#616455	General: Hypertrichosis, joint hyperextensibility, hepatosplenomegaly, and intellectual disability. H&N: Sensorineural deafness, thickeyebrows, wide and bifid nasal tip, gingival hyperplasia, macroglossia, and short neck.
Coffin-Siris 3	AD	22q11	#614608A	General: Intellectual disability, hypertrichosis, and poor growth. H&N: Microcephaly, coarse facies, thickeyebrows, long eyelashes, anteverted nostrils, macroglossia, and delayed dentition.
Donohue	AR	19p13	#246200	General: Cystic ovaries, delayed bone age,acanthosis nigricans, pachyderma, hypertrichosis, and precocious puberty. H&N: Elven facies, small face, large and low set ears, prominent eyes, gingival hyperplasia and macrostomia.
Warburg Micro 1	AR	2q21	#600118	General: Short stature, severe mental retardation, and hypogonadism. H&N: Microcephaly, micrognathia, large ears, microphthalmia, optic atrophy, ptosis, deep eyes, and facial hypertrichosis.
Trichohepatoneurodevelopmental	AR	17q23	#618268	General: Woolly hair, hypotonia,developmental delay, and hypertrichosis. H&N: Microcephaly, ptosis, hypertelorism, visual impairment, hyperopia, nasal bone hypoplasia, high arched palate, macroglossia, severe diastemas,crowding of teeth, microdontia, and prognathism.
Coffin-Siris 4	AD	19p13	#614609	General: Intellectual disability, hypertrichosis and poor growth. H&N: Microcephaly, hearing and visual impairment,long eyelashes, macrostomia, macroglossia, and delayed teething.

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Tenorio	AD	18q12	#616260	General: Intellectual disability, hypoglycemia, inflammatory diseases similar to Sjögren's syndrome, and hypertrichosis. H&N: Macrocephaly, telecanthus, dry keratoconjunctivitis, thick eyebrows, recurrent stomatitis, macroglossia, prognathism, and delayed dentition.
Warburg Micro 3	AR	10p12	#614222A	General: Severe mental retardation, hypogonadism and hypertrichosis. H&N: Microcephaly, brachycephaly, optic atrophy, nystagmus, blepharophimosis, down-turned corners of mouth, and prominent secondary alveolar ridges.
Sandestig-Stefanova	AR	9q34	#618804	General: Trigonocephaly, camptodactyly, delayed myelination and hypertrichosis. H&N: Microcephaly, trigonocephaly, retrognathia, arched eyebrows, epicanthus, cleft lip and palate, high arched palate, and short neck.
Coffin-Siris 2	AD	1p36	#614607	General: Intellectual disability, poor growth and hypertrichosis. H&N: Gross facies, thick eyebrows, long eyelashes, antevertednostrils, macrostomia, macroglossia, and delayed dentition.
Marshall-Smith	AD	19p13	#602535	General: Accelerated skeletal maturation, mentalretardation, and hypertrichosis. H&N: Micrognathia, retrognathia, prominent eyes, bluish sclera, thick eyebrows,glossoptosis, gingival hypertrophy, and irregular dentition.
Bloom	AR	15q26	#210900	General: Growth deficiency, telangiectatic skin and hypertrichosis. H&N: Dolicocephaly, microcephaly, malar hypoplasia, prominent nose and absence of upper lateral incisors.
Ambras	AD	8q22	% 145701	General: Generalized hypertrichosis, and hexadactyly. H&N: Facial roughness, wide intercanthal distance, anteverted nostrils, flat mentholabial groove, and dental abnormality.
Rabson-Mendenhall	AR	19p13	# 262190	General: Insulin resistant diabetes mellitus with pineal hyperplasia, skin abnormalities and hypertrichosis. H&N: Prognathism, macroglossia, fissured tongue, gingival hypoplasia, highly arched palate, prematureeruption of teeth, and dental anomalies.
Hunter	XLR	Xq28	# 309900	General: Skeletal deformities, developmental delay, hyperactivity, mental retardation, dementia, and hypertrichosis. H&N: Macrocephaly, papilledema, retinal pigmentation, ptosis, macroglossia, delayed tooth eruption, widely spaced teeth, and short neck.
Berardinelli-Seip	AR	11q12	# 269700	General: Adipose tissue shortage, hepatic steatosis, and hypertrichosis. H&N: Prognathism, triangular facies, acromegaloid appearance and large ears.
Gingival Overgrowth Syndrome	AD	11q13	# 618381	General: Delayed motor and intellectual development, and generalized hypertrichosis. H&N: Hypotonic facies, micrognathia, gingival growth, prominent lip vermilion and everted upper lip.

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Torg	AR	16q12.2	259600	General: Severe multicentric osteolysis and hypertrichosis. H&N: Corneal opacities, hyperpigmented skin patches, and gingival hypertrophy.
Okamoto	N/A	N/A	604916	General: Congenital hydronephrosis, severe mental retardation and growth deficiency. H&N: Cleft palate, hypoplasia of the mid-face, hypertrichosis, long eyelashes, prominent eyes, epicanthus, dysmorphic ears, short snub nose, and winged neck.
Coffin- Siris 8	AD	12q13	618362	General: Intellectual disability and hypoplastic or absent fifth finger phalanges. H&N: Rough facial features, hypertrichosis, thick eyebrows, long eyelashes, ptosis, anteverted nostrils, ophthalmologic abnormalities, anda snub nose.

Chart 2: Polymorphisms with hypertrichosis: features

DISEASE	OMIM	CHARACTERISTICS
Hypertrichosis Lanuginosa Congenita	145700	General: Universal hypertrichosis, skeletal disordersand mental retardation. H&N: Dental deformity, double eyebrows, andglaucoma.
Congenital Generalized Hypertrichosis, withor without Gingival Hyperplasia	135400	General: Generalized hypertrichosis. H&N: Hirsutism, epicanthal folds, and gingival fibromatosis.
Generalized Congenital Hypertrichosis	307150	General: Scoliosis and congenital generalized hypertrichosis in males. H&N: Deformed and badly positioned teeth and Hirsutism.
Potassium Channel,Subfamily K, Member 4	605720	General: Hypertrichosis, epilepsy, intellectual and developmental delay. H&N: Facial dysmorphism and gingival growthsyndrome.
Mandibulofacial dysostosis with macroblephon and macrostomia	602562	General: N/A. H&N: Micrognathia, retrognathism,hypertelorism, hypertrichosis of the eyebrows, anteverted nostrils, macrostomia, malpositioned teeth, and oligodontia.
Congenital glycosylation disorder, type Iaa	617082	General: Hypertrichosis, hypotonia, epilepsy, spasticity, and delayedpsychomotor development. H&N: Microcephaly, hearing and visual impairment,retinal pigmentary spotting and macular lesions.
Congenital glycosylation disorder, type Iq	612379	General: Ichthyosiform dermatitis, hyperkeratosis, hypertrichosis, and mental retardation. H&N: Brachycephaly, coloboma, hypertelorism, and visual loss.
Mental Retardation,X-Linked 99, Syndromic, Female Restricted	300968	General: Scoliosis, hypertrichosis, delayed psychomotor development,and muscular hypotomia. H&N: Brachycephaly, facial asymmetry, dysmorphic ears, eye abnormalities, and dentalabnormalities.

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Mental Retardation, Autosomal Dominant 57	618050	General: Scoliosis,hypertrichosis, neurological alterations, and muscularhypotonia. H&N: Microcephaly, asymmetrical face, blepharophimosis, telecanthus, epicanthal folds, microstomia, and deep palate.
Congenital Erythropoietic Porphyria	263700	General: Short stature, photosensitivities, hypertrichosis, and alopecia. H&N: Conjunctivitis, corneal scarring, red stainedteeth (erythrodontia).
Dental anomalies and short stature	601216	General: Short stature, delayed bone age, scoliosis, and hypertrichosis. H&N: Maxillary hypoplasia, oligodontia, amelogenesis imperfecta, microdontia, yellow teeth, severe diastemas, taurodontia, anadontia of permanent teeth.
Alpha B Lysosomal Mannosidosis	248500	General: Hypertrichosis, mental retardation,spasticity, and nystagmus. H&N: Macrocephaly, frontal bossing, prognathism, epicanthic folds, macroglossia, gingival hypertrophy and severe diastemas.
Mental Retardation, Autosomal Recessive 35	**% 615162**	General: Clinodactyly, globaldevelopmental delay, and hypertrichosis. H&N: Malar hypoplasia, dysmorphic ears, hypertelorism, upturned lower lip, and micrognathia.
Mullerian Derivatives, Persistence of, with Lymphangiectasia and Postaxial Polydactyly	% 235255	General: Hypertrichosis, and lymphedema. H&N: Micrognathia, hypertelorism, hypertrophied alveolar ridge, highly arched palate, cleft palate and short neck.
Agenesis of the Corpus Callosum, Cardiac, ocular andgenital	618929	General: Pectus excavatum, global developmental delay, and intellectual disability. H&N: Macrocephaly, frontal bossing, micrognathia, facial hypertrichosis, dysmorphic ears, hypertelorism, atresic palate, and winged neck.
Congenital Disorderof Glycosylation, Type IIe	608779	General: Hypertrichosis, global developmental delay, and muscular hypotonia. H&N: Microcephaly, micrognathia, retrognathia, flat malar region, protruding tongue, thick gums, and short neck.
Gm1-Gangliosidosis Type I	230500	General: Dwarfism, joint stiffness, dermal melanocytosis, hypertrichosis, and mental retardation. H&N: Coarse facies, hypertelorism, gingival hyperplasia and short neck.
Neurodevelopmental Disorder With Progressive Microcephaly, Spasticity and Brain Anomalies	617527	General: Pectus carinatum,hirsutism, muscular hypotonia, and mental retardation. H&N: Microcephaly, micrognathia, dysmorphic ears, nystagmus, optic atrophy, and highly arched palate.

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Atp Link CassetteA, Subfamily A, Member 5	612503	General: Generalized hypertrichosis and epilepsy. H&N: Severe gingival hyperplasia.
Trichomegaly	190330	General: Hereditary spherocytosis. H&N: Hypertrichosis of the cheeks, forehead and eyebrows, and long eyelashes.
Facial hypertrichosis	134000	General: N/A. H&N: Hypertrichosis of the face.
Gingival Fibromatosis with Hypertrichosis and Mental Retardation	605400	General: Mental retardation, epilepsy and brachymetacarpalia. H&N: Hirsutism,dysmorphic ears, and gingival hypertrophy.
Intellectual Developmental Disorder with Cardiac Defects andDysmorphic Facies	618316	General: Variable congenital heart disease and global developmental delay. H&N: Triangular face, deep eyes, hypertelorism, dysmorphic ears, very arched eyebrows and hypertrichosis.

Chart 3: Syndrome and polymorphisms with rare hypertrichoses and with relevant H&N involvement: features

CONDITIONS AND SYNDROMES	Chromosome	OMIM	MOI	FEATURES
Chromosome 17q12deletion syndrome.	17q12	# 614527	AD	General: Short stature, mental retardation, and autistic features. H&N: Dolicocephaly, micrognathia, retrognathia, hypertrichosis of the upper lip, and high palate.
Philippi Syndrome	2q13	# 272440	AR	General: Short stature, syndactyly, andintellectual disability. H&N: Microcephaly, hairy forehead, microdontia, dental anomaly, hypodontia, andserrated incisors.
Autosomal Recessive Spinocerebellar Ataxia 20	-	616354	-	General: Psychomotorproblems, and intellectual disability. H&N: Macrocephaly, epicanthal folds, highly arched palate, macroglossia, delayed tooth eruption, and tooth crowding.
Pontocerebellar Hypoplasia, Type 10	-	615803	-	General: Psychomotor problems, convulsions,and brain atrophy. H&N: Microcephaly, prominent eyes, long eyelashes, strabismus, nystagmus, and well arched palate.
Spinal Muscular Atrophy with Congenital Bone Fractures 1	-	616866	-	General: Delayed psychomotor development, and congenital bonefractures. H&N: Microretrognathia, hypertelorism,microstomia, highly arched palate.
Adducted Thumbs syndrome	N/A	%201550	AR	General: Generalized hypotonia, respiratory insufficiency and hypertrichosis. H&N: Myopathic rigid facies, open mouth, arched high palate, cleft palate, microcephaly and dysphagia.

H&N (head and neck); N/A (not available); AD (autosomal dominant); AR (autosomal recessive); OMIM (online Mendelian inheritance in man); MOI (mode of inheritance); Mi (mitochondrial)

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