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Hand-Foot-Genital Syndrome

Synonyms: HFGS, HFG Syndrome

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Summary

Clinical characteristics

Hand-foot-genital syndrome (HFGS) is characterized by limb malformations and urogenital defects. Mild-to-severe bilateral shortening of the thumbs and great toes, caused primarily by shortening of the distal phalanx and/or the first metacarpal or metatarsal, is the most common limb malformation and results in impaired dexterity or apposition of the thumbs. Urogenital malformations include abnormalities of the ureters and urethra and various degrees of incomplete müllerian fusion in females, and hypospadias of variable severity with or without chordee in males. Vesicoureteral reflux, recurrent urinary tract infections, and chronic pyelonephritis may occur; fertility is normal.

Diagnosis/testing

Diagnosis is based on physical examination including radiographs of the hands and feet and imaging studies of the kidneys, bladder, and female reproductive tract. Identification of a heterozygous *HOXA13* pathogenic variant can establish the diagnosis if clinical and radiographic features are inconclusive. Approximately 50%-60% of pathogenic variants are polyalanine expansions.

Management

Treatment of manifestations: Hand or foot surgery is not usually necessary. Ureteric reimplantation and surgical correction of bladder outlet abnormalities are often necessary. Surgical removal of a longitudinal vaginal septum is rarely indicated. Surgery for removal of a uterine septum or reunification of a bicornuate uterus is exceptional in the absence of recurrent mid-trimester pregnancy loss. Hymenectomy may be necessary for tight constriction ring.

Prevention of secondary complications: Prophylactic antibiotics or surgery as needed to prevent urinary tract infections or other complications of ureteral reflux or ureteropelvic junction obstruction; gynecologic examination prior to menstruation for small hymenal opening; pre-pregnancy evaluation of the vaginal and

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uterine anatomy because of the increased risk for premature labor and fetal loss associated with structural abnormalities of the uterus.

Surveillance: Follow up with a urologist in the presence of vesicoureteral reflux and/or documented urinary tract infection.

Genetic counseling

Hand-foot-genital syndrome is inherited in an autosomal dominant manner. The proportion of cases caused by a *de novo* pathogenic variant is unknown because of the small number of individuals described. If a parent of the proband is affected, the recurrence risk to the sibs is 50%. If the proband has a known *HOXA13* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. Each child of an individual with HFGS has a 50% chance of inheriting the pathogenic variant. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible if the pathogenic variant in the family is known.

Diagnosis

Suggestive Findings

Hand-foot-genital syndrome **should be suspected** in individuals with the following clinical and radiographic features.

Limb Malformations

Bilateral thumb and great-toe hypoplasia are the hallmark malformations, caused primarily by shortening of the distal phalanx and/or the first metacarpal or metatarsal. Shortening is often mild to moderate but on occasion may be more severe and may cause shortening of the distal phalanx of other digits (see Mortlock & Innis [1997], Goodman et al [2000] (family 5), and Imagawa et al [2014]). Additional findings that may be present:

- Limited metacarpophalangeal flexion of the thumb or limited ability to oppose the thumb and fifth finger
- Hypoplastic thenar eminences
- Hallus valgus of the distal phalanx of the great toe is common; hallux varus can be observed associated with significant metatarsal shortening.
- Small great toenail
- Sandal gap (i.e., increased gap between 1st and 2nd toes)

Other

- Fifth-finger clinodactyly, secondary to a shortened middle phalanx
- Short feet
- Altered dermatoglyphics of the hands; when present, primarily involving distal placement of the axial triradius, lack of thenar or hypothenar patterning, low arches on the thumbs, thin ulnar loops (deficiency of radial loops and whorls), and a greatly reduced ridge count on the fingers

Radiographic findings

- Hypoplasia of the distal phalanx and first metacarpal of the thumbs and great toes; rare hypoplasia of the distal phalanges of other digits
- Pointed distal phalanges of the thumb
- Lack of normal tufting of the distal phalanges of the great toes

- Fusions of the cuneiform to other tarsal bones or trapezium-scaphoid fusion of the carpals
- Short calcaneus
- Occasional bony fusions of the middle and distal phalanges of the second, third, fourth, or fifth toes
- Delayed carpal or tarsal maturation
- Metacarpophalangeal profile reflecting shortening of the first metacarpal, the first and second phalanges, and the second phalanx of the second and fifth digits

Urogenital Defects

Females may have the following:

- Vesicoureteral reflux secondary to ureteric incompetence
- Ectopic ureteral orifices
- Trigonal hypoplasia
- Hypospadiac urethra
- Subsymphyseal epispadias
- Patulous urethra
- Urinary incontinence
- Small hymenal opening
- Various degrees of incomplete müllerian fusion with or without two cervices or a longitudinal vaginal septum

Males may have the following:

- Vesicoureteral reflux
- Hypospadias of variable severity with or without chordee

Establishing the Diagnosis

The diagnosis of hand-foot-genital syndrome **is established** in a proband with characteristic fully penetrant limb malformations described in Suggestive Findings with or without incompletely penetrant urogenital defects.

The diagnosis of hand-foot-genital syndrome **can be confirmed** in a proband who has **one of the following** on molecular genetic testing (see Table 1):

- A heterozygous polyalanine expansion involving *HOXA13* (~50%-60% of affected individuals) [Quinonez & Innis 2014]
- A heterozygous sequence variant involving *HOXA13* (35% of affected individuals) [Quinonez & Innis 2014]

Allele sizes. HOXA13 protein has three extended polyalanine tracts encoded in the first exon, referred to as Tracts I, II, and III. Approximately 50%-60% of individuals with HFGS have a polyalanine expansion of one of the tracts. No affected individual has been described with expansions in more than one tract.

- **Normal alleles**
  - **Tract I.** p.Ala38[14] residues
  - **Tract II.** p.Ala73[12] residues
  - **Tract III.** p.Ala116[8], p.Ala116[12], or p.Ala116[18] residues
- **Reduced-penetrance alleles.** Not reported
- **Full-penetrance alleles**
  - **Tract I.** An allele with eight additional alanine residues (termed "+8" alleles) was reported in association with HFGS [Innis et al 2004].

- **Tract II.** An allele with six additional alanine residues (termed "+6" alleles) was reported in association with HFGS [Frisén et al 2003].
- **Tract III.** Polyalanine expansions of at least six additional polyalanine residues (termed "+6" alleles) to as many as 14 additional polyalanine residues (termed "+14" alleles) [Innis et al 2004, Utsch et al 2007] may cause HFGS.

- **Alleles of questionable significance – Tract III**
  - The significance of a shortened allele of eight polyalanine residues observed in one family is not clear given the occurrence of another disorder in the same family that complicates interpretation of the skeletal phenotype [Innis et al 2004]. A shortened allele of eight polyalanine residues was also reported in an unaffected woman [Owens et al 2013].
  - It is unknown whether a shortened allele of 12 polyalanine residues observed in expressed sequence tag databases [Lavoie et al 2003] is associated with phenotypic variation.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of hand-foot-genital syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with limb anomalies and/or urogenital anomalies are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of hand-foot-genital syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Targeted testing for the expanded polyalanine repeat in *HOXA13* is performed first.

  Sequence analysis of *HOXA13* can be performed next if no polyalanine repeat expansion is found on targeted testing.

- **A multigene panel** that includes *HOXA13* and other genes of interest (see Differential Diagnosis) may be considered. To date, next-generation sequencing strategies cannot identify expanded repeats and therefore cannot confirm the diagnosis in the majority of individuals with HFGS. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by limb anomalies, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) can be considered. To date, next-generation sequencing strategies cannot identify expanded repeats and therefore cannot confirm the diagnosis in the majority of individuals with HFGS. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Hand-Foot-Genital Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
HOXA13	Targeted testing for polyalanine repeat expansion [3]	~50%-60% [4]
	Sequence analysis [5]	~35% [4]
	Gene-targeted deletion/duplication analysis [6]	Unknown, none reported [7]
Unknown [8]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. PCR-based methods to identify *HOXA13* expansion (resulting in increased polyalanine residues)
4. Quinonez & Innis [2014]
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Other than in-frame contractions of polyalanine repeats, intragenic deletions causing HFGS that involve only part or all of *HOXA13* have not been reported. Large deletions including *HOXA13* and other surrounding genes have been reported [Devriendt et al 1999, Dunø et al 2004, Jun et al 2011, Pezzani et al 2015, Tas et al 2017]; however, these events result in additional clinical features (see Genetically Related Disorders).
8. A few individuals with the clinical features of HFGS do not have *HOXA13* pathogenic variants [Goodman et al 2000; Innis et al, unpublished].

Clinical Characteristics

Clinical Description

Hand-foot-genital syndrome (HFGS) has been reported in several families and individuals [Mortlock & Innis 1997, Devriendt et al 1999, Goodman et al 2000, Debeer et al 2002, Innis et al 2002, Utsch et al 2002, Frisén et al 2003, Innis et al 2004, Owens et al 2013]. Although some minor variation in the severity of limb defects may be observed, the defects are usually similar bilaterally. The radius/ulna, humerus, tibia/fibula, and femur are normal. With the exception of thenar hypoplasia, abnormalities of muscle have not been reported. There is intrafamilial variability.

HFGS may first be suspected in infants or children during evaluation for urogenital problems including hypospadias, ureteral reflux, urethral misplacement, recurrent urinary tract infections, or chronic pyelonephritis, or for small thumbs with impaired dexterity or apposition. Renal insufficiency leading to renal transplantation has been reported in one female.

Of all affected males, only one has had a documented history of urinary tract infection (UTI); two brothers had hypospadias (Grades II and III); one had bilateral vesicoureteral reflux with UTI, and the other had ureteropelvic junction (UPJ) obstruction. This family was first reported by Verp et al [1983] (family 1) and later by Donnenfeld et al [1992]. Retrograde ejaculation was reported in one affected male [Debeer et al 2002].

Affected males are not at increased risk for cryptorchidism and are fertile. No anomalies of the prostate or seminal vesicles have been described; however, directed examinations in males with HFGS to evaluate for such abnormalities have not been reported.

Menarche is usually normal. Females with varying degrees of incomplete müllerian fusion are at increased risk for premature labor, premature birth, second-trimester fetal loss, or stillbirth.

Other, possibly unrelated abnormalities are found rarely in individuals or families with HFGS:

- Strabismus
- Ventriculoseptal defect (propositus of Stern et al [1970])
- Inguinal hernia, epididymal cyst, short stature, cervical ribs, supernumerary nipple, lower limit of functioning, onychodysplasia
- Sacral dimple
- Psychomotor retardation, microcephaly, and hypertelorism (in 1 of 4 affected members of a single family in which HFGS occurs)
- Difficulty with balance when standing (in 1 adult)

The following are normal:

- Developmental milestones
- External ears and hearing

Genotype-Phenotype Correlations

Although the number of affected individuals in whom pathogenic variants in *HOXA13* have been identified is small, some genotype-phenotype correlations are emerging.

The limb malformations in individuals with the heterozygous pathogenic nonsense variants in either exon 1 or 2 or a polyalanine expansion in exon 1 are similar to those described in individuals with a cytogenetic deletion of the *HOXA* cluster and adjacent genomic DNA [Devriendt et al 1999, Tas et al 2017], suggesting that these typical features result from HOXA13 haploinsufficiency. Minor differences may be attributable to effects of other genetic loci or stochastic variables.

Generally speaking, *HOXA13* homeodomain pathogenic missense variants appear to produce more severe features or unusual digital malformations; the variant p.Asn372His was associated with a severe skeletal phenotype [Goodman et al 2000].

The variables that determine whether an individual heterozygous for a *HOXA13* pathogenic variant develops genitourinary problems are not clear. Hypospadias does not always occur in males with *HOXA13* pathogenic variants. When it does, it is most often glandular, although variability in severity occurs even in males with the same pathogenic variant. Females may be likely to have more severe genitourinary tract problems than males [Innis et al 2004]. The small number of families described limits further conclusions, although females with polyalanine expansions may have a greater frequency of urinary tract problems [Innis et al 2004].

Penetrance

Skeletal defects are 100% penetrant.

Penetrance for urogenital malformations is greater than 50% overall and may be greater for affected females.

Anticipation

Anticipation is not observed. Polyalanine expansions are stable for many generations.

Prevalence

HFGS is extremely rare.

Genetically Related (Allelic) Disorders

Guttmacher syndrome (OMIM 176305) refers to one family reported by Guttmacher [1993] in which features of HFGS were observed (e.g., preaxial deficiency, clinobrachydactyly, hypospadias) along with more unusual phenotypic features of upper-limb postaxial polydactyly and uniphalangeal second toes. Innis et al [2002] identified a pathogenic missense variant in the *HOXA13* homeodomain p.Gln371Leu (the so-called "homeodomain Q50L variant") in association, in *cis* configuration, with a dinucleotide deletion in the promoter region in this family.

An individual with a *de novo HOXA13* variant, p.Val375Phe, had features of HFGS including bilateral vesicoureteral junction obstruction with ectopic ureters and brachydactyly; however, small thumbs with atypical bilateral preaxial polydactyly was observed [Wallis et al 2016]. This individual also had a 0.5-Mb heterozygous deletion of 2p16.3 including the 5' exons of *NRXN1*.

Chromosome deletion. A microdeletion involving the *HOXA* cluster on chromosome 7p14-p15 was reported in an individual with features of HFGS and additional findings of velopharyngeal insufficiency, shortened soft palate, gastroesophageal reflux, and persistent patent ductus Botalli [Devriendt et al 1999]. Deletions involving *HOXA13* and additional genes with variable endpoints have been subsequently reported [Dunø et al 2004, Jun et al 2011, Pezzani et al 2015, Tas et al 2017].

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of Hand-Foot-Genital Syndrome (HFGS)

Clinical Features Overlapping w/HFGS	Differential Diagnosis Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features of Differential Diagnosis Disorder Distinguishing It from HFGS
Thumb hypoplasia, often in addition to other anomalies	Fanconi anemia	21 genes	AR AD XL	• Bone marrow failure • ↑ risk of malignancy
Incomplete müllerian fusion &/or longitudinal vaginal septum	Rothmund-Thomson syndrome	*RECQL4*	AR	• Rash, poikiloderma • Cataracts • ↑ risk of malignancy
	Holt-Oram syndrome	*TBX5*	AD	Cardiac malformation
	Lacrimo-auriculo-dento-digital syndrome (OMIM 149730)	*FGFR3* *FGF10* *FGFR2*	AD	• Characteristic facial features • Dental anomalies
	Nager syndrome (OMIM 154400)	*SF3B4*	AD	Characteristic facial features w/ear anomalies
	Townes-Brocks syndrome	*SALL1*	AD	Imperforate or stenotic anus
	SALL4-related disorders (incl Duane-radial ray syndrome & acro-renal-ocular syndrome)	*SALL4*	AD	• Radial ray malformation • Duane anomaly
	Bardet-Biedl syndrome	≥19 genes	AR	• Obesity • Rod-cone dystrophy

Table 2. continued from previous page.

Clinical Features Overlapping w/HFGS	Differential Diagnosis Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features of Differential Diagnosis Disorder Distinguishing It from HFGS
	Beckwith-Wiedemann syndrome	11p15 epigenetic & genomic alterations [1]	See footnote 1.	Somatic overgrowth
	Fraser syndrome (OMIM PS219000)	*FRAS1* *FREM2* *GRIP1*	AR	• Ocular involvement • Ear anomalies
	Meckel syndrome (OMIM PS249000)	~13 genes	AR	• Renal cystic dysplasia • Biliary abnormalities & liver fibrosis • Encephalocele

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

1. Beckwith-Wiedemann syndrome is associated with abnormal regulation of gene transcription in two imprinted domains on chromosome 11p15.5. Most individuals with BWS are reported to have normal chromosome studies or karyotypes. Approximately 85% of individuals with BWS have no family history of BWS; approximately 15% have a family history consistent with parent-of-origin autosomal dominant transmission.

Other disorders with incomplete müllerian fusion and/or longitudinal vaginal septum:

- **Fryns syndrome,** an autosomal recessive disorder of unknown genetic cause, can be distinguished from HFGS by ear anomalies and diaphragmatic defects.
- **Halal syndrome.** One family was reported with upper-limb hypoplasia and müllerian duct anomalies. Inheritance appeared to be autosomal dominant; the genetic cause is unknown [Halal 1986].

Note: *HOXA13* pathogenic variants have yet to be identified in individuals with isolated hypospadias (i.e., without skeletal malformations) [Utsch et al 2003] or isolated forms of incomplete müllerian fusion or uterovaginal septa [Jorgensen et al 2010; Innis, unpublished].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hand-foot-genital syndrome (HFGS), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Hand-Foot-Genital Syndrome

System/Concern	Evaluation	Comment
Musculoskeletal	Physical exam & radiographs of hands & feet	To evaluate for abnormalities that may affect function
Renal	Urologic assessment of bladder, ureter function, urethral competence & position	Incl renal ultrasound & VCUG for UPJ obstruction
Gynecologic	• Gynecologic exam prior to menstruation or pregnancy. • Eval may incl ultrasound, hysterosalpingogram, hysteroscopy, sonohysterogram, MRI, or other imaging studies.	• For evidence of incomplete müllerian fusion, longitudinal vaginal septum, or extremely small hymenal opening • Such studies could be accomplished at the same time as urologic imaging.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Other	Consultation w/clinical geneticist &/or genetic counselor	

UPJ = ureteropelvic junction; VCUG = voiding cystourethrogram

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Hand-Foot-Genital Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Bladder outlet abnormalities	Urologic referral	For surgical correction & ureteric implantation
Gynecologic anomalies	Gynecologic referral	• Surgical removal of longitudinal vaginal septum is rarely indicated, even in anticipation of labor. • Surgery for removal of a uterine septum or reunification of a bicornuate uterus is likewise exceptional in the absence of recurrent mid-trimester pregnancy losses. • Hymenectomy may be necessary for tight constriction ring.
Hallux varus & tarsal fusion	Orthopedic referral	Extremity surgery is usually unnecessary.

Prevention of Secondary Complications

The following are appropriate:

- Prophylactic antibiotics or surgery as needed to prevent urinary tract infections or other complications of ureteral reflux or UPJ obstruction
- Gynecologic examination prior to menstruation for small hymenal opening
- Pre-pregnancy evaluation of the vaginal and uterine anatomy because of the increased risk for premature labor and fetal loss associated with structural abnormalities of the uterus

Surveillance

Follow up with a urologist in the presence of vesicoureteral reflux and/or documented urinary tract infection is warranted.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify those at risk for genitourinary and reproductive tract complications.

Evaluations can include:

- Molecular genetic testing if the *HOXA13* pathogenic variant in the family is known;
- Physical examination, radiographic examination of hands and feet, and consideration of referral for urologic and/or gynecologic examination if the pathogenic variant in the family is not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

In women with HFGS, pregnancy loss is possible secondary to uterine malformation. Consultation with an obstetrician before pregnancy is recommended and should include evaluation for and discussion of potential

pregnancy complications. Affected fetuses are generally healthy, but could be at risk for premature birth secondary to maternal uterine malformation if the mother is also affected.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hand-foot-genital syndrome (HFGS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with HFGS have an affected parent.
- A proband with HFGS may have the disorder as the result of a *de novo HOXA13* pathogenic variant. The proportion of cases caused by *de novo* variants is unknown because of the small number of individuals described.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant. If a *HOXA13* pathogenic variant has not been identified in the proband, recommendations may also include history and physical examination followed by radiographic examination of hands and feet, and possibly referral for urologic and/or gynecologic examination.
- If the proband has a pathogenic variant that cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Somatic and germline mosaicism for a polyalanine expansion was reported in an unaffected parent who transmitted the polyalanine expansion to his affected offspring [Owens et al 2013].
- The family history of some individuals diagnosed with HFGS may appear to be negative because of failure to recognize the disorder in family members because of a milder phenotypic presentation or death of the parent before appropriate evaluation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the pathogenic variant and may be mildly/minimally affected or unaffected [Owens et al 2013].

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *HOXA13* pathogenic variant identified in the proband, the risk to the sibs is 50%.

- If the proband has a known *HOXA13* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Owens et al 2013].

Offspring of a proband. Each child of an individual with HFGS has a 50% chance of inheriting the *HOXA13* pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *HOXA13* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *HOXA13* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  Hand-foot-genital syndrome

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Hand-Foot-Genital Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HOXA13	7p15.2	Homeobox protein Hox-A13	HOXA13 database	HOXA13	HOXA13

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Hand-Foot-Genital Syndrome (View All in OMIM)

140000	HAND-FOOT-GENITAL SYNDROME; HFG
142959	HOMEOBOX A13; HOXA13

Molecular Pathogenesis

Introduction. Quinonez & Innis [2014] and Innis [2016] reviewed historical and evolutionary information about *HOX* genes, their roles as highly conserved, DNA-binding transcription factors in morphogenetic processes, and the consequences of pathogenic variants in ten of the 39 human *HOX* genes. There are many other well-written reviews detailing the basic science mechanisms underlying *HOX* gene regulation and the ways in which HOX proteins exert their effects in patterning and growth, much of which has been learned through animal models.

There are four *HOX* gene clusters, which map to four different human chromosomes. These clusters, labeled *HOXA*, *HOXB*, *HOXC*, and *HOXD*, are located on chromosomes 7p14, 17q21, 12q13, and 2q31, respectively. Each cluster has between nine and 11 genes, and members in similar positions among clusters, called paralogs, have an identical or nearly identical 60-amino acid "homeodomain" DNA-binding domain. *HOX* genes are expressed along the body axis in restricted anterior-posterior domains that map relative to their position in the cluster. For example, *HOXA1* is expressed more anteriorly, and *HOXA13* is expressed in distal/posterior structures including the hands/feet and distal axial structures of the reproductive and gastrointestinal systems. Their expression domains coincide with areas of malformation in the presence of pathogenic variants. Pathogenic variants lead to alteration in *HOX*-regulated genes and changes in structural identity or size. Molecular pathogenesis is detailed in Innis [2016].

Mechanism of disease causation. For both nonsense variants and pathogenic polyalanine tract expansions of *HOXA13*, haploinsufficiency is likely to be the basis for malformations. This is supported by chromosome deletions involving the entire *HOXA* gene cluster associated with HFGS features and mouse models. However, missense variants in the homeodomain may involve altered DNA site specificity and may result in a more severe or slightly unusual phenotype as in Guttmacher syndrome [Innis et al 2002] or as described for another homeodomain variant [Wallis et al 2016]. See Genetically Related Disorders.

***HOXA13*-specific laboratory considerations.** HFGS caused by expansion of *HOXA13* polyalanine repeat tracts, which are highly GC-rich, will not be routinely detected by next-generation sequencing analysis: assays specifically designed to detect a repeat expansion are required [Mortlock et al 2000, Innis et al 2004, Owens et al 2013].

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Chapter Notes

Author Notes

Author's website

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