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Hand-Foot-Genital Syndrome

[*HFGS, HFG Syndrome*]

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Summary

Disease characteristics. Hand-foot-genital syndrome (HFGS) is characterized by limb malformations and urogenital defects. Mild 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 abnormalities 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 are common; 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. *HOXA13* is the only gene known to be associated with HFGS. About 60% of mutations are polyalanine expansions. Molecular genetic testing is clinically available.

Management. Hand or foot surgery is not usually necessary. Ureteric reimplantation and surgical correction of bladder outlet abnormalities is 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. Surveillance involves 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 *de novo* mutations is unknown because of the small number of individuals described. If a parent of the proband is affected, the risk to the sibs is 50%. When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low. Each child of an individual with HFGS has a 50% chance of inheriting the mutation. Prenatal testing may be available through laboratories offering custom prenatal testing for families in which the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

Hand-foot-genital syndrome (HFGS) is characterized by fully penetrant limb malformations and incompletely penetrant urogenital defects caused by mutations in *HOXA13* [Mortlock & Innis 1997].

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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 but on occasion may be more severe; see Mortlock and Innis (1997) and Goodman et al (2000; family 5).

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
- Medial deviation of the great toe (hallux varus), a useful diagnostic sign when present
- Small great toenail

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
- 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

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- Various degrees of incomplete Müllerian fusion with or without two cervices or a longitudinal vaginal septum

Males may have hypospadias of variable severity with or without chordee. While hypospadias is often glandular, two males with grade II and III hypospadias and one with grade IV hypospadias have been reported. Therefore, physical examination and radiographic demonstration of characteristic hand and foot anomalies and possibly urogenital defects lead to suspicion of the diagnosis. A family history of similar features with autosomal dominant inheritance is supportive of the diagnosis but may not be present. Demonstration of a *HOXA13* mutation is confirmatory.

Testing

Cytogenetic testing. 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].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *HOXA13* is the only gene known to be associated with HFGS. Only 14 mutations have been reported to date; approximately 40% are point mutations and 60% are polyalanine expansions.

Other loci. A few individuals with the clinical features of HFGS do not have *HOXA13* mutations [Goodman et al 2000; Innis et al, unpublished].

Allele sizes. *HOXA13* has three polyalanine tracts in the first exon, referred to as tracts I, II, and III. About 50% of individuals with HFGS have a polyalanine expansion of one of the tracts. No affected individual has been described with an expansion in more than one tract.

- **Normal alleles:**
  - Tract I: 14 alanine residues
  - Tract II: 12 alanine residues
  - Tract III: 12 or 18 alanine 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 6 additional alanine residues (termed "+6" alleles) was reported in association with HFGS [Frisen et al 2003].
  - **Tract III.** Polyalanine expansions of at least 6 additional polyalanine residues (termed "+6" alleles) to as many as 14 additional polyalanine residues (termed "+14" alleles) [Innis et al 2004; Innis & Utsch, unpublished data] may cause HFGS.

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- **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].
  - Whether or not a shortened allele of 12 polyalanine residues observed in expressed sequence tag databases [Lavoie et al 2003] is associated with phenotypic variation is unknown.

Molecular genetic testing: Clinical use

- Confirmatory diagnostic testing

Molecular genetic testing: Clinical method

- **Sequence analysis.** Sequence analysis of the *HOXA13* gene in a small number of affected individuals detected nonsense or missense mutations or in-frame polyalanine expansions in the coding region in approximately 85% of affected individuals [unpublished observations].

Molecular genetic testing: Research

- **Sequence analysis.** Sequence analysis of the *HOXA13* promoter, coding sequence, and intron is available on a research basis only.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Rate [1]	Test Availability
Sequence analysis of coding region	*HOXA13* polyalanine expansion	~50%	Clinical Testing
	HOXA13 sequence variants	~35%	
Sequence analysis	*HOXA13* promoter, coding sequence, and intronic mutations	Unknown	Research only

1. In individuals fulfilling strict diagnostic criteria

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

In individuals with multiple anomalies in whom features of HFGS may also be present, chromosome analysis should be performed with attention to 7p14-p15.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with *HOXA13* mutations.

Chromosomal deletion. Chromosome 7p deletions involving the *HOXA* cluster may result in an HFGS-like syndrome with other anomalies [Devriendt et al 1999].

Clinical Description

Natural History

Hand-foot-genital syndrome (HFGS) has been reported in several families or individuals [Devriendt et al 1999, Goodman et al 2000, Becker et al 2002, Debeer et al 2002, Innis et al 2002, Utsch et al 2002, Frisen et al 2003, Innis et al 2004]. Although some minor variation in

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the severity of limb defects may be observed, the defects are usually similar bilaterally. The radius/ulna, humerus and tibia/fibula, and femur are normal. Abnormalities of muscle, other than thenar hypoplasia, have not been reported.

HFGS may first be suspected in infants or children during evaluation for urogenital problems such as hypospadias, ureteral reflux, urethral misplacement, recurrent urinary tract infections, chronic pyelonephritis, or 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. The 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.

Guttmacher syndrome refers to one family reported by Guttmacher (1993) in which features of HFGS were observed (i.e., preaxial deficiency, clinodactyly, hypospadias) along with more unusual phenotypic features of upper-limb postaxial polydactyly and uniphalangeal second toes. Innis et al (2002) identified a missense mutation in the *HOXA13* homeodomain (homeodomain Q50L) in association, in cis configuration, with a dinucleotide deletion in the promoter region in this family.

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

- Strabismus [Elias et al 1978]
- Ventriculoseptal defect [propositus of Stern et al (1970)]
- Inguinal hernia, epididymal cyst, short stature, cervical ribs, supernumerary nipple, lower limit of functioning, onychodysplasia [Halal 1988]
- Sacral dimple [Fryns et al 1993]
- Psychomotor retardation, microcephaly, and hypertelorism in one of four affected members of a single family in which HFGS occurs [Fryns et al 1993]
- One adult with difficulty with balance when standing

The following are normal:

- Developmental milestones
- External ears and hearing

Genotype-Phenotype Correlations

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

The limb malformations in individuals with the heterozygous nonsense mutations in either exon 1 or 2 or a polyalanine expansion in exon 1 are similar to those described in the individual with the cytogenetic deletion of the *HOXA* cluster [Devriendt et al 1999] suggesting that these

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typical features result from *HOXA13* haploinsufficiency. Minor differences may be attributable to effects of other genetic loci or stochastic variables.

Generally speaking, *HOXA13* homeodomain missense mutations appear to produce more severe features or unusual digital malformations.

- The individual with N51H had a more severe skeletal phenotype [Goodman et al 2000]
- The family with the Q50L mutation previously reported as having Guttmacher syndrome exhibited the novel feature of postaxial polydactyly in the upper limbs only and uniphalangeal second toes with absent nails [Innis et al 2002]. Males had hypospadias.

The variables that determine whether an individual heterozygous for a *HOXA13* mutation develops genitourinary problems are not clear. Hypospadias does not always occur in males with *HOXA13* mutations. When it does, it is most often glandular, although variability in severity occurs even in males with the same mutation. 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.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Thumb hypoplasia, often in addition to other anomalies, should prompt the consideration of the following disorders:

- Fanconi anemia syndrome
- Rothmund-Thomson syndrome
- Holt-Oram syndrome
- *SALL4*-related disorders (which includes Duane-radial ray syndrome and acro-renal-ocular syndrome
- Nager syndrome
- Townes-Brocks syndrome
- Lacrimo-auriculo-dento-digital (LADD) syndrome

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Incomplete Müllerian fusion and/or longitudinal vaginal septum should prompt the consideration of the following disorders:

- Acro-renal-mandibular syndrome
- Bardet-Biedl syndrome
- Beckwith-Wiedemann syndrome
- Fraser syndrome
- Fryns syndrome
- Halal syndrome
- Meckel syndrome
- Others [Simpson 1999]

The following individual case reports closely resemble HFGS, but molecular analysis has not been performed or failed to demonstrate a *HOXA13* mutation.

- Pinsky (1974) reviewed syndromes with similar features involving distal limb elements and urogenital defects including camptobrachydactyly, hydrometrocolpospolydactyly, and cryptophthalmos.
- The family studied by Hennekam (1989) had moderately shortened halluces, incomplete Müllerian fusion, and small, thickened, dysplastic helices (not typical for HFGS), but no hand anomalies or the typical HFGS metacarpophalangeal profile. No *HOXA13* mutation was identified [Goodman et al 2000].
- A report by Halal (1986) described a unique family with Müllerian duct anomalies and upper-limb hypoplasia of varying severity.
- Michels and Caskey (1978) described two individuals with Müllerian aplasia and hypoplastic thumbs.
- *HOXA13* mutations have not been identified yet in individuals with isolated hypospadias (i.e., without skeletal malformations) [Utsch et al 2003] or isolated forms of incomplete Müllerian fusion [Innis, unpublished].

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Physical examination and radiographs of the hands and feet to evaluate for characteristic abnormalities that may affect hand function such as small thumbs and fifth finger clinodactyly
- Urologic assessment of bladder/ureter function and urethral competence or position, including renal ultrasound examination and voiding cystourethrogram; examination for UPJ obstruction
- Gynecologic examination prior to menstruation or pregnancy for evidence of incomplete Müllerian fusion, longitudinal vaginal septum, or extremely small hymenal opening; including ultrasound, hysterosalpingogram, hysteroscopy, sonohysterogram, MRI, or other imaging studies. Such studies could be accomplished at the same time as urologic imaging.

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Treatment of Manifestations

Urologic referral is indicated. Surgical correction of bladder outlet abnormalities, ureteric implantation, and followup, particularly in the presence of vesicoureteral reflux and/or documented urinary tract infection.

Gynecologic referral is indicated. 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.

Usually, extremity surgery is not necessary, although repair of hallux varus [Cleveland & Holmes 1990] and tarsal fusion [Verp et al 1983] have been reported.

Prevention of Secondary Complications

- Prophylactic antibiotics or surgery as needed to prevent urinary tract infections or other complications of ureteral reflux or UPJ obstruction
- 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

Gynecologic examination prior to menstruation for small hymenal opening and prior to pregnancy for evidence of incomplete Müllerian fusion or longitudinal vaginal septum is recommended. Evaluation may include ultrasound examination, MRI, or other imaging studies.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with hand-foot-genital syndrome have an affected parent.
- A proband with HFGS may have the disorder as the result of a new gene mutation. The proportion of cases caused by *de novo* mutations is unknown because of the small number of individuals described.

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- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include history and physical examination followed by radiographic examination of hands and feet, and possibly referral for urologic and/or gynecologic examination. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: (1) Although some individuals diagnosed with HFGS have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members or death of the parent before appropriate evaluation. (2) Although it has not yet been reported, it is possible that a parent is the individual in whom the mutation first occurred and s/he may have somatic mosaicism for the mutation and may be mildly/minimally affected.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low, but may be greater than that of the general population if germline mosaicism exists.

Offspring of a proband. Each child of an individual with HFGS has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations include alternate paternity or undisclosed adoption.

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal testing *HOXA13* DNA mutation analysis has not been reported nor are any laboratories offering molecular genetic testing for prenatal diagnosis for hand-foot-genital syndrome listed in the GeneTests Laboratory Directory. However, prenatal

testing may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering custom prenatal testing, see Testing.

Fetal ultrasound examination. Prenatal ultrasound has not been reported in HFGS.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Hand-Foot-Genital Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
HOXA13	7p15-p14.2	Homeobox protein Hox-A13

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Hand-Foot-Genital Syndrome

140000	HAND-FOOT-UTERUS SYNDROME
142959	HOMEO BOX A13; HOXA13

Table C. Genomic Databases for Hand-Foot-Genital Syndrome

Gene Symbol	Entrez Gene	HGMD
HOXA13	3209 (MIM No. 142959)	HOXA13

For a description of the genomic databases listed, click here.

Normal allelic variants: The *HOXA13* gene has two exons. Extended polyalanine tracts of 14, 12 and 18 residues are encoded by the first exon of the usual *HOXA13* gene and are conserved in mammals [Mortlock et al 2000]. These encoded segments are referred to as tracts I, II, and III.

Pathologic allelic variants: Only 14 mutations have been reported to date; approximately 40% are point mutations and 60% are polyalanine expansions. No affected individual has been described with an expansion in more than one tract.

Normal gene product: HOXA13 is a homeobox transcription factor [Innis et al 2002].

Abnormal gene product: HOXA13 proteins with polyalanine expansions are stable [Innis et al 2004]. For both nonsense mutations and polyalanine tract mutations, haploinsufficiency is likely to be the basis for malformations. However, missense mutations of the homeodomain may involve altered DNA site specificity and may result in a more severe or slightly unusual phenotype. Also, at least in the mouse, frame-shifting mutations may lead to the production of novel, stable protein products with the potential for gain of function [Post et al 2000].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other

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organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

No specific resources exist for Hand-Foot-Genital Syndrome.

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Becker K, Brock D, Ludwig M, Bidlingmaier F, Albers N, Lentze MJ, Utsch B. Das dominant vererbte Hand-Foot-Genital-Syndrome: Malformationen der distalen Extremitaten mit Fehlbildungen des Urogenitaltraktes. Monatsschr Kinderh . 2002

Cleveland RH, Holmes LB. Hand-foot-genital syndrome: the importance of hallux varus. Pediatr Radiol. 1990;20:339–43. [PubMed: 2349017]

Debeer P, Bacchelli C, Scambler PJ, De Smet L, Fryns JP, Goodman FR. Severe digital abnormalities in a patient heterozygous for both a novel missense mutation in HOXD13 and a polyalanine tract expansion in HOXA13. J Med Genet. 2002;39:852–6. [PubMed: 12414828]

Devriendt K, Jaeken J, Matthijs G, Van Esch H, Debeer P, Gewillig M, Fryns JP. Haploinsufficiency of the HOXA gene cluster, in a patient with hand-foot-genital syndrome, velopharyngeal insufficiency, and persistent patent Ductus botalli. Am J Hum Genet. 1999;65:249–51. [PubMed: 10364539]

Donnenfeld AE, Schrager DS, Corson SL. Update on a family with hand-foot-genital syndrome: hypospadias and urinary tract abnormalities in two boys from the fourth generation. Am J Med Genet. 1992;44:482–4. [PubMed: 1442892]

Elias S, Simpson JL, Feingold M, Sarto G. The hand-foot-uterus syndrome: a rare autosomal dominant disorder. Fertil Steril. 1978;29:239–40.

Frisen L, Lagerstedt K, Tapper-Persson M, Kickum I, Nordenskjold A. A novel duplication in the HOXA13 gene in a family with atypical hand-foot-genital syndrome. J Med Gen. 2003;40:e49. [PubMed: 12676922]

Fryns JP, Vogels A, Decock P, van den Berghe H. The hand-foot-genital syndrome: on the variable expression in affected males. Clin Genet. 1993;43:232–4. [PubMed: 8375102]

Goodman FR, Bacchelli C, Brady AF, Brueton LA, Fryns JP, Mortlock DP, Innis JW, Holmes LB, Donnenfeld AE, Feingold M, Beemer FA, Hennekam RC, Scambler PJ. Novel HOXA13 mutations and the phenotypic spectrum of hand-foot-genital syndrome. Am J Hum Genet. 2000;67:197–202. [PubMed: 10839976]

Guttmacher AE. Autosomal dominant preaxial deficiency, postaxial polydactyly, and hypospadias. Am J Med Genet. 1993;46:219–22. [PubMed: 8484413]

Halal F. A new syndrome of severe upper limb hypoplasia and Mullerian duct anomalies. Am J Med Genet. 1986;24:119–26. [PubMed: 3706400]

Halal F. The hand-foot-genital (hand-foot-uterus) syndrome: family report and update. Am J Med Genet. 1988;30:793–803. [PubMed: 3189398]

Hennekam RC. Acral-genital anomalies combined with ear anomalies. Am J Med Genet. 1989;34:454–5. [PubMed: 2596533]

Innis JW, Goodman FR, Bacchelli C, Williams TM, Mortlock DP, Sateesh P, Scambler PJ, McKinnon W, Guttmacher AE. A HOXA13 allele with a missense mutation in the homeobox and a dinucleotide deletion in the promoter underlies Guttmacher syndrome. Hum Mutat. 2002;19:573–4. [PubMed: 11968094]

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Innis JW, Mortlock D, Chen Z, Ludwig M, Williams ME, Williams TM, Doyle CD, Shao Z, Glynn M, Mikulic D, Lehmann K, Mundlos S, Utsch B. Polyalanine expansion in HOXA13: three new affected families and the molecular consequences in a mouse model. Hum Mol Genet. 2004;13:2841–51. [PubMed: 15385446]

Lavoie H, Debeane F, Trinh QD, Turcotte JF, Corbeil-Girard LP, Dicaire MJ, Saint-Denis A, Page M, Rouleau GA, Brais B. Polymorphism, shared functions and convergent evolution of genes with sequences coding for polyalanine domains. Hum Mol Genet. 2003;12:2967–79. [PubMed: 14519685]

Michels VV, Caskey CT. Mullerian aplasia with hypoplastic thumbs: Two case reports. Int J Gynaecol Obstet. 1978;17:6–10. [PubMed: 39840]

Mortlock DP, Innis JW. Mutation of HOXA13 in hand-foot-genital syndrome. Nat Genet. 1997;15:179–80. [PubMed: 9020844]

Mortlock DP, Sateesh P, Innis JW. Evolution of N-terminal sequences of the vertebrate HOXA13 protein. Mamm Genome. 2000;11:151–8. [PubMed: 10656931]

Pinsky L. A community of human malformation syndromes involving the Mullerian ducts, distal extremities, urinary tract, and ears. Teratology. 1974;9:65–79. [PubMed: 4855855]

Post LC, Margulies EH, Kuo A, Innis JW. Severe limb defects in Hypodactyly mice result from the expression of a novel, mutant HOXA13 protein. Dev Biol. 2000;217:290–300. [PubMed: 10625554]

Simpson JL. Genetics of the female reproductive ducts. Am J Med Genet. 1999;89:224–39. [PubMed: 10727998]

Stern AM, Gall JC Jr, Perry BL, Stimson CW, Weitkamp LR, Poznanski AK. The hand-food-uterus syndrome: a new hereditary disorder characterized by hand and foot dysplasia, dermatoglyphic abnormalities, and partial duplication of the female genital tract. J Pediatr. 1970;77:109–16. [PubMed: 5450271]

Utsch B, Becker K, Brock D, Lentze MJ, Bidlingmaier F, Ludwig M. A novel stable polyalanine [poly (A)] expansion in the HOXA13 gene associated with hand-foot-genital syndrome: proper function of poly(A)-harbouring transcription factors depends on a critical repeat length? Hum Genet. 2002;110:488–94. [PubMed: 12073020]

Utsch B, Kaya A, Ozburun A, Lentze MJ, Albers N, Ludwig M. Exclusion of WTAP and HOXA13 as candidate genes for isolated hypospadias. Scand J Urol Nephrol. 2003;37:498–501. [PubMed: 14675924]

Verp MS, Simpson JL, Elias S, Carson SA, Sarto GE, Feingold M. Heritable aspects of uterine anomalies. I. Three familial aggregates with Mullerian fusion anomalies. Fertil Steril. 1983;40:80–5. [PubMed: 6862042]

Suggested Readings

Goodman FR, Scambler PJ. Human HOX gene mutations. Clin Genet. 2001;59:1–11. [PubMed: 11206481]

Innis JW. Role of HOX genes in human development. Curr Opin Pediatr. 1997;9:617–22. [PubMed: 9425595]

Innis JW. HOXA13: Hand-foot-genital and Guttmacher syndromes. In C Epstein, T Wynshaw-Boris, R Erickson (eds), Inborn Errors of Development, Oxford University Press, San Francisco. 2004

Chapter Notes

Author Notes

Web site: www.med.umich.edu/hg/RESEARCH/FACULTY/Innis/Innis.htm

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