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FGFR1-Related Hartsfield Syndrome

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Summary

Clinical characteristics

FGFR1-related Hartsfield syndrome comprises two core features: holoprosencephaly (HPE) spectrum disorder and ectrodactyly spectrum disorder.

- HPE spectrum disorder, resulting from failed or incomplete forebrain division early in gestation, includes alobar, semilobar, or lobar HPE. Other observed midline brain malformations include corpus callosum agenesis, absent septum pellucidum, absent olfactory bulbs and tracts, and vermian hypoplasia. Other findings associated with the HPE spectrum such as craniofacial dysmorphism, neurologic issues (developmental delay, spasticity, seizures, hypothalamic dysfunction), feeding problems, and endocrine issues (hypogonadotropic hypogonadism and central insipidus diabetes) are common.
- Ectrodactyly spectrum disorders are unilateral or bilateral malformations of the hands and/or feet characterized by a median cleft of hand or foot due to absence of the longitudinal central rays (also called split-hand/foot malformation). The number of digits on the right and left can vary. Polydactyly and syndactyly can also be seen.

Diagnosis/testing

The diagnosis of *FGFR1*-related Hartsfield syndrome is established in a proband with suggestive findings and either an *FGFR1* heterozygous pathogenic variant (in those with autosomal dominant inheritance) or *FGFR1* biallelic pathogenic variants (in those with autosomal recessive inheritance) identified by molecular genetic testing.

Management

Treatment of manifestations: Diabetes insipidus may require treatment with desmopressin; temperature dysregulation can be managed by modifying the environment; disturbance of sleep-wake cycles can be managed with good sleep hygiene and, if needed, use of melatonin or other sleep aids such as clonidine. Medically

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refractory epilepsy typically requires multiple anti-seizure medications. Developmental delay is managed with an emphasis on early intervention and an individualized education plan and therapies as needed. Spasticity can be treated with physical and occupational therapy and bracing, as well as muscle relaxants (when moderate or severe). Some children may require a gastrostomy and/or tracheostomy for feeding issues. Cleft lip/palate surgical repair is performed under the direction of a craniofacial team. Hand and foot malformations are managed with therapy and adaptive devices; surgery may be needed to improve dexterity.

Genetic counseling

FGFR1-related Hartsfield syndrome is typically an autosomal dominant (AD) disorder. In two families reported to date, *FGFR1*-related Hartsfield syndrome was inherited in an autosomal recessive (AR) manner.

- **AD inheritance.** Most probands have a *de novo FGFR1* pathogenic variant. Germline mosaicism has been observed in three unrelated families.
- **AR inheritance.** At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

Once the *FGFR1* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for a pregnancy at increased risk are possible.

Diagnosis

Suggestive Findings

FGFR1-related Hartsfield syndrome **should be suspected** in individuals with the following two core features:

- **Holoprosencephaly (HPE) spectrum disorder.** The spectrum results from failed or incomplete forebrain division early in gestation and includes brain malformations such as alobar, semilobar, or lobar HPE, corpus callosum agenesis, absent septum pellucidum, absent olfactory bulbs and tracts, and vermian hypoplasia. Facial malformations such as hypotelorism, cleft lip and palate (either median or bilateral), ocular malformations, and microcephaly are common.
- **Ectrodactyly spectrum disorder.** These unilateral or bilateral malformations of the hands and/or feet are characterized by a median cleft of hand or foot due to absence of longitudinal central rays (also called split-hand/foot malformation). The number of digits on the right and left hand/foot can vary. Polydactyly and syndactyly can be part of the spectrum.

Establishing the Diagnosis

The diagnosis of *FGFR1*-related Hartsfield syndrome **is established** in a proband with suggestive findings and either an *FGFR1* heterozygous pathogenic (or likely pathogenic) variant (in those with autosomal dominant inheritance) or *FGFR1* biallelic pathogenic (or likely pathogenic) variants (in those with autosomal recessive inheritance) [Simonis et al 2013, Dhamija et al 2014] identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *FGFR1* variant of uncertain significance does not establish or rule out the diagnosis.

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. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *FGFR1*-related Hartsfield syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *FGFR1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. Typically, if no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date such variants have not been identified as a cause of this disorder.

A multigene panel that includes *FGFR1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **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 *FGFR1*-Related Hartsfield Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Identified by Method
FGFR1	Sequence analysis [3]	35/35 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Metwalley Kalil & Fargalley [2012], Simonis et al [2013], Dhamija et al [2014], Hong et al [2016], Shi et al [2016], Takagi et al [2016], Lansdon et al [2017],Oliver et al [2017], Courage et al [2019]
5. 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.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

FGFR1-related Hartsfield syndrome is characterized by findings of the holoprosencephaly (HPE) spectrum in combination with findings of the ectrodactyly spectrum.

To date, 35 individuals with *FGFR1*-related Hartsfield syndrome have been identified [Metwalley Kalil & Fargalley 2012, Simonis et al 2013, Dhamija et al 2014, Hong et al 2016, Shi et al 2016, Takagi et al 2016, Lansdon et al 2017, Oliver et al 2017, Courage et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

HPE spectrum malformations include alobar, semilobar, or lobar holoprosencephaly. Other observed midline brain malformations include corpus callosum agenesis, absent septum pellucidum, absent olfactory bulbs and tracts, and vermian hypoplasia. Other findings associated with the HPE spectrum such as craniofacial dysmorphism, neurologic issues, feeding problems, and endocrine issues are common and detailed later in this section.

Ectrodactyly spectrum malformations are unilateral or bilateral malformations of the hands and/or feet characterized by a median cleft of hand or foot due to absence of the longitudinal central rays (also called split-hand/foot malformation). The number of digits on the right and left can vary. Polydactyly and syndactyly can also be seen.

Craniofacial dysmorphism

- Microcephaly; hypotelorism or hypertelorism; eye anomalies such as microphthalmia and coloboma; malformed, low-set, and posteriorly rotated ears; and cleft lip and or palate (median or bilateral) are common.
- Craniosynostosis (metopic and coronal) has been reported [Vilain et al 2009].

Neurologic issues

- Varying degrees of developmental delay can occur.
- Spasticity is common.
- Seizures are common and may be difficult to control.
- Hypothalamic dysfunction, manifesting as temperature dysregulation and erratic sleep patterns, can occur.

Gastrointestinal problems. Feeding difficulties as a result of axial hypotonia, gastrointestinal reflux, and oromotor dysfunction may be a major problem and result in slow growth.

Respiratory concerns. Aspiration pneumonia can result from poorly coordinated suck and swallow.

Endocrine issues. Because of midline brain defects that involve the pituitary, central endocrine disorders (including growth hormone deficiency, central diabetes insipidus, and hypogonadotropic hypogonadism) are common.

Genitourinary findings. Some males have micropenis, cryptorchidism (due to hypogonadotropic hypogonadism), and hypospadias.

Skeletal anomalies. Other skeletal anomalies include vertebral anomalies and radial and ulnar aplasia.

Cardiovascular malformations are rare but reported [Courage et al 2019].

Phenotype of Autosomal Recessive *FGFR1*-Related Hartsfield Syndrome

Compared with four individuals with a heterozygous *FGFR1* pathogenic variant, the two with biallelic *FGFR1* pathogenic variants had a more severe phenotype [Simonis et al 2013]:

- **HPE spectrum**
  - Alobar holoprosencephaly (1/2)
  - Diminished cortical thickening (2/2)
  - Absent corpus callosum (2/2)
  - Median cleft (1/2)
  - Hypotelorism (2/2)
  - Severe developmental delay and growth restriction (2/2)
- **Ectrodactyly spectrum.** Split-hand/foot malformation of both hands and feet, and fewer than three digits bilaterally (2/2)
- **Death** before age five years (2/2)

Nomenclature

In the older literature, *FGFR1*-related Hartsfield syndrome has been referred to as:

- Holoprosencephaly and split-hand/foot syndrome;
- Holoprosencephaly, hypertelorism, and ectrodactyly syndrome (HHES).

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Biallelic pathogenic variants in *FGFR1* have been found in two individuals with a more severe Hartsfield syndrome phenotype as compared to those with a heterozygous pathogenic variant [Simonis et al 2013].

Prevalence

Thirty-five individuals with *FGFR1*-related Hartsfield syndrome have been reported in the literature.

Genetically Related (Allelic) Disorders

Germline pathogenic variants in *FGFR1* are known to be associated with a wide spectrum of phenotypes (see Table 2).

Table 2. *FGFR1* Allelic Disorders

FGFR1 Germline Pathogenic Variants Causing:	Phenotype
Loss of function [1]	Isolated gonadotropin-releasing hormone (GnRH) deficiency
	Kallmann syndrome
	Kallmann syndrome w/additional features incl: digital anomalies that are distict from ectrodactyly; mild expression of HPE (e.g., corpus callosum agenesis, central incisor)
	Septooptic-like dysplasia
Gain of function	Pfeiffer syndrome (See *FGFR*-Related Craniosynostosis Syndromes.)
	Osteoglophonic dysplasia

1. Villanueva & de Roux [2010], Jarzabek et al [2012], Vizeneux et al [2013], Sarfati et al [2015], Villanueva et al [2015]

Mosaic activating pathogenic variants in *FGFR1* are associated with encephalocraniocutaneous lipomatosis (ECCL). The pathogenic variants reported in ECCL are of postzygotic origin but arise early during development. ECCL comprises a spectrum of predominantly congenital anomalies. In its typical form, ECCL is characterized by congenital skin, eye, and brain anomalies, in particular intracranial and spinal lipomas.

Differential Diagnosis

Holoprosencephaly (HPE). See Holoprosencephaly Overview.

Ectrodactyly, ectodermal dysplasia, cleft lip/palate syndrome 3 (EEC3) – an autosomal dominant disorder caused by pathogenic variants in *TP63* (see *TP63*-Related Disorders) – is associated with:

- Limb anomalies in 68%-90% of individuals, with 60% having tetramelic involvement. A cohort of 152 individuals with EEC3 showed split-hand/foot malformation in 68% and syndactyly in 43%.
- Ectodermal defects. Skin tends to be dry but erosions are not present. Hair changes become more obvious with age and are seen in 60%-80% of individuals. Hair is typically silvery blond, coarse, and dry. Eyebrows and eyelashes are sparse. Nail dysplasia is common. Dental anomalies include malformed teeth and hypodontia.
- Cleft lip with or without cleft palate, present in 60%-75% and bilateral in half of cases. Clefting can include submucous cleft palate only, cleft of the soft and/or the hard palate only, cleft lip only, or the combination of cleft lip and cleft palate.
- Absent lacrimal puncta (90% of individuals)
- Genitourinary malformations (45% of individuals)

Overexpression of *ANOS1* (formerly *KAL1*). One male with hyperosmia, ectrodactyly, genital anomalies, and mild intellectual disability had partial duplication of the X-linked gene *ANOS1*. ANOS1 protein at high levels may interfere with FGFR1 signaling activity, leading to an overlapping phenotype [Sowińska-Seidler et al 2015].

Microduplication of Xq24. One individual with duplication of Xq24 and a Hartsfield syndrome phenotype has been reported [Takenouchi et al 2012]. This individual was reported prior to the identification of *FGFR1* as the causative gene for *FGFR1*-related Hartsfield syndrome and so did not have molecular genetic testing for a pathogenic variant.

Management

No clinical practice guidelines for *FGFR1*-related Hartsfield syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *FGFR1*-related Hartsfield syndrome, 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 *FGFR1*-Related Hartsfield Syndrome

System/Concern	Evaluation	Comment
Neurologic	Brain MRI	Determine type of holoprosencephaly (alobar, semilobar, or lobar).
	Neurologic eval	• Consider EEG if seizures are a concern. • Eval for evidence of central diabetes insipidus, temperature dysregulation, &/or disturbance of sleep-wake cycles

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Development	Developmental assessment incl evidence for spasticity	• Incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval for evidence of problems that may result from cleft lip/ palate &/or oromotor dysfunction	• Incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in those w/dysphagia &/or aspiration risk.
Cleft lip/palate	Referral to craniofacial team	
Endocrine	Evaluate for evidence of endocrine deficiency (growth hormone deficiency, hypogonadotropic hypogonadism).	
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	Incl assessment of: • Extent of ectrodactyly • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
	Neuroimaging for tethered spinal cord if suspicion (rare)	
Cardiac	Referral to pediatric cardiologist for eval for cardiovascular malformation	Incl echocardiogram
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of this disorder to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADL = activities of daily living; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *FGFR1*-Related Hartsfield Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Hypothalamic dysfunction assoc w/holoprosencephaly	• Central diabetes insipidus may require treatment w/desmopressin. • Temperature dysregulation can be managed by modifying environment. • Manage disturbance of sleep-wake cycles w/ good sleep hygiene & (if needed) use of melatonin or other sleep aids such as clonidine.	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Medically refractory epilepsy typically requires multiple ASMs. • Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Spasticity	• PT, OT, & bracing • Muscle relaxants may be used to treat moderate or severe spasticity.	Surgery may be required.
Tethered spinal cord (rare)	Surgery may be required.	
Feeding issues	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Tracheostomy may be needed to prevent aspiration in some.
Cleft lip/palate	Surgical repair under direction of craniofacial team	
Hand & foot malformations	• OT, PT, & adaptive devices • Surgery may be needed to improve dexterity.	

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.

    - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
    - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 5. Recommended Surveillance for Individuals with *FGFR1*-Related Hartsfield Syndrome

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures, changes in tone, mvmt disorders.	
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

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

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

FGFR1-related Hartsfield syndrome is typically an autosomal dominant disorder. In two families reported to date, *FGFR1*-related Hartsfield syndrome was inherited in an autosomal recessive manner [Simonis et al 2013].

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most probands reported to date with *FGFR1*-related Hartsfield syndrome whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo FGFR1* pathogenic variant.
- Molecular genetic testing for the *FGFR1* pathogenic variant identified in the proband is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism [Dhamija et al 2014, Shi et al 2016, Courage et al 2019]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If the *FGFR1* pathogenic variant identified in the proband 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 (germline mosaicism has been observed in 3 unrelated families) [Dhamija et al 2014, Shi et al 2016, Courage et al 2019].

Offspring of a proband. To date, individuals with *FGFR1*-related Hartsfield syndrome are not known to reproduce.

Other family members. Given that most probands with autosomal dominant *FGFR1*-related Hartsfield syndrome reported to date have the disorder as a result of a *de novo FGFR1* pathogenic variant or an *FGFR1* pathogenic variant inherited from a parent with germline mosaicism, the risk to other family members is presumed to be low.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *FGFR1* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *FGFR1* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- The heterozygous parents of a proband with autosomal recessive *FGFR1*-related Hartsfield syndrome are expected to be asymptomatic (in 1 of the 2 families with autosomal recessive inheritance reported to date, the heterozygous parents of the proband were asymptomatic; the parents of the other proband with biallelic *FGFR1* pathogenic variants were not evaluated [Simonis et al 2013]).

Sibs of a proband

- If both parents are known to be heterozygous for an *FGFR1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither of the familial *FGFR1* pathogenic variants.
- The heterozygous sibs of a proband with autosomal recessive *FGFR1*-related Hartsfield syndrome are expected to be asymptomatic.

Offspring of a proband. To date, individuals with *FGFR1*-related Hartsfield syndrome are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *FGFR1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *FGFR1* pathogenic variants in the family.

Related Genetic Counseling Issues

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *FGFR1* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *FGFR1*-related Hartsfield syndrome 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.

- **Born a Hero**
  www.bornahero.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Holoprosencephaly Information Page

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. FGFR1-Related Hartsfield Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FGFR1	8p11.23	Fibroblast growth factor receptor 1	FGFR1 database	FGFR1	FGFR1

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 FGFR1-Related Hartsfield Syndrome (View All in OMIM)

136350	FIBROBLAST GROWTH FACTOR RECEPTOR 1; FGFR1
615465	HARTSFIELD SYNDROME; HRTFDS

Molecular Pathogenesis

FGFR1 is a member of the receptor tyrosine kinase superfamily. The fibroblast growth factor (FGF) signaling pathway is a major factor in embryonic development. FGFR1 is expressed in cranial neural crest cell-derived mesenchyme and plays an important role during embryogenesis by deregulating cell death at early stages of limb initiation. A full-length representative protein consists of an extracellular region, comprising three immunoglobulin-like domains, a single hydrophobic membrane-spanning segment, and a cytoplasmic tyrosine kinase domain. The extracellular portion of the protein interacts with fibroblast growth factors, setting in motion a cascade of downstream signals, ultimately influencing mitogenesis and differentiation [Groth & Lardelli 2002, Li et al 2005, Tole et al 2006, Mason 2007]. *FGFR1* pathogenic variants perturb RAS/ERK1/2 signaling and indicate that dysregulated autophagy is a contributing mechanism to developmental anomalies in Hartsfield syndrome [Palumbo et al 2019].

Mechanism of disease causation. Loss-of-function variants in *FGFR1* are associated with a wide phenotypic spectrum and identical variants may present with a variable phenotype attributable to reduced penetrance and variable expressivity [Simonis et al 2013]. Hartsfield syndrome can result from loss-of-function variants of *FGFR1* [Simonis et al 2013, Dhamija et al 2014]. Some pathogenic variants affecting the tyrosine kinase domain of *FGFR1* have been demonstrated to result in dominant-negative effects altering normal signaling in zebrafish [Hong et al 2016].

Cancer and Benign Tumors

Sporadic tumors occurring as single tumors in the absence of any other findings of Hartsfield syndrome may contain somatic variants and/or copy number changes in *FGFR1* that are not present in the germline; thus, predisposition to these tumors is not heritable [Ahmad et al 2012].

Chapter Notes

Revision History

- 12 May 2022 (aa) Revision: encephalocraniocutaneous lipomatosis added to Genetically Related Disorders
- 2 December 2021 (ha) Comprehensive update posted live
- 3 March 2016 (bp) Review posted live
- 12 November 2015 (rd) Original submission

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