Original Research
Stomatology

Dental anomalies in syndromes displaying hypertrichosis in the clinical spectrum

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Abstract: Hypertrichosis and dental anomalies may occur alone or in combination in the spectrum of many syndromes. To identify genetic entities characterized by hypertrichosis and dental anomalies, a search was performed in the Mendelian Inheritance in Man database with the terms "*hypertrichosis*" or "*hirsutism*" and "tooth" or "dental abnormalities." Nondependent androgen metabolism disturbances were classified as hypertrichosis. Genetic entities with hypertrichosis and dental anomalies were included in the study. Additional searches were performed in the PubMed and Orphanet databases, when necessary, in order to include data from scientific articles. An integrative analysis of the genes associated with the identified syndromes was conducted using STRING to characterize biological processes, pathways, and interactive networks. The p-values were subjected to the false discovery rate for the correction of multiple tests. Thirty-nine syndromes were identified, and dental agenesis was the most frequent dental anomaly present in 41.02% (n = 16) of the syndromes. Causative genes were identified in 33 out of 39 genetic syndromes. Among them, 39 genes were identified, and 38 were analyzed by STRING, which showed 148 biological processes and three pathways that were statistically significant. The most significant biological processes were the disassembly of the nucleosome (GO:0006337, p = 1.09e-06), chromosomal organization (GO:0051276, p = 1.09e-06) and remodeling of the chromatin (GO: 0006338, p = 7.86e-06), and the pathways were hepatocellular carcinoma (hsa05225, p = 5.77e-05), thermogenesis (hsa04714, p = 0.00019), and cell cycle (hsa04110, p = 0.0433). Our results showed that the identification of hypertrichosis and dental anomalies may raise the suspicion of one of the thirty-nine syndromes with both phenotypes.

Keywords: Hypertrichosis; Genetic Disease, Inborn; Tooth Abnormalities.

Introduction

Hypertrichosis is characterized by an abnormal increase in hair anywhere in the body and is independent of androgens. It can result from the use of drugs, hereditary factors, or metabolic disorders, and occurs in an isolated form or is associated with other clinical

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manifestations constituting a syndrome. The isolated form is infrequent, with an unknown incidence, but its frequency increases when it participates as a phenotype of syndromes.[1]

Although important genetic features can be found in syndromic forms, which provide data for the definition of the phenotype,[2] clinical descriptions are useful for patient care, especially in complex cases. Dental anomalies are common clinical manifestations associated with hypertrichosis, including variations in color, eruption, number, size, and form of teeth, and their occurrence varies based on the type of anomaly, dentition, and population. Dental anomalies are relevant clinical signs and can provide important clues for the suspicion of a genetic entity and for the differential diagnosis of the syndromes with hypertrichosis.[3] Thus, the aim of this study was to identify the set of genetic syndromes with dental anomalies coinciding with the clinical presence of hypertrichosis.

Methodology

A search was performed from June 2020 to October 2021 in the Mendelian Inheritance in Man database (OMIM, https://www.omim.org) with the associations of the terms "*hypertrichosis*" or "*hirsutism*" and "tooth" or "dental abnormalities". Nondependent androgen metabolism disturbances were classified as hypertrichosis. An additional search was performed using the PubMed and Orphanet databases (https://pubmed.ncbi.nlm.nih.gov and https://www.orpha.net/consor/cgi-bin/index.php, respectively), using the same search terms, in order to include data from scientific articles. Phenotypic and genotypic manifestations were predominantly collected at OMIM by a single collaborator. Dental anomalies were grouped according to the classification established by De La Dure-Molla et al.[3] STRING, protein-protein interaction network functional enrichment analysis (http://string-db. org), was used to investigate the biological processes, pathways, and interaction network. The p-values were subjected to the false discovery rate to correct multiple tests, and values ≤ 0.05 were considered significant.

Results

Seventy-seven entries were identified; however, 39 syndromes with hypertrichosis and dental anomalies in the clinical spectrum were included in the study (Table 1). Entries with a description of genes or those related to hirsutism were excluded; however, overlapping syndromes were also included. Only segmental odontomaxillary dysplasia was not found in OMIM, but was found in scientific articles in PubMed.

The frequencies of the dental anomalies are listed in Table 2. Dental agenesis was the most frequent dental anomaly in this study, present in 41.02% (n = 16) of the syndromes. Other common anomalies included delayed tooth eruption (35.89%, n = 14), widely spaced teeth (28.20%, n = 11), dental malocclusion (25.64%, n = 10), and tooth shape changes (25.64%, n = 10).

Among the identified syndromes, 15 (38.46%) were inherited as autosomal recessive traits, and 15 (38.46%) were autosomal dominant. Isolated cases (n = 4), X-linked dominant inheritance (n = 4), X-linked recessive inheritance (n = 2), and mosaicism (n = 1) were also identified. Causative genes were recognized in 33 of 39 syndromes. Among them, 39 genes were recognized; nevertheless, a genetic entity can be linked to more than 1 gene, and some entities have not been related to any gene until now. STRING analyses were performed with 38 genes because 1 gene was not recognized by the software (*RFF125*), and it showed 148 biological processes and 3 pathways. Figure shows the protein-protein interaction network. The most significant biological processes were nucleosome disassembly (GO:0006337, p = 1.09e-06), chromosome organization (GO:0051276, p = 1.09e-06), and chromatin remodeling (GO:0006338, p = 7.86e-06), and the pathways were hepatocellular carcinoma (hsa05225, p = 5.77e-05), thermogenesis (hsa04714, p = 0.00019), and cell cycle (hsa04110, p = 0.0433) (Tables 3 and 4).

Discussion

In the current study, 39 syndromes with dental anomalies associated with hypertrichosis were identified

Table 1. Syndromes with hypertrichosis and dental anomalies.

Syndrome	OMIM	Inheritance	Gene	Chromosomal	Dental Anomalies	Reference
Alazami-Yuan syndrome	#617126	AR	*TAF6*	7q22.1	Crowded teeth	12
Barber-Say syndrome	#209885	AD	*TWIST2*	2q37.3	Taurodontism in the molar tooth, early apical closure in permanent and incisive blade-shaped anterior teeth, delayed tooth eruption, infra-occluded molars and wide alveolar grooves	13
Bloom syndrome	#210900	AR	*RECQL3* (*WRN*)	15q26.1	Agenesis of the upper lateral incisors	14
Cantu syndrome	#239850	AD	*ABCC9*	12p12.1	Dental malocclusion	15
Chromosome 17q21.31 duplication syndrome	#613533	IC	-	17q21.31	Crowded incisor	16
Coffin-siris syndrome	#135900	AD	*ARID1B*, *ARID1A*, *SMARCB1*, *SMARCA4*, *SMARCE1*	6q25.3	Abnormal dental shape and hypodontia	17
	#614607			1p36.11		
	#614608			22q11.23		
	#614609			19p13.2		
	#616938			17q21.2		
Cornelia de Lange syndrome	#122470	AD	*NIPBL*,	5p13.2	Agenesis of the lower lateral incisors, agenesis of deciduous second molars, deciduous macrodontic teeth, permanent macrodontic teeth, agenesis of the lower deciduous lateral incisors, conoid incisor, delayed tooth eruption, microdontia, dysmorphic teeth and widely spaced and rotated teeth	18
Crouzon syndrome	#123500	AD	*FGFR2*	10q26.13	Agenesis of deciduous second molars and dental crowding	19
Dental anomalies and short stature	#601216	AR	*LTBP3*	11q13.1	Enamel hypoplasia, widely spaced teeth, retention of deciduous teeth, delayed eruption of permanent teeth, imperfect amelogenesis, taurodontic pulp chambers, microdontic primary teeth, permanent tooth oligodontics and enamel discoloration	20
Developmental and epileptic encephalopathy 85 with or without midline brain defects	#301044	XLD	*SMC1A*	Xp11.22	Crowded teeth, single central incisor	21
Ectodermal dysplasia 14, hair/tooth type with or without hypohidrosis	#618180	AR	*TSPEAR*	21q22.3	Oligodontics, conoid teeth	22
Ehlers-Danlos syndrome	#225410	AR	*ADAMTS2*	5q35.3	Upper canine agenesis, lower premolar agenesis, lower molar agenesis, lower incisor agenesis and lower premolar agenesis, permanent teeth with color change, microdontia, malocclusion	23
Fillippi syndrome	#272440	AR	*CKAP2L*	2q14	Microdontia, hypodontia (rare), saw teeth, widely spaced teeth	24
Fontaine Progeroid syndrome	#612289	AD	*SLC25A24*	1p13.3	Hypodontia, microdontia, oligodontia and widely spaced teeth, bell-shaped crown, spindle-shaped roots and small or absent pulp chamber	25

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Continuation

Frontometaphyseal dysplasia	#305620	XLR	*FLNA*	Xq28	Selective tooth agenesis, delayed tooth eruption, retained deciduous teeth, malocclusion, irregularly implanted teeth.	26
	#617137	AD	*MAP3K7*	6q15		
Hypertrichosis, congenital generalized	#307150	XLD	-	Xq27.1	Delay in tooth eruption, hypodontia, and dental shape alteration.	27
Hypertrichosis, congenital generalized, with or without gingival hyperplasia	#135400	AR	*ABCA5*	17q24.2-q24.3	Widely spaced teeth, delayed tooth eruption	
Hypomelanosis of Ito	#300337	Somatic Mosaic	-	Xp11	Upper incisors with claw-shaped cusps and anterior deciduous teeth with yellowish-brown crowns and widely spaced teeth	28
Hajdu-Cheney syndrome	#102500	AD	*NOTCH2*	1p12	Early tooth loss and malocclusion	29
Hennekan Lymphangiectasia-Syndrome 1	#235510	AR	*CCBE1*	18q21.32	Oligodontia, peg-shaped incisors and delayed eruption	30
Immunodeficiency 49	#617237	AD	*BCL11B*	14q32.2	Neonatal teeth	31
Kabuki syndrome 2	#300867	XLD	*KDM6A*	Xp11.3	Macrodontics, dental malocclusion, agenesis of upper lateral incisors and inner central incisors, neonatal teeth (rare)	32
Hypomyelinating leukodystrophy-17	#618006	AR	*AIMP2*	7p22.1	Widely spaced teeth	33
Lichtenstein syndrome	#246550	IC	-	-	Enamel hypoplasia and discolored teeth	34
Mandibulofacial dysostosis with macroblepharon and macrostomia	#602562	IC	-	-	Ectopic teeth and oligodontics	35
Mannosidosis, alpha B, lysosomal	#248500	AR	*MAN2B1*	19p13.13	Teeth widely spaced	36
Marshall-Smith Syndrome	#602535	AD	*NFIX*	19p13.13	Dental malocclusion	37
Mental retardation, X-linked 99, syndromic, female-restricted	#300968	XLD	*USP9x*	Xp11.4	Widely spaced teeth, malocclusion, crowding, tooth agglomeration	38
Mucopolysaccharidosis, type II	#309900	XLR	*IDS*	Xq28	Delay in tooth eruption and widely spaced teeth	39
Ramon syndrome	#266270	AR	-	-	Delay in tooth eruption	40
Rubinstein-Taybi syndrome	#180849	AD	*CREBBP*	16p13.3	Dental crowding, upper incisors with claw-shaped cusps, malocclusion, wedge-shaped or screwdriver and enamel discoloration	41
Segmental Odontomaxillary Dysplasia	-	IC	-	-	Pre-molar agenesis and delayed eruption of permanent molars	42
Schinzel-Giedion syndrome	#269150	AD	*SETBP1*	18q12.3	Macrodontics, tooth eruption delays, agenesis of the upper deciduous lateral incisors and agenesis of the lower deciduous lateral incisors	43
Specific granule deficiency 2	#617475	AR	*SMARCD2*	17q23.3	Irregularly shaped teeth, misaligned teeth and incomplete amelogenesis	44
Spinocerebellar ataxia, autosomal recessive 20	#616354	AR	*SNX14*	6q14.3	Delay in tooth eruption and crowding	45
Spondyloepimetaphyseal dysplasia, Camera-Genevieve type	#610442	AR	*NANS*	9q22.33	Dental misalignment	46

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Continuation						
Trichhepatoneurodevopmental Syndrome	#618268	AR	*CCDC47*	17q23.3	Widely spaced teeth, dental crowding, microdontia, dental malocclusion	47
Tenorio syndrome	#616260	AD	*RFF125*	18q12.1	Delay in tooth eruption	48
Weidemann-Steinner syndrome	#605130	AD	*KMT2A*	11q23.3	Delay in tooth eruption, supernumerary tooth between central incisor and deciduous canine, malocclusion, hypodontia and ectopic teeth	49
Zimmermann-Laband syndrome	#135500	AD	*KCNH1*	1q32.2	Delay in dental eruption	50

AD: autosomal dominant; AR: autosomal recessive; OMIM: Online Mendelian Inheritance in Man; XLD: x-linked dominant; XLR: x-linked recessive; IC: isolated cases.

Table 2. Frequency of the dental anomalies in syndromes hypertrichosis.

Dental anomalies*	n (%)
Dental agenesis	16 (41.02)
Delay in tooth eruption	14 (35.89)
Widely spaced teeth	11 (28.20)
Dental malocclusion	10 (25.64)
Tooth shape change	10 (25.64)
Dental crowding	9 (23.07)
Tooth malposition	7 (17.94)
Microdontics	6 (15.38)
Macrodontics	4 (10.25)
Tooth color anomaly	3 (7.69)
Neonatal Tooth	2 (5.12)
Taurodontism	2 (5.12)

*Description according to De La Dure-Molla *et al.* (2019)

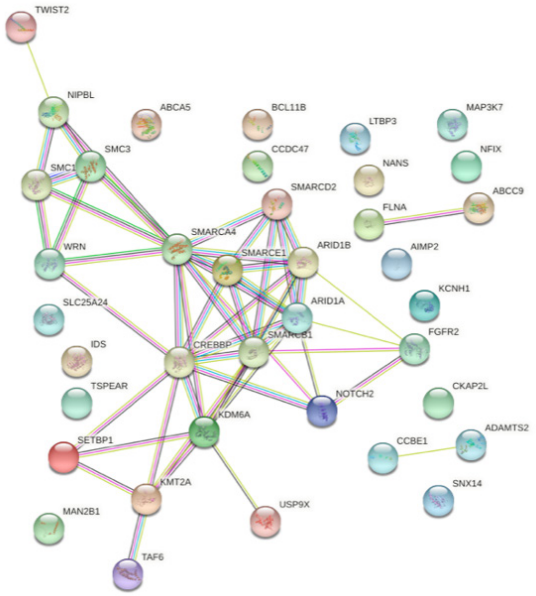

Figure 1. Protein-protein interaction network with the genes associated with syndromes with hypertrichosis and dental anomalies. Nineteen out of 38 genes formed a node including *ARID1A*, *ARID1B*, *CREBBP*, *FGFR2*, *KDM6A*, *KMT2A*, *NIPBL*, *NOTCH2*, *SETBP1*, *SMARCA4*, *SMARCB1*, *SMARCD2*, *SMARCE1*, *SMC1A*, *SMC3*, *TAF6*, *TWIST2*, *USP9X*, and *WRN* ($p < 1.0e-16$). Different colors represent different levels of evidence of connection between proteins. Light blue represents curated databases, purple experimental evidence, green gene neighborhood, red gene fusions, blue gene co-occurrence, light green evidence from text mining, black co-expression, and violet protein homology. This analysis had an average confidence score of 0.472, suggesting a low rate for false-positive interactions.

together with other important clinical features. Despite differences in the final structures and functions, this association is possible because ectodermal organs, such as the hair and teeth, originate from the epithelium and mesenchyme. The mesenchyme typically provides the first instructive signal, which is followed by the development of an early signaling node, the epithelial placode.[4] Morphogenesis is supported by placode buds into or out of the mesenchyme and subsequent proliferation, cell movements, and epithelium and mesenchyme differentiation.[4] Thus, countless genes can participate in these processes.

This highlights the degree to which common molecular mechanisms regulate many aspects of early hair and teeth development. This study found 7 genes in the BMP, 6 in the FGF, 7 in the Shh, and 18 in the Wnt pathways. In addition, there were significant differences between hair and teeth, especially in the spatial and temporal dynamics of placode growth, suggesting that in different

Table 3. Main biological processes characterized with the list of altered genes in syndromes with hypertrichosis and dental anomalies.

Gene	Term description	Observed gene count	Background gene count	False discovery rate	Matching proteins in your network
GO:0006337	nucleosome disassembly	5	18	1.09e-06	*SMARCB1, ARID1A, SMARCE1, SMARCD2, SMARCA4*
GO:0051276	chromosome organization	14	999	1.09e-06	*CREBBP, SMARCB1, NIPBL, WRN, ARID1A, SMC1A, SMARCE1, ARID1B, SMC3, MAP3K7, KDM6A, SMARCD2, SMARCA4, KMT2A*
GO:0006338	chromatin remodeling	7	156	7.86e-06	*SMARCB1, ARID1A, SMARCE1, ARID1B, KDM6A, SMARCD2, SMARCA4*
GO:0006325	chromatin organization	10	683	0.00015	*CREBBP, SMARCB1, ARID1A, SMARCE1, ARID1B, MAP3K7, KDM6A, SMARCD2, SMARCA4, KMT2A*
GO:0010604	positive regulation of macromolecule metabolic process	19	3081	0.00020	*AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, MAP3K7, KDM6A, NFIX, SMARCD2, SMARCA4, CCBE1, FGFR2, KMT2A*
GO:0019219	regulation of nucleobase-containing compound metabolic process	22	4133	0.00020	*NOTCH2, CREBBP, SMARCB1, SETBP1, NIPBL, WRN, USP9X, ARID1A, SMC1A, SMARCE1, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*
GO:0045934	negative regulation of nucleobase-containing compound metabolic process	13	1424	0.00028	*CREBBP, NIPBL, USP9X, ARID1A, SMC1A, SMARCE1, SMC3, FLNA, NFIX, SMARCA4, FGFR2, KMT2A, TWIST2*
GO:0045935	positive regulation of nucleobase-containing compound metabolic process	14	1770	0.00040	*CREBBP, SMARCB1, NIPBL, WRN, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, NFIX, SMARCD2, SMARCA4, FGFR2, KMT2A*
GO:0051173	positive regulation of nitrogen compound metabolic process	18	2946	0.00040	*AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, MAP3K7, NFIX, SMARCD2, SMARCA4, CCBE1, FGFR2, KMT2A*
GO:2000112	regulation of cellular macromolecule biosynthetic process	21	4050	0.00040	*NOTCH2, CREBBP, SMARCB1, SETBP1, NIPBL, USP9X, ARID1A, SMC1A, SMARCE1, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*

Table 4. Activated pathways characterized with syndromes with hypertrichosis and dental anomalies-containing-genes.

Variable	Term description	Observed gene count	Background gene count	False discovery rate	Matching proteins in your network
hsa05225	Hepatocellular carcinoma	6	163	5.77e-05	*SMARCB1, ARID1A, SMARCE1, ARID1B, SMARCD2, SMARCA4*
hsa04714	Thermogenesis	6	228	0.00019	*SMARCB1, ARID1A, SMARCE1, ARID1B, SMARCD2, SMARCA4*
hsa04110	Cell cycle	3	123	0.0433	*CREBBP, SMC1A, SMC3*

contexts, there may be specific means of modulating the signaling pathways and of the 39 genes found, 16 not participating in the four main pathways. It is likely that deregulation of these pathways (BMP, FGF, Shh, and Wnt) is responsible for the occurrence of hypertrichosis and dental anomalies.

Extensive genetic studies of defective mouse mutants have shown that signaling pathways (BMP,

FGF, Shh, and Wnt) are used reiteratively in many stages of the production of various skin appendages and of teeth, in biological processes through pathways such as the cell cycle.[5] The Wnt pathway plays an essential role during hair follicle induction and in the dental development. Shh is related to morphogenesis and differentiation at an advanced stage, whereas BMP is related to cell differentiation.[5]

Lymphoid augmentation factor 1 (Lef-1) is necessary for the development of multiple organ systems, including hair and teeth, and its role in Wnt signaling has been established. The expression of Lef-1 regulates the signaling of Wnt and target genes of Wnt, as well as mechanisms of cell proliferation, while miR-26b reduces the levels of expression of the Wnt target gene.[6] Lef-1 is regulated by FGF signaling, and the overexpression of Lef-1 in cells results in increased epithelial invagination and formation of extra hair follicles. Lef-1 deficiency results in dental morphogenesis stuck in the late phase of the button, and Lef-1 is only needed temporarily in the dental epithelium for tooth development.[6] At the molecular level, Lef-1 is necessary to induce an expression of FGF4, which regulates an expression of FGF3 and Shh in the tooth germ.[6]

Shh is critical for dental epithelial cells during tooth development, and inhibition of Shh signaling results in apoptosis located in the dental epithelium.[7] Hence, in both, disruption of individual signaling pathways also causes related developmental defects. Shh also promotes cell proliferation in anagen hair follicles.[5]

The antagonistic interactions between FGF and BMP in the oral epithelium play an important role in the positioning of the tooth formation sites. These FGF-BMP interactions control the expression of *Bmp4, Pax9, Barx1, Msx1, Msx2, Dlx* and other genes in the mesenchyme, whose combinatorial expression influences the type, number, size, and shape of the tooth.[5] During the beginning of dental formation, the BMP signaling in the epithelium antagonizes the FGF pathways, and this interaction is designed to determine the locations of dental formation. The interruption of BMP activity due to the excessive expression of noggin blocks the molar development and the differentiation of epithelial cells in the final stage.[8] BMP signaling has an inhibitory role in hair follicle induction and morphogenesis, which needs to be antagonized mainly by noggin to facilitate placebo induction. Overexpression of noggin in the epidermis results in the thickening of the epidermis, increased hair density, and the alteration of hair types.[8]

Ontology analysis revealed 148 biological processes and three pathways (hepatocellular carcinoma, thermogenesis, and cell cycle) formed by genes that interact with each other and constitute a large network. In most cases, dental agenesis is caused by mutations that interrupt epithelial Wnt/β-catenin signaling.[9] It is one of the fundamental signaling pathways for the growth and development of hair follicles and teeth, but is also responsible for contributing to the development of hepatocellular carcinoma and hepatoblastoma.[10,11] It is suggested that mutations in the genes found in the present study may interfere with the Wnt/β-catenin pathway.

The activation or under-activation of signaling pathways, such as Shh, Notch, TFG, BMP, and Wnt/β-catenin, plays a key role in the hair cycle.[5,8] This knowledge supports the understanding of the molecular basis of disturbances and the identification of intracellular targets for the development of therapies, such as hair loss treatment.[10]

Conclusion

Together, our results highlight that the identification of hypertrichosis and dental anomalies should raise the suspicion of the possibility of one of the thirty-nine genetic syndromes of the health professional for the proper management and care of the patient. The main dental anomalies described in individuals with genetic alterations associated with the clinical presence of hypertrichosis are agenesis, delayed tooth eruption, and widely spaced teeth. Further studies are required to better understand these associations.

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