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HIST1H1E Syndrome

Synonym: Rahman Syndrome

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Summary

Clinical characteristics

The name HIST1H1E syndrome has been proposed as a mnemonic for the characteristic features of this emerging, recognizable phenotype: *h*ypotonia; *i*ntellectual disability with behavioral issues; *s*keletal; *t*estes (undescended) and *t*hyroid; *h*eart anomalies (most commonly atrial septal defect); and *e*ctodermal issues (including sparse hair, thin nails, and abnormal dentition). In the 47 affected individuals reported to date, predominant findings were intellectual disability (ranging from mild to profound) and behavioral issues (combinations of anxiety/phobias, obsessive behaviors, attention-deficit/hyperactivity disorder, and autistic spectrum disorder/traits among others). Skeletal involvement can include scoliosis and decreased bone mineral density. Other findings in some include seizures, craniosynostosis, and hearing loss. Life expectancy does not appear to be reduced in HIST1H1E syndrome.

Diagnosis/testing

The diagnosis of HIST1H1E syndrome is established in a proband with suggestive findings and a heterozygous pathogenic variant in *H1-4* (formerly *HIST1H1E*) identified by molecular genetic testing.

Management

Treatment of manifestations: Management by multidisciplinary specialists is recommended, including but not limited to developmental pediatrics/behavioral psychology, neurosurgery/neurology, urology, cardiology, endocrinology, ophthalmology, orthopedics, and dentistry.

Surveillance: Routine periodic assessment of significant issues as per multidisciplinary specialists.

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Genetic counseling

HIST1H1E syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. To date, all probands reported with HIST1H1E syndrome whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo H1-4* pathogenic variant. If the *H1-4* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism. Once the *H1-4* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for HIST1H1E syndrome have been published.

Suggestive Findings

HIST1H1E syndrome **should be considered** in individuals with the following clinical findings [Tatton-Brown et al 2017, Duffney et al 2018, Takenouchi et al 2018, Burkardt et al 2019, Flex et al 2019].

Clinical findings include mild-to-profound developmental delay or intellectual disability AND a combination of the following features presenting in infancy or childhood:

- Generalized hypotonia of infancy
- Characteristic facial features including [Burkardt et al 2019, Figure 3]:
  - In early childhood, full cheeks and a high hairline, bitemporal narrowing, deep-set eyes, downslanting palpebral fissures, and hypertelorism
  - In later childhood and adulthood, a notable high frontal hairline, frontal bossing, and deep-set eyes
- Ectodermal abnormalities including thin and/or brittle, slow growing hair, reduced body hair, and thin nails
- Abnormal dentition including crumbling teeth, dental caries, and enamel hypoplasia
- Behavioral issues including anxiety disorder, attention-deficit/hyperactivity disorder, aggression, sleep disturbances, and/or autism spectrum disorder
- Cryptorchidism in males
- Congenital cardiac anomalies, most frequently atrial septal defect
- Hypothyroidism
- Skeletal involvement including combinations of craniosynostosis, kypho/scoliosis, lower limb asymmetry, distal brachydactyly, camptodactyly, overlapping toes, and multiple fractures

Establishing the Diagnosis

The diagnosis of HIST1H1E syndrome **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *H1-4* (formerly *HIST1H1E*) 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 section is understood to include likely pathogenic variants. (2) Identification of a heterozygous *H1-4* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **gene-targeted testing** (single-gene testing, multigene panel) and/or **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 HIST1H1E syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of HIST1H1E syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *H1-4* is performed. Of note, the variants that have to date been shown to cause HIST1H1E syndrome are frameshift variants that cluster within the carboxy terminal domain. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, typically 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.
- **An intellectual disability multigene panel** that includes *H1-4* 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

When the diagnosis of HIST1H1E syndrome has not been considered, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) is an option. **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.

Epigenetic signature analysis / methylation array. A distinctive epigenetic signature (disorder-specific genome wide changes in DNA methylation profiles) in peripheral blood leukocytes has been identified in individuals with HIST1H1E syndrome [Burkardt et al 2019, Levy et al 2021]. Epigenetic signature analysis of a peripheral blood sample or DNA banked from a blood sample can therefore be considered to clarify the diagnosis in individuals with: (1) suggestive clinical findings of HIST1H1E syndrome but in whom no pathogenic variant in H*1-4* has been identified via sequence analysis or genomic testing; or (2) suggestive clinical findings of HIST1H1E syndrome and a *H1-4* variant of uncertain clinical significance identified by molecular genetic testing. For an introduction to epigenetic signature analysis click here.

Table 1. Molecular Genetic Testing Used in HIST1H1E Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
H1-4	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None [4]

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 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.
4. To date all individuals reported with the recognizable pattern of findings characteristic of HIST1H1E syndrome have had frameshift variants in the carboxy terminal domain. No affected individuals with other sequence variants or gene dosage abnormalities have been reported.
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.

Clinical Characteristics

Clinical Description

HIST1H1E syndrome is characterized by intellectual disability and a distinctive facial gestalt [Burkardt et al 2019, Figure 3].

To date, 47 individuals have been identified with a heterozygous pathogenic variant in *H1-4* (formerly *HIST1H1E*). Table 2 provides data on the phenotypic features of 46 affected individuals in four studies and two case reports [Tatton-Brown et al 2017, Duffney et al 2018, Takenouchi et al 2018, Burkardt et al 2019, Flex et al 2019, Ciolfi et al 2020]. Because the earliest identified published report of an individual with a *H1-4* pathogenic variant mentioned "Sotos syndrome-like features" and autism spectrum disorder, but no other clinical information [Helsmoortel et al 2015], it was not included in this tabulation.

Table 2. Features of HIST1H1E Syndrome

Feature	Proportion of Persons w/Feature	Comment
Cognition & motor development	100% (46/46)	ID is highly variable, ranging from mild to severe.
Abnormal brain MRI	92% (22/24)	Corpus callosal abnormalities are most frequent; 2 persons w/ seizures
Cryptorchidism	75% (15/20 males)	
Hypotonia	67% (29/43)	
Behavioral issues	59% (23/39)	Anxiety, phobias, obsessive behaviors, ADD, aggression, auditory hypersensitivity, & AS disorder/traits
Skeletal features	54% (22/41)	A range of skeletal features are described.
Abnormal dentition	51% (22/43)	Crumbling teeth, missing teeth (primary & adult) & multiple dental caries
Congenital cardiac anomalies / Abnormal echocardiogram	40% (16/41)	Atrial septal defect is most frequent.
Hypothyroidism	29% (6/21)	

ID = intellectual disability; ADD = attention-deficit disorder; AS = autism spectrum

Phenotypic Features

Cognition. All children have had some degree of intellectual disability (ID) ranging from mild to severe.

- Mild ID typically describes an individual who had delayed milestones but attended a mainstream school with additional help, and as an adult lived independently with support (5 individuals described to date).
- Moderate ID typically describes an individual who required high-level support in a mainstream school or had special educational needs schooling, and as an adult lived with support (most frequently characterized among individuals old enough for evaluation; 17 individuals described to date).
- Severe ID typically describes an individual who required special educational needs schooling, had limited speech, and did not live independently as an adult (4 individuals described in the literature).

Speech was significantly delayed in most individuals, with expressive language more severely affected than receptive language skills.

Motor milestones were notably delayed, with range of walking independently between ages 15 and 66 months (mean 31 months) [Flex et al 2019].

Behavioral issues included combinations of anxiety/phobias (4 individuals), obsessive behaviors (2 individuals), attention-deficit/hyperactivity disorder (3); autistic spectrum disorder/traits (4); head banging (2), auditory hypersensitivity (1), and aggression (1).

Sleep issues were reported in three individuals and mostly included restlessness / difficulty staying asleep.

Neurologic phenotype [Burkardt et al 2019, Flex et al 2019]

- **Abnormal tone.** Hypotonia in the neonatal period or early childhood was reported across studies. Increased tone was described in two neonates.
- **Seizures.** Two individuals had afebrile seizures: one with childhood focal seizures and one with recurrent status epilepticus necessitating anti-seizure medication. Febrile seizures in childhood were reported in six children. No specific EEG findings were reported among those studied.
- **Brain MRI.** The most frequent were abnormalities of the corpus callosum (most commonly slender or hypoplastic). Hydrocephalus (usually mild ventricular enlargement sometimes with relative macrocephaly) and arachnoid cysts were also reported (2 individuals) with mild inferior vermian hypoplasia noted in one individual and a "periventricular white matter abnormality" in another [Duffney et al 2018].

Ophthalmologic findings included strabismus (4 individuals) and astigmatism (5).

Cryptorchidism was either unilateral or bilateral. One male with cryptorchidism experienced urinary tract obstruction as a result of a kidney stone. No additional renal anomalies were reported in those who were imaged.

Skeletal involvement includes combinations of kypho/scoliosis (7 individuals), camptodactyly (4 individuals), lower-limb asymmetry (3), clinodactyly/contracture of fifth finger proximal interphalangeal joint (3), distal brachydactyly (7), multiple fractures related to osteopenia (3), overlapping toes (2), and craniosynostosis presenting as dolichocephaly, scaphocephaly or mild turricephaly (7 of 12 individuals evaluated).

Advanced bone age was identified in four of 20 individuals evaluated in early childhood [Duffney et al 2018, Burkardt et al 2019, Flex et al 2019]. Tall stature is not a common finding, in contrast to the authors' initial reports suggesting that HIST1H1E syndrome was an overgrowth-intellectual disability syndrome [Tatton-Brown et al 2017]. In a study of 30 individuals the mean postnatal height was 0.4 SD (range -1.8 SD to 8.3 SD) [Burkardt et al 2019].

Additional findings [Burkardt et al 2019, Flex et al 2019]:

- **Congenital cardiac anomalies** included atrial septal defect (11 individuals), ventricular septal defect (2), patent foramen ovale (1), patent ductus arteriosus (1), and persistent superior vena cava.
- **Hypothyroidism** was a frequent (and possibly under-reported) finding. Ages of testing of thyroid function ranged from infancy to late childhood.
- **Ectodermal abnormalities** included thin and/or brittle, slow growing hair (11 individuals), reduced body hair (3), thin or dysplastic nails (7).
- **Abnormal dentition** included: a range from small, widely spaced teeth to missing variable numbers of permanent teeth and small, fragile teeth; thin enamel, with erosions / crumbling teeth: and multiple dental caries.

Other

Hearing loss (both sensorineural and/or conductive) was reported in seven individuals, three of whom had recurrent otitis media.

Ophthalmologic abnormalities among those evaluated included strabismus/amblyopia (9 individuals), astigmatism (7), myopia (3), and hypermetropia (1).

Note: Given that this is an ultra-rare disorder, it is uncertain if clinical features reported in one or two individuals are true associations or incidental findings.

Gestational/Neonatal Course

While the majority of pregnancies were uneventful and delivery was at term, two had complications. In one, there was ventriculomegaly with macrocephaly on ultrasound examination at 32 weeks' gestation and decreased fetal movement and fetal heart rate decelerations at 38 weeks' gestation; intubation and ventilatory support were required at birth. In the other, delivery at 34 weeks' gestation was followed by a three-week NICU stay.

Two other term neonates required postnatal NICU stays: one for four days of ventilatory support using positive end expiratory pressure; the other for hypoglycemia / feeding difficulties and jaundice [Flex et al 2019].

Prognosis

There is no evidence currently that life expectancy is reduced in HIST1H1E syndrome. The oldest reported individual is age 49 years [Flex et al 2019]. However, as many adults with disabilities do not have ready access to genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

Data are currently insufficient to determine the penetrance of *H1-4* germline pathogenic variants

Nomenclature

HIST1H1E neurodevelopmental syndrome (HNDS) has been proposed as an alternative name for HIST1H1E syndrome.

Prevalence

HIST1H1E syndrome was only recently described; data to date are insufficient to estimate prevalence.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline heterozygous pathogenic variants in *H1-4* (formerly *HIST1H1E*).

Differential Diagnosis

All disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis of HIST1H1E syndrome. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

While it has previously been suggested that HIST1H1E syndrome belongs to the family of overgrowth-intellectual disability syndromes [Tatton-Brown et al 2014], recent data suggest that most children with HIST1H1E syndrome do not have tall stature or macrocephaly [Burkardt et al 2019].

Management

No clinical practice guidelines for HIST1H1E syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with HIST1H1E syndrome, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with HIST1H1E Syndrome

System/Concern	Evaluation	Comment
Development	Developmental assessment	To incl: • Motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Behavior	Neuropsychiatric eval	For persons age >12 mos: evaluate for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD.
Neurologic	Neurologic eval	• EEG if seizures are a concern • Consider brain MRI if there are focal neurologic findings.
Genitourinary	Examine males for cryptorchidism.	If present, referral to pediatric urologist.
Cardiovascular	Echocardiogram	To evaluate for structural cardiac anomalies
Endocrine	TSH & T4	To evaluate for hypothyroidism
Skeletal abnormalities	Assessment of head shape & for sutural ridging in infants	If abnormal, consider head CT w/3D reconstruction to assess for craniosynostosis.
	Physical exam to assess for evidence of scoliosis	Consider spine radiographs if scoliosis is evident on physical exam.
	Inquire about history of fractures.	Consider referral to orthopedic specialist to evaluate bone mineral density in those w/frequent or unexplained fracture(s).
Abnormal dentition	Dental eval to assess for caries, evidence of thin enamel, hypodontia	Panorex may be considered if hypodontia is suspected
Eyes	Ophthalmology eval	To assess for strabismus, refractive error

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To inform persons & their families re nature, MOI, & implications of HIST1H1E syndrome 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.	

3D = 3-dimensional; ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; MOI = mode of inheritance; TSH = thyroid-stimulating hormone

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Following initial evaluation, treatment is symptomatic.

Management by multidisciplinary specialists is recommended, including (but not limited to) developmental pediatrics / behavioral psychology, neurosurgery/neurology, urology, cardiology, endocrinology, ophthalmology, orthopedics, and dentistry.

Table 4. Treatment of Manifestations in Individuals with HIST1H1E Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Behavioral	Behavioral mgmt strategies & consideration of medication to treat ADHD	In consultation w/developmental pediatrician or psychiatrist
Seizures	Standardized treatment w/ASMs by experienced neurologist	Education of parents/caregivers [1]
Cryptorchidism in males	Standard treatment per urologist	
Congenital heart defects	Standard treatment per cardiologist	
Hypothyroidism	Thyroid hormone replacement per endocrinologist	
Craniosynostosis	Standard treatment, ideally through a craniofacial center	Treating physicians may incl neurosurgeons & plastic surgeons.
Scoliosis	Standard treatment per orthopedist	
Decreased bone mineral density	• Treatment of fractures by orthopedist w/expertise in disorders w/low bone density • Avoidance of activities that ↑ risk of fracture	
Abnormal dentition	By a pediatric dentist specializing in care of children w/ neurodevelopmental disorders &/or enamel hypoplasia	When possible
Hearing loss	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district; if conductive hearing loss, pressure-equalizing tube placement could be considered.
Strabismus / Refractive error	Standard treatment per ophthalmologist	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Consider involvement in adaptive sports or Special Olympics.

ADHD = attention-deficit/hyperactivity disorder; ASM = anti-seizure medication
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.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - 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.

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 HIST1H1E Syndrome

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior, as developmentally appropriate for age	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations (e.g., seizures, changes in tone).	
Genitourinary	Assessment of testicular location & for testicular lumps/masses in males w/ history of cryptorchidism	
Skeletal abnormalities	• Assessment of head shape in infants & young children • Physical examination for presence &/or progression of scoliosis • Enquire about signs &/or symptoms of bony fractures.	
Dental	Dental eval	Every 6 mos, starting at age ~2-3 yrs
Ears/Hearing	Assessment for frequent otitis media	At each visit
	Audiology eval	Annually until adulthood or as clinically indicated
Endocrine	Thyroid function studies to incl TSH & free T4	Annually

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Eyes	Ophthalmology eval	Annually or as clinically indicated
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit
	Reevaluation by a clinical geneticist for new developments &/or recommendations	Per clinical geneticist

TSH = thyroid-stimulating hormone

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

HIST1H1E syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- All probands reported to date with HIST1H1E syndrome whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo H1-4* (formerly *HIST1H1E*) pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant (i.e., a proband who appears to be the only affected family member).
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.
- Theoretically, if the parent is the individual in whom the *H1-4* pathogenic variant first occurred, the parent may have somatic (and germline) mosaicism for the variant and may be mildly/minimally affected.

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

- If a parent of the proband has the *H1-4* pathogenic variant, the risk to the sibs of inheriting the variant is 50%.
- If the *H1-4* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. To date, individuals with HIST1H1E syndrome have not been known to have children; however, many affected individuals are not yet of reproductive age.

Other family members. Given that all probands with HIST1H1E syndrome reported to date whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo H1-4* pathogenic variant, the risk to other family members is presumed to be low.

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 *H1-4* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo H1-4* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

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.

- **HIST1H1E Syndrome**
  Email: info@hist1h1e.org
  www.hist1h1e.org
- **Patient Insights Network Registry**
  Hist1H1E Syndrome (HNDS)

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. HIST1H1E Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
H1-4	6p22.2	Histone H1.4	H1-4	H1-4

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 HIST1H1E Syndrome (View All in OMIM)

142220	HISTONE GENE CLUSTER 1, H1 HISTONE FAMILY, MEMBER E; HIST1H1E
617537	RAHMAN SYNDROME; RMNS

Molecular Pathogenesis

H1-4 (formerly *HIST1H1E*), a single-exon gene, encodes the H1.4 linker histone which is part of the HIST1 histone cluster. Linker histones associate with the DNA between nucleosomes, help organize DNA as chromatin, and play a role in compacting DNA, in regulating gene expression, and in DNA replication, recombination, and repair. Each H1 histone isoform has a "tripartite" structure consisting of a highly conserved globular domain and two less conserved N-terminal and C-terminal tails.

Mechanism of disease causation. To date, all reported *H1-4* pathogenic variants are frameshift variants clustered in the C terminus. It is hypothesized that these protein-truncating variants escape nonsense-mediated RNA decay and that the resultant abnormal stable proteins (which have a reduced net positive charge) disrupt the normal binding between the positively charged H1.4 linker histone and negatively charged DNA [Tatton-Brown et al 2017]. The cells expressing these mutated proteins have been shown to have a reduced proliferation rate and competence, to rarely enter into the S phase of the cell cycle, and to undergo accelerated senescence [Flex et al 2019].

Moreover, methylome analysis in individuals with *H1-4* pathogenic variants demonstrated a specific "epi-signature" characterized by hypomethylation of specific regulatory regions of genes predominantly expressed in the brain – including genes encoding *N*-methyl-D-aspartate receptors (*GRIN1*, *GRIN2D*), G proteins (*GNG4*), adenylyl cyclases (*ADY8*), neuroligins (*NLGN2*), discs large associated proteins (*DLGAP1/2*), and receptor-type protein tyrosine phosphatase D (*PTPRD*) [Flex et al 2019, Ciolfi et al 2020]. Overall, these studies suggest that protein-truncating variants in *H1-4* result in dysregulation of epigenetic control of genes encoding proteins involved in synaptic transmission and neuronal function.

***H1-4*-specific laboratory technical considerations.** *H1-4* is a single-exon gene. Only frameshift variants in the C-terminal region have been associated with disease (Table 6).

Table 6. Notable *H1-4* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comments
NM_005321.2	c.360_361insA	p.Ala123GlyfsTer73	Most 5' disease-assoc variant
	c.406_407insT	p.Lys136IlefsTer60	
	c.407dupA	p.Lys137GlufsTer59	
	c.408dupG	p.Lys137GlufsTer59	
	c.414dupC	p.Lys139GlnfsTer57	
	c.416dupA	p.Lys140GlufsTer56	
	c.425delinsAG	p.Thr142LysfsTer54	
	c.425_431delinsAGGGGGTT	p.Thr142LysfsTer54	

Table 6. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comments
	c.430dupG	p.Ala144GlyfsTer52	Recurrent pathogenic variant
	c.431dupC	p.Ala145GlyfsTer51	
	c.433dup	p.Ala145GlyfsTer51	
	c.435dupC	p.Thr146HisfsTer50	
	c.436_458del23	p.Thr146AspfsTer42	
	c.437_438del	p.Pro147GlnfsTer48	
	c.447dupG	p.Ser150GlufsTer46	
	c.454_455insT	p.Lys152IlefsTer44	
	c.464dupC	p.Lys157GlufsTer39	Most 3' disease-assoc variant

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Cancer and Benign Tumors

H1-4 somatic variants have been associated with chronic lymphocytic leukemia as well as diffuse large B-cell lymphoma [Lohr et al 2012, Mareschal et al 2017, González-Rincón et al 2019] and myeloma [Walker et al 2015]. Unlike the germline variant spectrum of HIST1H1E syndrome, the somatic variant spectrum of associated cancers includes missense and in-frame variants (COSMIC database, accessed 6-29-2023).

Chapter Notes

Author Notes

Professor Kate Tatton-Brown is a clinical geneticist. She also runs a research study to investigate the genetic causes and clinical presentations of conditions associated with a learning disability and increased growth. KTB is funded by the Baily Thomas Charitable fund and the St George's Charity.

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Revision History

- 15 December 2022 (sw) Revision: epigenetic signature analysis (Establishing the Diagnosis, Option 2)
- 3 December 2020 (bp) Review posted live
- 19 March 2020 (ktb) Original submission

References

Literature Cited

Burkardt DD, Zachariou A, Loveday C, Allen CL, Amor DJ, Ardissone A, Banka S, Bourgois A, Coubes C, Cytrynbaum C, Faivre L, Marion G, Horton R, Kotzot D, Lay-Son G, Lees M, Low K, Luk HM, Mark P, McConkie-Rosell A, McDonald M, Pappas J, Phillipe C, Shears D, Skotko B, Stewart F, Stewart H, Temple IK, Mau-Them FT, Verdugo RA, Weksberg R, Zarate YA, Graham JM, Tatton-Brown K. HIST1H1E heterozygous protein-truncating variants cause a recognizable syndrome with intellectual disability and distinctive facial gestalt: A study to clarify the HIST1H1E syndrome phenotype in 30 individuals. Am J Med Genet A. 2019;179:2049–55. PubMed PMID: 31400068.

Ciolfi A, Aref-Eshghi E, Pizzi S, Pedace L, Miele E, Kerkhof J, Flex E, Martinelli S, Radio FC, Ruivenkamp CAL, Santen GWE, Bijlsma E, Barge-Schaapveld D, Ounap K, Siu VM, Kooy RF, Dallapiccola B, Sadikovic B, Tartaglia M. Frameshift mutations at the C-terminus of HIST1H1E result in a specific DNA hypomethylation signature. Clin Epigenetics. 2020;12:7. PubMed PMID: 31910894.

Duffney LJ, Valdez P, Tremblay MW, Cao X, Montgomery S, McConkie-Rosell A, Jiang YH. Epigenetics and autism spectrum disorder: A report of an autism case with mutation in H1 linker histone HIST1H1E and literature review. Am J Med Genet B Neuropsychiatr Genet. 2018;177:426–33. PubMed PMID: 29704315.

Flex E, Martinelli S, Van Dijck A, Ciolfi A, Cecchetti S, Coluzzi E, Pannone L, Andreoli C, Radio FC, Pizzi S, Carpentieri G, Bruselles A, Catanzaro G, Pedace L, Miele E, Carcarino E, Ge X, Chijiwa C, Lewis MES, Meuwissen M, Kenis S, Van der Aa N, Larson A, Brown K, Wasserstein MP, Skotko BG, Begtrup A, Person R, Karayiorgou M, Roos JL, Van Gassen KL, Koopmans M, Bijlsma EK, Santen GWE, Barge-Schaapveld DQCM, Ruivenkamp CAL, Hoffer MJV, Lalani SR, Streff H, Craigen WJ, Graham BH, van den Elzen APM, Kamphuis DJ, Õunap K, Reinson K, Pajusalu S, Wojcik MH, Viberti C, Di Gaetano C, Bertini E, Petrucci S, De Luca A, Rota R, Ferretti E, Matullo G, Dallapiccola B, Sgura A, Walkiewicz M, Kooy RF, Tartaglia M. Aberrant function of the C-terminal tail of HIST1H1E accelerates cellular senescence and causes premature aging. Am J Hum Genet. 2019;105:493–508. PubMed PMID: 31447100.

González-Rincón J, Méndez M, Gómez S, García JF, Martín P, Bellas C, Pedrosa L, Rodríguez-Pinilla SM, Camacho FI, Quero C, Pérez-Callejo D, Rueda A, Llanos M, Gómez-Codina J, Piris MA, Montes-Moreno S, Bárcena C, Rodríguez-Abreu D, Menárguez J, de la Cruz-Merino L, Monsalvo S, Parejo C, Royuela A, Kwee I, Cascione L, Arribas A, Bertoni F, Mollejo M, Provencio M, Sánchez-Beato M. Unraveling transformation of follicular lymphoma to diffuse large B-cell lymphoma. PLoS One. 2019;14:e0212813. PubMed PMID: 30802265.

Helsmoortel C, Vandeweyer G, Ordoukhanian P, Van Nieuwerburgh Fm Van der Aa N, Kooy RF. Challenges and opportunities in the investigation of unexplained intellectual disability using family-based whole-exome sequencing. Clin Genet. 2015;88:140–8. PubMed PMID: 25081361.

Levy MA, McConkey H, Kerkhof J, Barat-Houari M, Bargiacchi S, Biamino E, Bralo MP, Cappuccio G, Ciolfi A, Clarke A, DuPont BR, Elting MW, Faivre L, Fee T, Fletcher RS, Cherik F, Foroutan A, Friez MJ, Gervasini C, Haghshenas S, Hilton BA, Jenkins Z, Kaur S, Lewis S, Louie RJ, Maitz S, Milani D, Morgan AT, Oegema R, Østergaard E, Pallares NR, Piccione M, Pizzi S, Plomp AS, Poulton C, Reilly J, Relator R, Rius R, Robertson S, Rooney K, Rousseau J, Santen GWE, Santos-Simarro F, Schijns J, Squeo GM, St John M, Thauvin-Robinet C, Traficante G, van der Sluijs PJ, Vergano SA, Vos N, Walden KK, Azmanov D, Balci T, Banka S, Gecz J, Henneman P, Lee JA, Mannens MMAM, Roscioli T, Siu V, Amor DJ, Baynam G, Bend EG, Boycott K, Brunetti-Pierri N, Campeau PM, Christodoulou J, Dyment D, Esber N, Fahrner JA, Fleming MD, Genevieve D, Kerrnohan KD, McNeill A, Menke LA, Merla G, Prontera P, Rockman-Greenberg C, Schwartz C, Skinner SA, Stevenson RE, Vitobello A, Tartaglia M, Alders M, Tedder ML, Sadikovic B. Novel diagnostic DNA

methylation episignatures expand and refine the epigenetic landscapes of Mendelian disorders. HGG Adv. 2021;3:100075. PubMed PMID: 35047860.

Lohr JG, Stojanov P, Lawrence MS, Auclair D, Chapuy B, Sougnez C, Cruz-Gordillo P, Knoechel B, Asmann YW, Slager SL, Novak AJ, Dogan A, Ansell SM, Link BK, Zou L, Gould J, Saksena G, Stransky N, Rangel-Escareño C, Fernandez-Lopez JC, Hidalgo-Miranda A, Melendez-Zajgla J, Hernández-Lemus E, Schwarz-Cruz y Celis A, Imaz-Rosshandler I, Ojesina AI, Jung J, Pedamallu CS, Lander ES, Habermann TM, Cerhan JR, Shipp MA, Getz G, Golub TR. Discovery and prioritization of somatic mutations in diffuse large B-cell lymphoma (DLBCL) by whole-exome sequencing. Proc Natl Acad Sci U S A. 2012;109:3879–84. PubMed PMID: 22343534.

Mareschal S, Pham-Ledard A, Viailly PJ, Dubois S, Bertrand P, Maingonnat C, Fontanilles M, Bohers E, Ruminy P, Tournier I, Courville P, Lenormand B, Duval AB, Andrieu E, Verneuil L, Vergier B, Tilly H, Joly P, Frebourg T, Beylot-Barry M, Merlio JP, Jardin F. Identification of somatic mutations in primary cutaneous diffuse large B-cell lymphoma, leg type by massive parallel sequencing. J Invest Dermatol. 2017;137:1984–94. PubMed PMID: 28479318.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Takenouchi T, Uehara T, Kosaki K, Mizuno S. Growth pattern of Rahman syndrome. Am J Med Genet A. 2018;176:712–4. PubMed PMID: 29383847.

Tatton-Brown K, Loveday C, Yost S, Clarke M, Ramsay E, Zachariou A, Elliott A, Wylie H, Ardissone A, Rittinger O, Stewart F, Temple IK, Cole T; Childhood Overgrowth Collaboration. Mahamdallie S, Seal S, Ruark E, Rahman N. Mutations in epigenetic regulation genes are a major cause of overgrowth with intellectual disability. Am J Hum Genet. 2017;100:725–36. PubMed PMID: 28475857.

Tatton-Brown K, Seal S, Ruark E, Harmer J, Ramsay E, Del Vecchio Duarte S, Zachariou A, Hanks S, O'Brien E, Aksglaede L, Baralle D, Dabir T, Gener B, Goudie D, Homfray T, Kumar A, Pilz DT, Selicorni A, Temple IK, Van Maldergem L, Yachelevich N, van Montfort R, Rahman N, et al. Mutations in the DNA methyltransferase gene DNMT3A cause an overgrowth syndrome with intellectual disability. Nat Genet. 2014;46:385–8. PubMed PMID: 24614070.

Walker BA, Boyle EM, Wardell CP, Murison A, Begum DB, Dahir NM, Proszek PZ, Johnson DC, Kaiser MF, Melchor L, Aronson LI, Scales M, Pawlyn C, Mirabella F, Jones JR, Brioli A, Mikulasova A, Cairns DA, Gregory WM, Quartilho A, Drayson MT, Russell N, Cook G, Jackson GH, Leleu X, Davies FE, Morgan GJ. Mutational spectrum, copy number changes, and outcome: results of a sequencing study of patients with newly diagnosed myeloma. J Clin Oncol. 2015;33:3911–20. PubMed PMID: 26282654.

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