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Minireview

Human *HOX* gene disorders

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ABSTRACT

The Hox genes are an evolutionarily conserved family of genes, which encode a class of important transcription factors that function in numerous developmental processes. Following their initial discovery, a substantial amount of information has been gained regarding the roles Hox genes play in various physiologic and pathologic processes. These processes range from a central role in anterior–posterior patterning of the developing embryo to roles in oncogenesis that are yet to be fully elucidated. In vertebrates there are a total of 39 Hox genes divided into 4 separate clusters. Of these, mutations in 10 Hox genes have been found to cause human disorders with significant variation in their inheritance patterns, penetrance, expressivity and mechanism of pathogenesis. This review aims to describe the various phenotypes caused by germline mutation in these 10 Hox genes that cause a human phenotype, with specific emphasis paid to the genotypic and phenotypic differences between allelic disorders. As clinical whole exome and genome sequencing is increasingly utilized in the future, we predict that additional Hox gene mutations will likely be identified to cause distinct human phenotypes. As the known human phenotypes closely resemble gene-specific murine models, we also review the homozygous loss-of-function mouse phenotypes for the 29 Hox genes without a known human disease. This review will aid clinicians in identifying and caring for patients affected with a known Hox gene disorder and help recognize the potential for novel mutations in patients with phenotypes informed by mouse knockout studies.

Contents

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1. Introduction

Since their initial discovery in 1978, the Hox genes have captivated a diverse group of investigators ranging from developmental biologists to pure clinicians. Hox genes are a group of evolutionarily conserved genes that encode a family of transcription factors that regulate early developmental morphogenetic processes and continue to be expressed into adulthood. The homeodomain, a highly conserved 60 amino acid helix-turn-helix motif, is the essential DNA-binding domain contained in all Hox genes identified to date. In vertebrates, specifically humans and mice, there are a total of 39 Hox genes organized into 4 distinct clusters. Through a process of tandem duplication and divergence, a single prototypic Hox gene gave rise to the initial Hox gene cluster which later gave rise to the multiple clusters seen in higher order organisms [1]. The 4 clusters in humans map to 4 different chromosomes and contain between 9 and 11 genes. These clusters, labeled HOXA, HOXB, HOXC and HOXD, are located on chromosomes 7p14, 17q21, 12q13 and 2q31, respectively.

The first Hox gene cluster was discovered in *Drosophila melanogaster* and consists of 9 genes divided into 2 subclusters (Antennapedia and Bithorax clusters) [2]. Since their initial discovery, Hox genes have been identified to be important regulators of anterior–posterior (AP) axis development [2]. The term "homeotic" was initially used to describe them, as mutations caused one body segment to appear similar to another segment. In humans, the gene clusters are organized in a 3′ to 5′ orientation with paralog group 1 (e.g., *HOXA1*, *HOXB1*, *HOXD1*) genes at the 3′ end of the cluster and higher number groups located at the 5′ end. Paralogs are highly similar not only in relative position in the clusters, but also in sequence due to creation by duplication of ancestral Hox clusters. The Hox clusters display a number of biologically important, but incompletely understood phenomena: 1) Spatial colinearity, 2) temporal colinearity, 3) posterior prevalence and 4) non-allelic non-complementation.

A clusters' spatial colinearity is represented as a pattern of expression over the AP axis corresponding to the order of a Hox gene in its gene cluster [3]. Specifically, 3′ genes in a cluster are expressed in more anterior portions of the developing embryo with the 5′ genes expressed more posteriorly. In addition to spatial colinearity, a cluster is also expressed temporally in a 3′ to 5′ manner. Taken together, genes at the 3′ end of clusters are expressed more anteriorly and earlier while genes at the 5′ end of clusters are expressed more posteriorly and later in development. In adjacent areas of expression, posteriorly expressed genes act dominantly over more anteriorly expressed genes, a phenomenon termed posterior prevalence [3,4]. Loss-of-function studies involving murine Hox genes classically cause an anterior homeotic transformation, with the transformed body segment more severely affected in its most anterior expression domain [5–7]. Homeotic transformations are not absolute yet result from gene expression overlap with other Hox genes. In areas patterned by only one Hox gene, instead of homeotic transformations, structural deficiencies are observed with mutations [3,8]. The outcome of mutations depends, therefore, on the extent of overlapping expression domains of both paralogous and adjacent, non-paralogous Hox genes [7,9,10].

Due to the duplication and divergence of ancestral Hox genes, vertebrates have been afforded functional redundancy in the form of the 4 Hox gene clusters [3]. Each paralogous group, composed of between 2 to 4 genes, shares the ability to influence development in areas of expression in the embryo, a phenomenon called non-allelic non-complementation. This is evident in studies involving single Hox loss-of-function mutations which show either a normal or mild phenotype, but exhibit a much more severe phenotype when double or triple knockouts are produced [8,11,12]. The concept of a "Hox code" has arisen based on the results of numerous elegant knockout studies. These have shown, through the knockout of single, double, triple and entire Hox clusters, that a given domain is patterned by the combination of the actively expressed Hox genes [13].

A total of 10 *HOX* genes have been found to cause human conditions (*HOXA1*, *HOXA2*, *HOXA11*, *HOXA13*, *HOXB1*, *HOXB13*, *HOXC13*, *HOXD4*, *HOXD10*, and *HOXD13*) [14,15]. Heterogeneity of inheritance, penetrance, expressivity and mechanism of pathogenesis is observed. Illustrating the highly conserved nature of the Hox genes, the human phenotypes strongly resemble homologous mouse mutants. Here, we review the HOX genes in which germline mutations have been identified to cause an abnormal human phenotype.

2. HOXA1

2.1. Clinical description

2.1.1. Bosley–Salih–Alorainy syndrome

Bosley–Salih–Alorainy syndrome (BSAS) was initially described in 9 individuals of Saudi Arabian and Turkish descent [16]. The phenotype consists of Duane retraction syndrome (DRS) type 3 (congenital horizontal gaze palsy), sensorineural hearing loss, inner ear abnormalities, delayed motor milestones and internal carotid artery malformations (Fig. 1). Neuroimaging typically reveals abnormalities that include unidentifiable abducens cranial nerves and abnormal inner ear anatomy with common cavity deformity, absence of the cochclea, semicircular canals or vestibule [16,17]. Internal carotid artery malformations are common as well and can range from unilateral hypoplasia to bilateral agenesis [16]. Typically the cerebrum, cerebellum and brainstem are normal [16,17]. Less frequently these individuals exhibit cardiovascular malformations (ventricular septal defect, Tetralogy of Fallot, total anomalous pulmonary venous return, interrupted aortic arch), minor facial dysmorphic features, limb anomalies, autism spectrum disorder, seizures and facial twitching or paresis [17]. Facial dysmorphisms can include low-set ears, flattened ear helices and/or bony facial asymmetry. Limb anomalies can include polydactyly, brachydactyly and/or clubfoot.

2.1.2. Athabascan brainstem dysgenesis syndrome

Athabascan brainstem dysgenesis syndrome (ABDS) is the more severe of the two *HOXA1*-associated conditions and has only been reported in individuals of Athabascan descent [17]. Patients typically present with horizontal gaze palsy, profound sensorineural hearing loss, severe intellectual disability, facial and bulbar weakness, central hypoventilation and conotruncal cardiac malformations [18]. Other less frequent findings include internal carotid artery malformations (though not all reported patients have undergone appropriate workups), facial twitching, facial and bulbar paresis and seizure disorders. It has been hypothesized that severe intellectual disability may result from global brain hypoxia secondary to hypoventilation, cerebrovascular malformations and the high altitude at which the Athabascan population lives [18]. Though there is significant overlap between ABDS and BSAS, patients with ABDS can be differentiated typically based on the presence of central hypoventilation and bulbar paresis as well as the lack of facial dysmorphisms and/or limb anomalies [17].

To date a total of 16 molecularly confirmed BSAS and 13 ABDS patients have been reported. The clinical distinction between BSAS and ABDS can be difficult to determine and in these cases molecular analysis should be used [17].

2.2. Molecular genetics

Like all Hox genes, *HOXA1* is composed of 2 coding exons, and all mutations have been identified in *HOXA1* exon 1. A total of 3 different homozygous mutations have been reported in BSAS: c.185delG, c.175–176insG and c.84C>G [17]. The c.185delG and c.175–176insG mutations have been described in patients of Saudi Arabian ancestry, with the c.84C>G mutation reported in a patient of Turkish descent. ABDS is caused by a homozygous c.76C>T mutation in individuals of Athabascan (Navajo and Apache) descent [17]. All 4 mutations predict a translationally truncated protein that lacks the homeodomain required for DNA-binding. An exact genotype–phenotype correlation is currently lacking to explain the different findings of BSAS and ABDS. Given that both conditions occur as a result of a truncated protein lacking the homeodomain, but have clear phenotypic differences, it has been suggested that variation is secondary to genetic modifiers specific to the isolated populations [16]. If stable proteins are produced from the mutant alleles, differences in phenotype could also depend on residual protein functions.

The *Hoxa1* knockout mouse has a phenotype very similar to that of ABDS patients, and *Hoxa1*$^{-/-}$ newborns typically die early on as a result of respiratory failure [16]. Knockout mice also have cardiac outflow tract abnormalities similar to human patients [2,19].

3. HOXA2

3.1. Clinical description

Only 4 individuals have been reported with *HOXA2*-associated autosomal recessive microtia [20]. All identified individuals are from a single consanguineous Iranian family with only 3 completing detailed clinical evaluation. Facial findings in all patients include grade II microtia, a short and narrowed auditory canal, cleft palate and occasionally unilateral facial paresis (Fig. 2) [20]. Radiographic findings can variably include unilateral or bilateral hypoplastic tympanic membranes, poorly developed mastoid air cells, small middle ear cavity and absent inner-ear structures. All have bilateral severe to profound mixed hearing impairment at all frequencies tested. Heterozygous carriers appear to be unaffected with normal audiometric testing and normal external ear anatomy.

3.2. Molecular genetics

Using genome-wide linkage analysis, a homozygous mutation (c.556C>A; p.Q186K) was identified in affected individuals [20]. The glutamine at position 186 is evolutionarily conserved and affects position 44 of the homeodomain, which normally functions in the recognition helix [20]. The *Hoxa2*$^{-/-}$ mouse displays similar findings, with both microtia and cleft palate [5,6,21]. Of note, 8 Hispanic and African-American non-syndromic microtia patients underwent sequencing of *HOXA2* and *SIX2*, a downstream target of *Hoxa2* in mice, with no pathogenic mutations identified [22]. Thus, *HOXA2* is likely not a frequent cause of non-syndromic microtia.

4. HOXA11

4.1. Clinical description

The principal findings of affected patients include radioulnar synostosis and thrombocytopenia [23]. Thompson and Nguyen identified 2 affected, unrelated families. The fathers and their children all had radioulnar synostosis, with 3 of the 4 affected children also affected with symptomatic thrombocytopenia [23]. The thrombocytopenia caused congenital bruising and bleeding and required correction via bone marrow or umbilical cord stem-cell transplantation [23].

4.2. Molecular genetics

A 1 base-pair *HOXA11* deletion (c.872delA) was found to cause RUSAT in all affected individuals. This deletion affects the homeodomain of exon 2 and results in a frameshift and premature translational stop codon that truncates the protein by 22 amino acids [23]. Heterozygous and homozygous mutant *Hoxa11* mice show both forelimb and hindlimb malformations, but not thrombocytopenia [24]. Connell et al. also showed that *Hoxa11*$^{-/-}$ mice lacked uterosacral ligaments suggesting *HOXA11* is essential for its development [25]. A cohort of 18 women requiring surgery for symptomatic pelvic organ prolapse (POP), compared to 10 women with normal pelvic support, showed a reduction in uterosacral ligament *HOXA11* expression [25].

5. HOXA13

5.1. Clinical description

Heterozygous mutations in *HOXA13* cause hand–foot–genital syndrome (HFGS, OMIM # 140000) and Guttmacher syndrome (OMIM #

176305) [26–28]. HFGS is an autosomal dominant condition characterized by limb malformations and urogenital defects [29]. Guttmacher syndrome not only has similar limb malformations and urogenital defects to HFGS but also includes additional hand findings including postaxial polydactyly [30]. HFGS is caused by *HOXA13* polyalanine expansions or point mutations and rare heterozygous locus chromosomal deletion, while Guttmacher syndrome has only been identified in individuals carrying a specific missense mutation within the homeodomain [26–28].

5.1.1. Hand–foot–genital syndrome

HFGS is an autosomal dominant condition characterized by both limb and urogenital malformations. The skeletal malformations are completely penetrant with urogenital defects exhibiting approximately 50% penetrance. The hallmark findings of HFGS are bilateral thumb and hallux hypoplasia caused by shortening of the distal phalanx and/or the first metacarpal or metatarsal (Fig. 3) [26,27]. Additional limb findings can include hypoplasia of the thenar eminences, hallux varus, small hallux toenail, fifth finger clinodactyly or short feet. Radiographically, HFGS is characterized by hypoplasia of the distal phalanx and first metacarpal of the thumbs and halluces, pointed distal phalanges of the thumb, short calcaneus, and occasional bony fusions of the middle and distal phalanges of the second through fifth toes [26,27]. Shortening of the thumbs and halluces is frequently mild but can be more severe in individuals carrying missense mutations [26,27]. Urogenital findings in affected females can include various degrees of incomplete Müllerian fusion, vesicoureteral reflux, urethral hypospadias, urinary incontinence or trigonal hypoplasia. In males urogenital defects can include hypospadias with or without chordee which can range in severity from mild to severe [26,27]. Fertility is normal in affected individuals.

5.1.2. Guttmacher syndrome

Guttmacher syndrome is characterized by limb and urogenital malformations similar to HFGS but with additional limb abnormalities [30]. Unique skeletal defects include postaxial polydactyly of the hands and short or uniphalangeal second toes with absent nails [28].

5.2. Molecular genetics

Mortlock and Innis identified a *HOXA13* nonsense mutation (c.1107G>A, W369X) in the originally reported HFGS family [26].

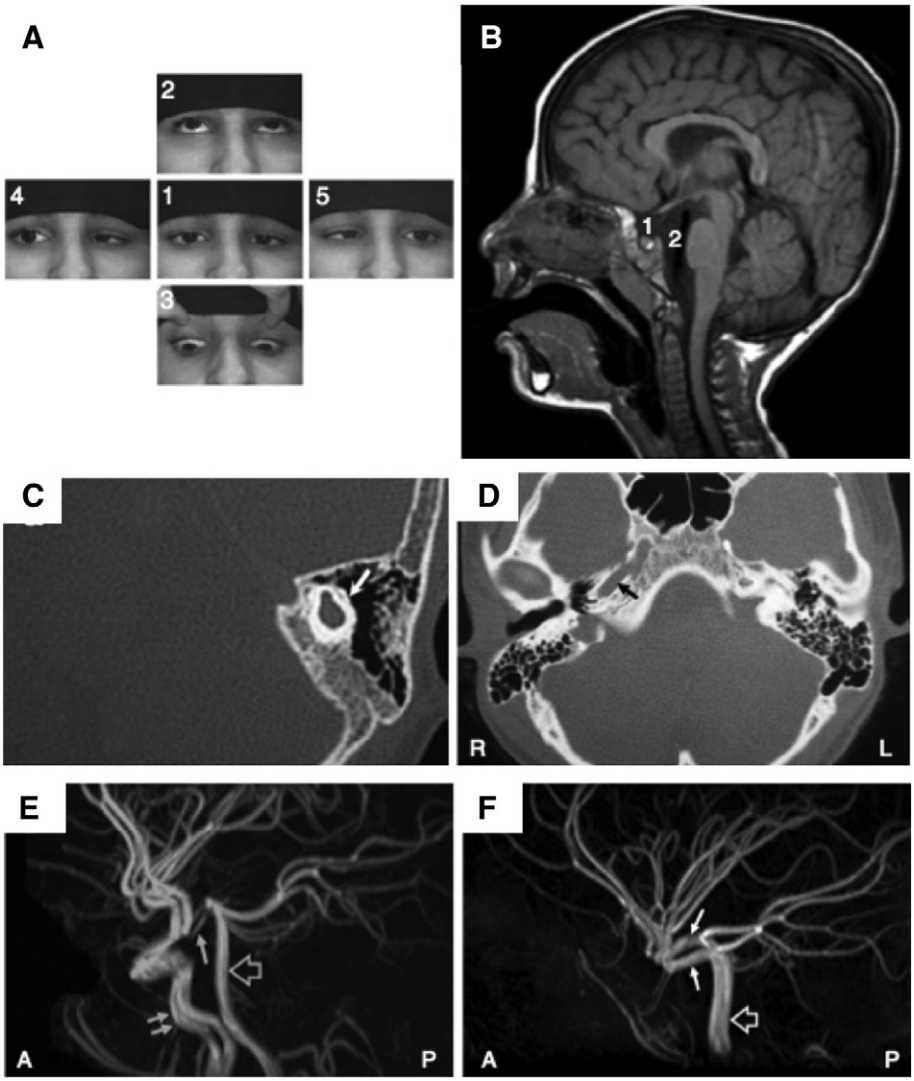

Fig. 1. Clinical features of BSAS caused by homozygous *HOXA1* mutations. A. Bilateral Duane syndrome. Primary gaze (1), upward gaze (2), downward gaze (3), limited abduction with retraction of globe and narrowing of the palpebral fissure with rightward (4) and leftward (5) gaze. B. Brain MRI showing normal cerebrum and cerebellum of affected patient but with enlarged suprasellar (1) and prepontine (2) cisterns. C. CT of the temporal bone showing underdevelopment of the left inner ear with the presence of a common cavity (arrow). D. CT of the skull base showing an absent left carotid canal (black arrow). E. Control brain MRI showing normal basilar artery (open arrow), posterior communicating arteries (single arrow) and overlapped left and right internal carotid arteries (double arrows). F. Brain MRI from an affected patient showing bilateral absent internal carotid arteries, enlargement of the basilar arteries (open arrow) and posterior communicating arteries (arrows).
Adapted from Tischfield et al. [16].

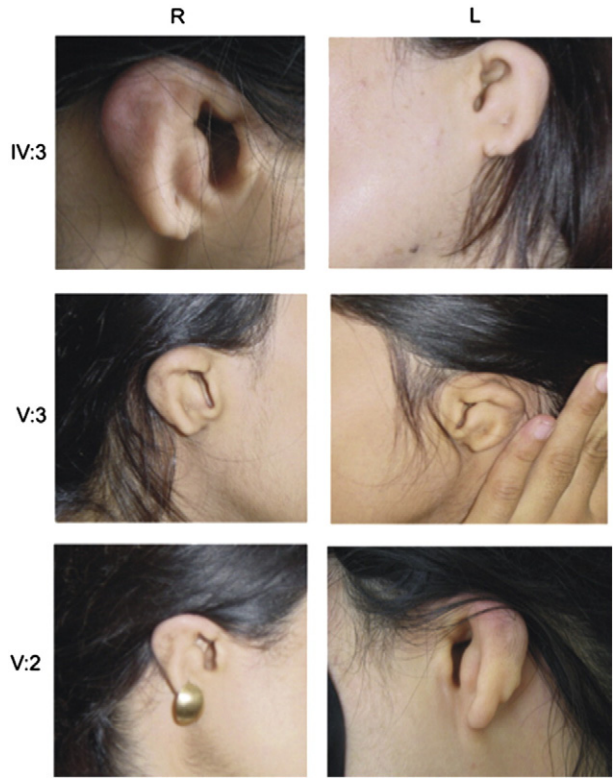

Fig. 2. Three affected patients with *HOXA2*-associated microtia. Reprinted from Alasti et al. [20].

Since that time a total of 16 different mutations have been reported with point mutations accounting for 40% and polyalanine expansion accounting for 60%. *HOXA13* has 3 large polyalanine tracts with pathogenic expansions identified in all 3 [27,31–34]. Pathogenic expansions range from an additional 6 Ala residues reported in Tract II to an additional 14 residues reported in Tract III [31,33]. Contrary to *HOXD13* (discussed below), contractions of *HOXA13* polyalanine tract III have been reported in unaffected individuals and may be benign variants [31,34,35]. Pathogenic point mutations include both nonsense and missense mutations [26,27]. The missense mutation c.1114A>C converts the 51st homeodomain residue, an asparagine, to a histidine and causes a more severe phenotype than that seen with either nonsense mutations or polyalanine expansions [27]. Polyalanine expansions and nonsense mutations likely result in disease via a loss-of-function mechanism while the reported missense mutation likely functions through a mixed loss-of-function/gain-of-function mechanism [27,31].

A specific missense mutation, c.1112A>T; Q371L, was identified in the original family described with Guttmacher syndrome [28]. A 2 base pair deletion within the promoter region (−79-79delGC) was also identified on the same allele but by itself appears to have no phenotypic consequence [28]. The altered glutamine is an important residue in the homeodomain with substitution likely resulting in both a loss and gain of function [28].

6. HOXB1

6.1. Clinical features

A total of 4 patients (2 sibling pairs) have been identified with identical homozygous *HOXB1* mutations. Characteristic features include congenital facial palsy, hearing loss, strabismus, midface retrusion and an upturned nose (Figs. 4A, B, F) [36]. Additional findings may include feeding difficulties, speech delay, a smooth philtrum and posteriorly rotated ears. Brain imaging revealed facial nerve agenesis and abnormal tapering of the basal turn of the cochlea which was seen in 1 of the 4 reported patients (Figs. 4C, D, E) [36]. Carriers appear to be unaffected, although 1 carrier father of a sibling pair had a history of speech delay and bilateral sensorineural hearing loss for which brain imaging was not performed [36].

6.2. Molecular genetics

Autosomal recessive inheritance was suspected based on parental consanguinity in 1 affected sibling pair. Using homozygosity mapping and exome sequencing a homozygous c.619C>T; R207C mutation in *HOXB1* was found [36]. Homozygosity for this identical mutation was observed in an additional affected sibling pair [36]. The mutated arginine is highly conserved and lies within the homeodomain of the protein, with the mutation likely affecting DNA binding. The phenotype of the 4 reported individuals is very similar to *Hoxb1*$^{-/-}$ mice, which display absence or reduction in size of the facial motor nerve and abnormal contralateral vestibuloacoustic neuron migration that may explain the hearing loss [37,38]. This data suggests that the human mutation is a loss of function allele.

7. HOXB13

7.1. Clinical features

Missense germline *HOXB13* mutations, most commonly G84E, have been associated with early-onset prostate cancer and possibly associated with breast cancer and colorectal cancer [39–41]. Carriers exhibit an incompletely penetrant increased cancer incidence with no other known phenotypic abnormalities.

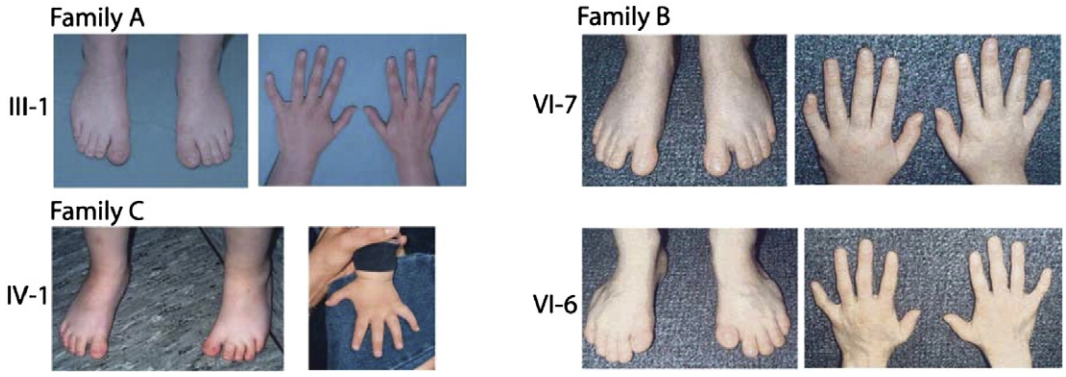

Fig. 3. Limb phenotype of affected individuals with polyalanine expansions in *HOXA13*. Note shortened thumbs and halluces and clinobrachydactyly of the second and fifth fingers. Reprinted from Innis et al. [31].

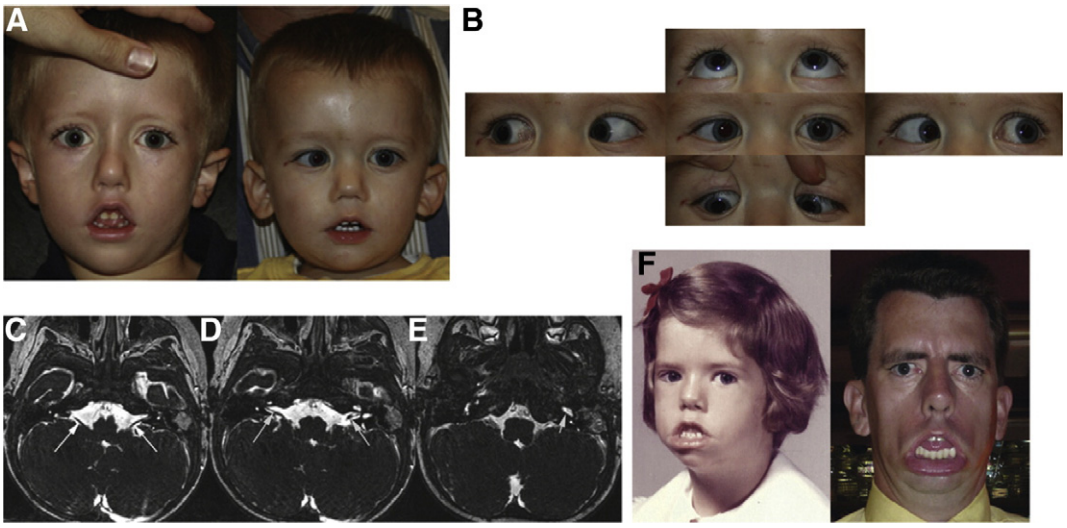

Fig. 4. Clinical features of patients with homozygous *HOXB1* mutations. (A) "Masked facies" of affected patients due to bilateral facial weakness. (B) Right esotropia of an affected patient. (C–E) Brain MR of affected patients. (C) Vestibulocochlear nerves (arrows) shown exiting the pontomedullary junction bilaterally and traversing the cerebellopontine angle cisterns. Absent facial nerves. (D) Right vestibulocochlear nerve (arrow) entering the internal auditory meatus with continued absence of the facial nerve, which would normally be located ventrally. (E) Basal turn of the cochlea (arrow) with an abnormal tapering. (F) Facial features of 2 affected siblings showing masked facies and bilateral facial weakness, as exhibited in the male sibling's attempt to smile. Both siblings with midface retrusion, upturned nasal tips and micrognathia. Male sibling also with right exotropia and low set ears.
Reprinted from Webb et al. [36].

7.1.1. Prostate cancer

Ewing et al. initially reported discovery of a *HOXB13* missense mutation (G84E) at a higher incidence in early-onset prostate cancer families [39]. Subsequent analyses have confirmed these initial findings and estimated an increased risk of 5–10 fold for prostate cancer in individuals with the G84E mutation [39,42,43]. Of European families affected with prostate cancer, the G84E *HOXB13* mutation is observed in approximately 1–5% of cases and is noticeably higher in Nordic countries [39,42–44]. The association is stronger in individuals diagnosed with cancer at a younger age (≤55 years of age) and those with a positive family history. The G84E missense mutation primarily affects individuals of European ancestry and has not been identified in a significant number of other ethnic groups including African, Ashkenazi Jewish and Chinese [43,45]. A rarer c.404G>A; p.G135E mutation causes an increased risk of prostate cancer in Chinese men [45].

7.1.2. Breast cancer

Conflicting reports exist regarding an association between *HOXB13* mutations and breast cancer [41,46]. The largest of the 2 studies failed to identify an association [46].

7.1.3. Colorectal cancer

A significant association between the G84E mutation and colorectal cancer was seen following evaluation of Canadian and Australian patients [40]. No other investigations into this risk have been performed.

7.2. Molecular genetics

The *HOXB13* missense mutation, G84E, accounts for the majority of missense mutations identified. As mentioned, this mutation primarily affects individuals of European descent with the highest carrier frequency seen in Nordic countries [43]. Other missense mutations have been identified in different ethnic groups and impart an increased risk of cancer. All mutations have been missense besides 1 patient with a c.853delT mutation that results in loss of a stop codon and extension of the wild type protein by 96 amino acids [42]. The G84E mutation changes a glycine within the MEIS interacting domain of exon 1 [39,47]. Additional missense mutations also affect the MEIS interacting domain while others lie within the homeodomain [39].

MacInnis et al. provided a population-based estimate of prostate cancer risk of G84E that varied based on the age and birth-year of carriers [48]. The pathogenic mechanism is unclear at this time. Ewing et al. suggested a gain of function mechanism based on the lack of truncating mutations and recurrent nature of the G84E mutation [39]. Mice homozygous for *Hoxb13* loss-of-function mutations show overgrowth of tail bud structures due to increased cell proliferation and decreased apoptosis [1,49].

8. HOXC13

8.1. Clinical features

Homozygous loss-of-function *HOXC13* mutations cause ectodermal dysplasia 9, hair/nail type (pure hair and nail ectodermal dysplasia; OMIM # 602032) [50]. This rare autosomal recessive condition has been identified in consanguineous Chinese and Pakistani families [50–52]. *HOXC13*, unlike other Hox genes, appears to violate the spatial colinearity principle as it is expressed in the vibrissae, filiform papillae of the tongue and all body hair follicles at later developmental stages [53].

Ectodermal dysplasia 9, hair/nail type, is characterized by hypotrichosis and nail dystrophy without other manifestations (Fig. 5) [50,51]. Hypotrichosis can vary from mild hair loss to congenital atrichia with nail dystrophy usually present at the time of birth. Individuals have no abnormalities of the nervous system, skeleton, sweat glands, eyes, teeth or growth. Heterozygous carriers of loss-of-function mutations are unaffected with normal hair and nail growth [50].

8.2. Molecular genetics

HOXC13 homozygous, loss-of-function mutations have been identified in all affected individuals with ectodermal dysplasia 9 [50,52,53]. A total of 6 families have been identified harboring novel truncating mutations in exon 1 of *HOXC13* (c.390C>A, p.Y130X; 27.6 kb deletion involving exon 1 and part of the intron; c.355delC, p.L119Wfs*20; c.200_203dupGCCA, p.H68Qfs*84; c.404C>A, p.S135X) [50,52,53]. Lin et al. (2012) detected decreased *HOXC13* mRNA levels in skin tissue of an affected patient and weak protein staining in hair follicles suggesting

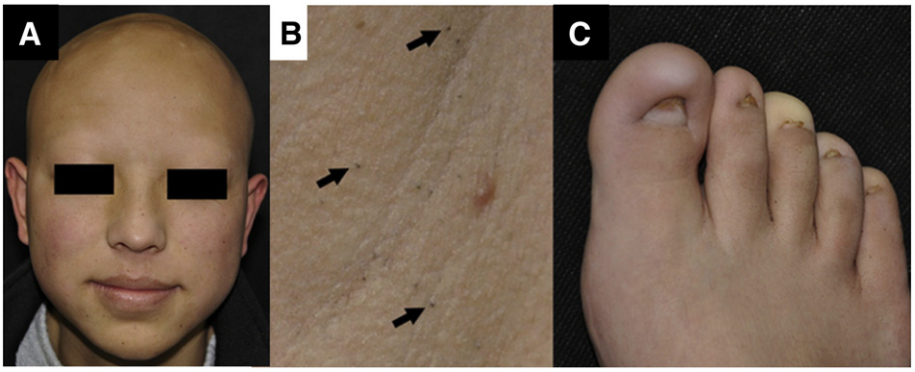

Fig. 5. *HOXC13* causing pure hair and nail ectodermal dysplasia syndrome. A. Male patient congenital alopecia involving scalp, beard, eyebrows and eyelashes. B. Axillary area showing broken hair shafts. Arrow shows hair remnants. C. Nail dystrophy.
Reprinted from Lin et al. [50].

nonsense-mediate mRNA decay or protein instability [50]. *Hoxc13*-null mice recapitulate the human phenotype with both alopecia and nail defects [54].

9. HOXD4

9.1. Clinical description

Van Scherpenzeel et al. initially described 2 patients with heterozygous, missense *HOXD4* substitution in a cohort of 86 children diagnosed with acute lymphoid malignancy with or without skeletal anomalies [55]. Both patients had a hematologic malignancy but only 1 was found to have a skeletal abnormality, which included bilateral cervical ribs and right sacralization of L5 [55]. Both patients inherited the mutation from apparently unaffected parents.

9.2. Molecular genetics

Both affected patients had a *HOXD4* missense mutation, c.242A>T; p.E81V, inherited from an unaffected parent [55]. Using a reporter construct composed of the luciferase gene and the *HOXD4* autoregulatory enhancer, the E81V mutant displayed approximately 40% lower transcriptional activity compared to another allele, suggesting a partial loss-of-function [55]. Both patients' *HOXD4* mutation was found linked to 3 variants of the HOXD cluster of unknown significance or function, possibly suggesting a combinatorial effect of the variants [55]. No subsequent patients harboring *HOXD4* mutations have been reported to date. *Hoxd4* heterozygous and homozygous mutant mice are viable and fertile and show abnormalities of the cervical spine including anterior transformation of C2 and C7 cervical ribs [56,57]. These results are consistent with those observed in the one human heterozygote. Though no hematopoietic abnormalities have been reported in *Hoxd4*$^{-/-}$ mice, paralogous *Hoxb4*$^{-/-}$ mice exhibit reduced proliferative capacity of bone marrow and liver hematopoietic stem cells [58].

10. HOXD10

10.1. Clinical description

A *HOXD10* missense mutation was identified in a family of 17 individuals affected with isolated CVT, isolated CMT, or CVT with CMT. Of those 17 patients, 12 (71%) presented with bilateral isolated CVT, 2 (12%) presented with bilateral CMT, 2 (12%) presented with both CVT and CMT and 1 (6%) presented with CVT in one foot and CMT in the other (Fig. 6) [59]. All individuals had normal intelligence and no hand or vertebral abnormalities. The diagnosis of CMT was by clinical examination with no nerve conduction or electromyographic testing performed.

An additional 6 individuals from an unrelated family with the same mutation were reported with findings of isolated bilateral CVT [60]. Nerve conduction studies of these individuals were within normal limits with no other signs of CMT on physical examination. Taken together, the gene mutation is likely completely penetrant, but with variable expressivity as 78% of reported patients have isolated CVT, 9% have bilateral CMT, 9% have both CVT and CMT and 4% have a more complicated distribution of CVT and CMT [59,60]. Further study of additional patients by nerve conduction velocity and electromyography may more accurately define the incidence of CMT in *HOXD10* mutation carriers.

10.2. Molecular genetics

Using genome-wide linkage and candidate gene analysis, Shrimpton et al. identified a heterozygous missense mutation (c.956T>A; M319K) in *HOXD10* that segregated with disease [59]. The same mutation was discovered in patients identified by Dobbs et al. [60]. The altered residue is a methionine within the homeodomain of *HOXD10* and may cause disease through haploinsufficiency and/or a novel gain of function [59].

Hoxd10$^{-/-}$mice exhibit changes in the vertebral column and bones of the hindlimb with an accompanying decreased number of nerves that innervate the musculature of the hindlimb [61]. Mutant mice specifically exhibit sacral vertebrae homeotic transformation to the next most anterior vertebrae and altered patellar position, an outward rotation of

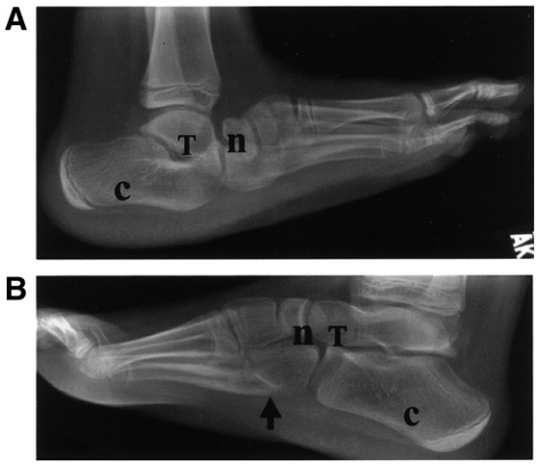

Fig. 6. Nine-year-old female patient with *HOXD10*-associated congenital vertical talus (A) and Charcot–Marie–Tooth disease (B) as evidenced by pes cavus (arrow). c = calcaneus; n = navicular; t = talus.
Reprinted from Shrimpton et al. [59].

the lower leg and occasional production of an anterior sesamoid bone [61].

11. HOXD13

11.1. Clinical features

Following the discovery of *HOXD13* polyalanine expansions in synpolydactyly type II (OMIM # 186000), *HOXD13* mutations were identified to also cause Brachydactyly type D (OMIM # 113200), Brachydactyly type E (OMIM # 113300), brachydactyly–syndactyly syndrome (OMIM # 610713) and Syndactyly type V (OMIM # 186300) [14,15,62]. A *HOXD13* intragenic deletion has also been identified in a female patient with VACTERL (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities) association [63]. Given the phenotypic overlap between the various conditions, Zhao et al. proposed the term "*HOXD13* limb morphopathies" to describe the spectrum of limb disorders caused by *HOXD13* mutations [64].

11.1.1. Synpolydactyly, type II

Synpolydactyly type II (SPD) is an autosomal dominant condition that exhibits both incomplete penetrance (97%) and variable expressivity, including both inter- and intra-familial variability [65]. SPD is characterized by distal limb malformations consisting of soft-tissue syndactyly between fingers 3 and 4 and between toes 4 and 5 as well as variable postaxial polydactyly involving the same digits (Fig. 7) [65,66]. Sayli et al. evaluated a large Turkish pedigree consisting of 182 affected individuals and found 4 major categories of malformations: 1) those with typical synpolydactyly (84.9% of the kindred); 2) those with both pre- and postaxial synpolydactyly; 3) those with postaxial polydactyly type A; and 4) those with bilateral, complete synpolydactyly caused by homozygosity at the *HOXD13* locus [65]. Other variable features include clinodactyly, camptodactyly and/or brachydactyly of the fifth fingers and syndactyly and brachydactyly of the second to the fifth toes with hypoplasia or absence of the middle phalanges [65,66]. Males harboring a large expansion (14 alanine residues) have presented with hypospadias as well [67].

Radiographic evaluation of patients affected with typical SPD reveals metacarpal abnormalities (structural and duplications) in 80.7% of patients and metatarsal abnormalities (duplications) in 83.9% of patients [14,15,65]. Homozygosity for the causative polyalanine expansion causes a more severe phenotype consisting of short hands with wrinkled fatty skin and short feet, complete soft tissue syndactyly of all four limbs, polydactyly of the preaxial, mesoaxial and postaxial digits of the hands and severe bone malformations of the hands and feet [68].

Atypical cases of SPD have been reported in patients with both intragenic deletions and missense mutations (c.916C>T, R306W; c.683G>T, G228V) within *HOXD13* [69–71]. Frameshifting *HOXD13* deletions cause a dominantly inherited phenotype consisting of novel foot abnormalities and variable findings of classic SPD [69]. Besides typical SPD findings, feet malformations included duplication of the bases of the second metatarsal in the first web spaces and frequent duplications of the fourth metatarsal in the fourth web spaces [69]. The *HOXD13* missense mutation R306W causes an incompletely penetrant mild SPD phenotype similar to that caused by intragenic deletions [70]. A total of 17 individuals have been identified, with 3 affected with SPD and all others exhibiting only bilateral fifth finger clinodactyly [70]. The G220V *HOXD13* mutation causes a mild SPD phenotype similar to those caused by moderate polyalanine tract expansions (7–9 additional Ala residues) [71]. Affected individuals exhibit variable findings consisting of synpolydactyly of fingers 3 and 4, fifth finger clinodactyly, fifth finger and fifth toe camptodactyly, and cutaneous syndactyly of toes 2 and 3 and toes 3 and 4 [71].

11.1.2. Brachydactyly types D and E

Missense mutations (c.947C>G, S316C; c.964A>C, I322L) within the homeodomain of *HOXD13* cause a phenotype consisting of overlap between Brachydactyly, types D and E (OMIM # 13200 and 13300, respectively) [72,73]. Cardinal features of Brachydactyly type D include short and broad terminal phalanges of the thumbs and halluces while Brachydactyly type E consists of shortening of the metacarpals and metatarsals. Individuals with a *HOXD13* I322L mutation exhibit generalized brachydactyly and variable findings including middle-finger metacarpal brachydactyly, fifth finger distal phalanx hypoplasia/aplasia, fourth finger phalangeal duplication and syndactyly of fingers 3 and 4. Other findings include fourth and fifth finger clinodactyly and fifth toe distal phalangeal hypoplasia/aplasia with absent or immature nails [72,73]. The *HOXD13* missense mutation S316C causes a variable phenotype that consists of metacarpal and/or metatarsal shortening, distal phalangeal shortening or elongation (typically the first and fifth) and carpal bone fusion [72].

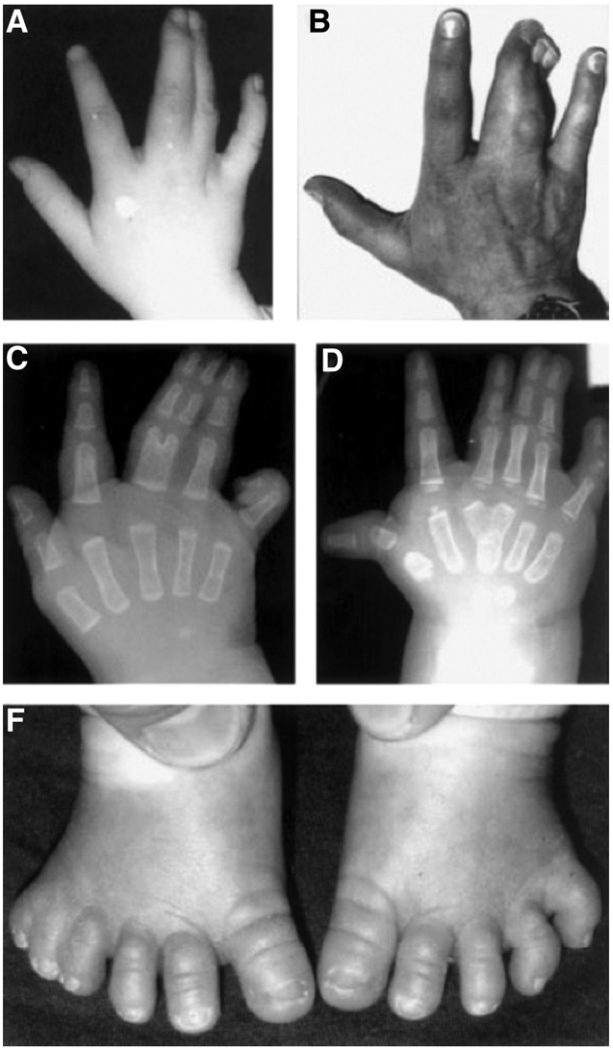

Fig. 7. Synpolydactyly caused by *HOXD13* polyalanine expansion. A. Syndactyly between fingers 3 and 4. B. Synpolydactyly with syndactyly between fingers 3 and 4 with an extra digit present between these fingers. C. Duplicated 3rd distal and middle phalanges, bifid third proximal phalanx and hypoplastic 5th middle phalanx. D. Duplicated 3rd distal, middle and proximal phalanges, bifid 3rd metacarpal, hypoplastic 5th middle phalanx and radially deviated thumb with a short 1st metacarpal. E. Polysyndactyly with syndactyly between toes 4 and 5 and an extra toe.
Reprinted from Goodman [62].

11.1.3. Syndactyly type V

A *HOXD13* missense mutation (c.974A>G; Q325R) has been reported in a large Han Chinese family with Syndactyly type V [64]. The classic findings of Syndactyly type V are metacarpal and metatarsal fusion. Zhao et al. investigated 23 variably affected individuals with Syndactyly type V [64]. The degree of fusion in affected individuals is variable with

synostosis occasionally extending to the phalanges of fingers 4 and 5. Other hand malformations include ulnar deviation of fingers 2 through 5, Y-shaped fingers 4 and 5, fifth finger clinodactyly, short distal phalanges affecting numerous digits, cutaneous syndactyly of fingers 3 and 4 and finger camptodactyly [64]. Variable feet findings include varus deviation of the first metatarsals, valgus deviation of toes 1 through 4, hypoplasia and shortening of metatarsals 2 through 5 and mild cutaneous syndactyly of toes 2 and 3 and/or toes 3 and 4 [64]. One male individual has been reported to have postaxial polydactyly and hypospadias [64].

11.1.4. Brachydactyly–syndactyly

A novel brachydactyly–syndactyly syndrome was identified in a Han Chinese family carrying a 21 base pair deletion (c.157_177del) in *HOXD13* resulting in a contraction of 7 alanine residues from the large 15 residue polyalanine tract in exon 1 [64]. Individuals with this contraction exhibit generalized brachydactyly of the hands and feet, broad and short distal phalanges of thumbs, cutaneous syndactyly of toes 2 and 3 and absence of the middle phalanges of toes 2 through 5 with short middle phalanges of the fifth finger [64]. Other variable radiographic abnormalities can be present with almost all limb anomalies typically present bilaterally. Overall the phenotype overlaps that of Brachydactyly type A4, Brachydactyly type D, Brachydactyly type E and Syndactyly type I [64].

11.1.5. VACTERL association

A *de novo* 7 alanine contraction in the large polyalanine tract of *HOXD13* was identified in a female patient with VACTERL association [63]. Her features included anal atresia, Tetralogy of Fallot, bilateral vesicoureteral reflux and fusion of the distal interphalangeal joints of toes 4 and 5 [63].

11.2. Molecular genetics

Various mutation types and mechanisms of pathogenesis have been implicated in the *HOXD13* limb morphopathies. Review and discussion of all reported mutations in *HOXD13* is beyond the scope of this article. For further information we refer readers to other references [74,75].

As mentioned above, in SPD type II a polyalanine expansion was the first identified mutation in *HOXD13* [14,15]. Polyalanine tracts are a common motif of transcription factors, with the normal length typically conserved and normally 20 alanine residues or fewer. Goodman et al. correlated the phenotypes of affected patients with the size of *HOXD13* expansions and found that both penetrance and severity increased with increasing expansion size [67]. A 7 alanine expansion appears to be the minimum number required for the development of SPD [67]. These expansions likely cause disease via a dominant negative mechanism through the formation of intracytoplasmic aggregation of the mutant protein [35,76,77]. Mutations resulting in the atypical form of SPD with foot anomalies include truncating deletions and missense mutations and cause disease likely through a dominant loss-of-function/haploinsufficiency mechanism [70,71,78].

The missense mutation c.964A>C, I322L causing Brachydactyly types D and E exhibits a more complicated pathogenesis with selective loss of function depending on the target tested [72,73]. The c.947C>G; S316C mutation, also responsible for Brachydactyly types D and E, may have a very subtle effect on DNA binding yet no differences were observed using electrophoretic mobility shift assay (EMSA) analysis when

Table 1
Human Hox gene disorders. Bolded features can be used to separate allelic syndromes.

Condition	Gene	OMIM #	Inheritance	Phenotype	Mechanism
Bosley–Salih–Alorainy syndrome	*HOXA1*	601536	AR	Horizontal gaze palsy, SNHL, ID, cardiac defects, **facial dysmorphisms** and **limb anomalies**	LOF
Athabascan brainstem dysgenesis syndrome	*HOXA1*	601536	AR	Horizontal gaze palsy, SNHL, ID, cardiac defects, **central hypoventilation**	LOF
Microtia, hearing impairment and cleft palate	*HOXA2*	612290	AR	Microtia, hearing loss, cleft palate, inner ear anomalies	? LOF
Radioulnar synostosis with amegakaryocytic thrombocytopenia	*HOXA11*	605432	AD	Radioulnar synostosis and thrombocytopenia	LOF
Hand–foot–genital syndrome	*HOXA13*	140000	AD	Thumb and hallux hypoplasia, urogenital malformations	LOF (polyalanine expansions/ nonsense mutations) and mixed LOF/GOF (missense mutation)
Guttmacher syndrome	*HOXA13*	176305	AD	Thumb and hallux hypoplasia, urogenital malformations, **postaxial polydactyly**	LOF/GOF (Q50L missense mutation)
Hereditary congenital facial paresis-3	*HOXB1*	614744	AR	Congenital facial palsy, hearing loss, dysmorphic features	? LOF
Breast and prostate cancer susceptibility	*HOXB13*	–	AD	Increased incidence of prostate and breast cancer	?
Ectodermal dysplasia 9, hair/nail type	*HOXC13*	602032	AR	Hypotrichosis and dystrophic nails	LOF
Lymphoid malignancy and skeletal malformations	*HOXD4*	610997/114480	AD	Acute lymphoblastic leukemia with or without skeletal malformations	LOF
Congenital vertical talus and Charcot–Marie–Tooth disease	*HOXD10*	192950	AD	CVT and/or CMT	? LOF or GOF
Synpolydactyly type II	*HOXD13*	186000	AD	Hand and feet SPD, rarely hypospadias	Dominant negative (PA expansion) and LOF (deletions and missense mutations)
Brachydactyly types D and E	*HOXD13*	113200/113300	AD	Generalized brachydactyly, 5th finger distal hypoplasia/aplasia, phalangeal duplication, fingers 3–4 syndactyly, metacarpal/metatarsal shortening	LOF
Syndactyly type V	*HOXD13*	186300	AD	Metacarpal synostosis, 5th finger clinodactyly, cutaneous syndactyly of fingers 3 and 4, mild cutaneous toe syndactyly	Mixed LOF and GOF
Brachydactyly–syndactyly	*HOXD13*	610713	AD	Generalized brachydactyly of hands, broad and short distal thumb phalanges, cutaneous toe syndactyly, absence of middle phalanges of toes 2–5, 5th finger clinodactyly	Dominant negative and ? LOF

Table 2
Mouse single gene loss-of-function homozygote phenotypes. No double or triple mutation phenotypes included.

Gene	Mouse single gene homozygous loss-of-function phenotypes	Reference
Hoxd1	Abnormal skin nocioceptor innervation with decreased sensitivity to cold.	[81]
Hoxb2	Anterior transformation of C2. C1 and sternum malformations. Facial paralysis with abnormal cranial nerve VII.	[82–84]
Hoxa3	Absence of the thymus and parathyroid gland and decreased thyroid tissue. Throat, cardiovascular, craniofacial and cervical vertebral malformations.	[85,86]
Hoxb3	Mild malformations of C1 and C2. Malformation of cranial nerve IX.	[87]
Hoxd3	Malformations and anterior transformation of C1 and C2.	[88]
Hoxa4	Partial anterior transformation of C3. Posterior transformation of C7 to T1, with the presence of a C7 cervical rib. Malformation of the sternum.	[89,90]
Hoxb4	Partial anterior transformation of C2. Malformations of the sternum. Decreased spleen and bone marrow cellularity with accompanying anemia.	[91,58]
Hoxc4	T2 to T11 vertebral malformations. Esophageal dysfunction due to disorganized musculature.	[92]
Hoxa5	Trachea and lung malformations causing perinatal lethality. Posterior transformation of C7, with the presence of a C7 cervical rib.	[93,94]
Hoxb5	Forelimbs shifted anteriorly relative to the axial skeleton producing a V-shaped shoulder girdle. Abnormal brachial plexus location. Malformations of C6 and C7. Mild lung malformations.	[95,96]
Hoxc5	No defects identified grossly.	[97]
Hoxa6	Posterior transformation of C7, with the presence of a C7 cervical rib.	[90]
Hoxb6	Anterior transformation of C6 through T1. First and second rib defects and abnormal intercostal nerve innervation.	[96]
Hoxc6	Malformation and anterior transformation of the T2 vertebrae. Abnormal mammary gland development.	[98]
Hoxa7	No defects identified.	[99]
Hoxb7	Abnormal rib patterning with fusions between the first and second rib pairs. Abnormal sternum segmentation.	[99]
Hoxb8	Malformations of T1 and T2 ribs, sternum and T2 spinous process. Anterior transformation of T3 spinous process and C7 vertebrae. Abnormal C2 spinal ganglion morphology. Pathological excessive grooming.	[100–102]
Hoxc8	T7, T8 and L1 anterior transformations. Anterior transformation of S1 to L6 vertebrae. Transitional vertebrae shifted from T10 to T12. Mild malformation of the deltoid crest.	[102,103]
Hoxd8	Anterior transformations of T8 and L1 vertebrae.	[102]
Hoxa9	Anterior transformation of L1 with the presence of a supernumerary rib. Anterior transformation of L2, L3, L4 and L5. Defects in myeloid, erythroid and lymphoid hematopoiesis.	[104,105]
Hoxb9	First and second rib fusions. Abnormal sternum segmentation with an additional rib attached.	[106]
Hoxc9	Anterior transformation of T10 through L1. Abnormal sternum ossification with 1–2 additional ribs attached.	[107]
Hoxd9	Anterior transformations of L3 to L5 and S2, S4 and C1. Decreased sacral region size.	[105]
Hoxa10	Anterior transformation of L1 to L6 with a supernumerary rib present. Abnormal rib formation and sternum articulation. Fusion of the S2–S4 spinous processes and broadening of the transverse processes of S4 and C1. Abnormal spinal nerve innervation. Male-specific: Cryptorchidism and sterility. Anterior transformation of the cranial ductus deferens with hypomorphism of the seminal vesicles in males. Decreased size and branching of the coagulating gland of the prostate with occasional posterior transformation. Female-specific: Failure of implantation of fertilized embryos. Homeotic transformation of the proximal uterus into oviduct.	[108–111]
Hoxc10	Posterior transformation of T9, T13, L1, S1 and L6. Anterior transformation of S4 and caudal vertebrae #1. Delayed calcification of the pelvic cartilaginous bridge. Presence of ectopic branch of the ileofemoral ligament and poor development of the hip joint cartilage. Shortened femur with shortened thigh musculature. Decrease in motor neuron number.	[112]
Hoxc11	Anterior transformation of S3 and caudal vertebrae #1. Femoral vessel enlargement.	[113]
Hoxd11	Anterior transformation of S1 through S4. Shortened metacarpals and phalanges of forelimbs. Forelimbs also with malformed carpals and occasional fusion of wrist bones with slightly malformed distal ulna and radius. Hindlimbs with hypoplasia/aplasia of the tibiale mediale and fusion of the tarsal navicular and cuneiform 3.	[114]
Hoxc12	No mouse model reported	–
Hoxd12	Decreased length of the forelimb metacarpals and phalanges and malformations of the distal carpal bones.	[115]

compared to wild type [72]. Syndactyly type V, caused by a Q325R missense mutation, is caused by a loss-of-function mechanism with additional gain-of-function activity also possible [64]. The substituted glutamine, located at position 50 in the homeodomain, is important for base-specific DNA binding in the major groove [79,80]. The novel brachydactyly–syndactyly phenotype caused by a 7 alanine contraction may arise via a dominant-negative mechanism but with a concurrent loss-of-function mechanism also possible based on differences in secondary structure of the protein product [64]. A similar 7 alanine contraction (c.163_193del) was found in a female patient with VACTERL association. This mutation may help explain the hand phenotype of the patient but is of uncertain significance in the other organ system involvement especially given that no other patient with VACTERL association has been reported with a *HOXD13* mutation [63]. Clearly, additional patients with similar contractions would be helpful to support the proposed pathogenesis.

12. Conclusion

The human Hox genes are an evolutionarily conserved class of genes initially discovered in *D. melanogaster* [2]. Since that time, mutations in 10 *HOX* genes have been identified to cause an abnormal human phenotype (Table 1). The resultant phenotypes typically follow the spatiotemporal expression of the individual Hox genes with more 3′ genes causing malformations in more anterior and proximal areas and more 5′ genes causing defects in more posterior, distal body segments and organs. An apparent trend for more 3′ anterior genes to be associated with recessive disorders may reflect the underlying biology (overlapping, cooperative paralog expression) of the HOX proteins or could represent failure to identify dominantly acting mutations in single genes in humans. In addition, cell and tissue expression domains that are patterned by only a single Hox gene, such as the thumb and *HOXA13*, are likely much more sensitive to decreases in gene dosage and therefore more likely to display a visible malformation in individuals harboring a heterozygous loss-of-function mutation.

The 10 Hox genes associated with human disorders represent only one-quarter of the 39 human Hox genes. The majority of the remaining Hox genes have been knocked out in the mouse. Table 2 lists these genes and the resultant single gene knockout phenotypes. It is not surprising that the majority of Hox genes affect the skeleton, primarily vertebral column and only slightly less frequently the bones of the forelimb and hindlimb. Providing further evidence for the importance of Hox genes in body development, there are a number of unique phenotypic consequences that result from individual Hox gene loss-of-function. These include, but are not limited to, the multi-organ malformations that accompany *Hoxa3* loss-of-function, the hematologic abnormalities of *Hoxb4* or *Hoxa9* loss-of-function, the esophageal dysfunction and disorganized throat musculature of *Hoxc4* loss-of-function and the pathologic excessive grooming behavior of *Hoxb8* mutants [58,85,86,91,92,100-102]. The murine Hox genes also exhibit sex-specific phenotypes including abnormal mammary gland development and absent milk production seen in *Hoxc6* loss-of-function females and male and female infertility in *Hoxa10* mutants [98,108–111]. As the human Hox phenotypes typically

mirror those seen in the mouse models, it is likely that review of Table 2 will allow clinicians to anticipate what would be expected in a patient affected with mutation(s) in a given *HOX* gene.

The limited number (10) of documented human Hox disorders is likely due to both the overlapping expression domains of paralogous groups, which would complement single loss of function alleles, and the current limits of non-systematic molecular testing in patients with malformation syndromes. In the future, as clinical next-generation sequencing is further utilized in the form of whole-genome, whole-exome and panel-based sequencing, clinicians are likely to identify human malformations associated with mutations in additional *HOX* genes.

Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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