Received: 7 June 2021 | Revised: 20 September 2021 | Accepted: 21 September 2021

DOI: 10.1002/mgg3.1825

Molecular Genetics & Genomic Medicine Open Access WILEY

ORIGINAL ARTICLE

Expanding the mutational spectrum of Rahman syndrome: A rare disorder with severe intellectual disability and particular facial features in two Chinese patients

Jianbo Zhao[1] | **Guizhen Lyu**[2] | **Changhong Ding**[1] | **Xiaohui Wang**[1] | **Jiuwei Li**[1] | **Weihua Zhang**[1] | **Xinying Yang**[1] | **Victor Wei Zhang**[2]

[1]Department of Neurology, Beijing Children's Hospital, National Center for Children's Health, Capital Medical University, Beijing, China

[2]AmCare Genomics Laboratory, Guangzhou, China

Correspondence
Jianbo Zhao, Department of Neurology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, No.56, Nanlishi Road, Xicheng District, Beijing 100045, China.
Email: jianbo04429@126.com

Abstract

Background: The study aimed to investigate the clinical and genetic features of Rahman syndrome caused by *HIST1H1E* gene mutations.

Methods: We retrospectively analyzed the clinical information and genetic testing results of a Rahman syndrome family in an outpatient clinic in August 2020 and summarized the clinical characteristics of the *HIST1H1E* gene mutations in conjunction with peer-reviewed reports.

Results: A 4-year-old boy was diagnosed with severe developmental delay and with specific features (large head, full cheeks, high hairline, low-set ear, sparse eyebrows, and short neck) similar to his mother (mild intellectual disability, high hairline, reduced hair, ptosis, sagging skin, and hyperkeratosis) and premature aging. Trio whole exome sequencing (WES) revealed a novel maternal c.368dup (p.G124Rfs*72) heterozygous mutation in the *HIST1H1E* gene. There have been only a few reported cases with mainly de novo mutations. Only six peer-reviewed articles in English and one in Chinese have been published regarding this syndrome. From 48 children with Rahman syndrome, 21 were males and 27 were females encompassing 25 mutations in the *HIST1H1E* gene. All mutations located in C-terminal tail were frameshift mutations leading to premature protein termination.

Conclusion: Rahman syndrome, caused by the *HIST1H1E* gene mutation, is a rare autosomal dominant disorder in which the patient has an unusual facial appearance with high hairline and full cheeks, and clinical manifestations of mild to severe intellectual disability, motor delay and speech delay. Genetic testing may assist in the diagnosis of these patients. This diagnosis will permit early speech rehabilitation to improve their quality of life.

KEYWORDS

frameshift mutation, *HIST1H1E* gene, histone H1, intellectual disability, Rahman syndrome

1 | INTRODUCTION

HIST1H1E is a single exon gene encoding histone H1-4, a component of the nucleosome-linked histone H1, which is involved in the dynamic regulation of chromosome structure and epigenetic modification of the genome. Each H1 histone isoform has a "tripartite" structure consisting of a highly conserved globular domain and two less conserved N-termini and C-termini tails (Flex et al., 2019; Hergeth & Schneider, 2015). Histones mediate the dynamic packaging of nuclear DNA in chromatin, a process that is precisely controlled in vivo to ensure efficient genome compactness and proper chromosome segregation during cell division, and to accomplish DNA replication, transcription, and repair. Due to the important structural and regulatory roles of histones, the dysfunctional or abnormal conditions of histones may have a serious impact on a wide range of cellular processes that may affect development or promote cellular transformation.

HIST1H1E (MIM *142220) gene-related disorder is Rahman syndrome (RMNS, MIM #617537)/ HIST1H1E neurodevelopmental syndrome (HNDS), which is autosomal dominant. HIST1H1E syndrome is named as a combination of abbreviations to facilitate identification of the phenotype: H for hypotonia, I for intellectual disability with behavioral problems, S for skeletal, T for testicular (undescended) and thyroid, H for cardiac abnormalities, and E for ectodermal problems (including thinning hair, thin nails, and abnormal dentition) (Burkardt et al., 2019). The main clinical manifestations are mild to severe mental retardation and peculiar facial features. Other possible symptoms include skeletal abnormalities, visual disturbances, dental abnormalities, and skin nevi. Fewer cases have been reported nationally and internationally, with de novo variants predominating (Tatton-Brown et al., 2017).

All reported *HIST1H1E* pathogenic mutations to date are frameshift mutations clustered at the C-terminus, resulting in protein length changes and net charges that disrupt normal binding between positively charged H1-4 junction histones and negatively charged DNA, affecting human epigenetic regulatory processes (Ciolfi et al., 2020; Flex et al., 2019; Tatton-Brown et al., 2017). At present, there are few reports related to RMNS, with only one Chinese case, four English studies, and two case reports of 46 patients. Herein, we report clinical data and genetic test results of one child with RMNS and review the relevant literature to summarize the clinical phenotype, genetic features, and key points for diagnosis and treatment.

2 | SUBJECTS AND METHODS

2.1 | Subjects and clinical information

At the age of 52 months, the child was admitted to Beijing Children's Hospital because of his speech delay and developmental delay, intellectual disability, and the fact that his parents had plans to have more children. The child, P1G1, male, Han nationality, was full term, head circumference was not measured, length of 54 cm (+2 SD), and weighed 4.75 kg (+3 SD) at birth. At the time of presentation (4 years, 19 August 2020), his head circumference was 57 cm (+5 SD), body length was 105 cm (normal), and his weight was 21.67 kg (+1 SD). Birth history and feeding history was unremarkable. The child began to walk independently at 2 years of age. He spoke his first words at the age of 3 years, but only in simple, nonverbal sentences to date. The child's parents claimed that they are not consanguineous and there is no family history of hereditary diseases. The vital signs upon physical examination were normal. He had distinctive facial features with full cheeks, broad forehead, high hairline, slightly wide-spaced eyes, narrow eyelid fissures, low flat nasal bridge, upturned broad nose, slightly low-set ear, sparse eyebrows, short neck, and uneven teeth (Figure 1a). His mother had similar peculiar facial features with a broad prominent forehead, high hairline, shallow eyebrows, narrow eyelid fissures, deep-set eyes, uneven teeth, and mental retardation with premature aging (Figure 1b). His parents claimed that their child had no visual, gonadal, cutaneous, or skeletal problems and no bone fragments.

He was diagnosed with severe intellectual disability with an intellectual developmental quotient (DQ) score of 35, age-appropriate intelligence of 18.2 months, age-appropriate motor skills of 18.9 months, age-appropriate language skills of 19 months, and age-appropriate social adjustment skills of 18.67 months. To further exclude metabolic disorders, blood amino acids, blood lipid acylcarnitine profile, and urine organic acid analyses were performed. The results suggest elevated C8/C3 in blood, elevated ketone bodies in urine, and slightly elevated bicarboxylic acid. The results from these tests were unremarkable. In addition, magnetic resonance imaging (MRI) showed ventricular enlargement and Chiari malformation (Figure 1c).

2.2 | Whole exome sequencing

To further clarify the diagnosis, 5 ml of peripheral blood was drawn from the child and his parents for whole exome germline gene sequencing after the parents signed

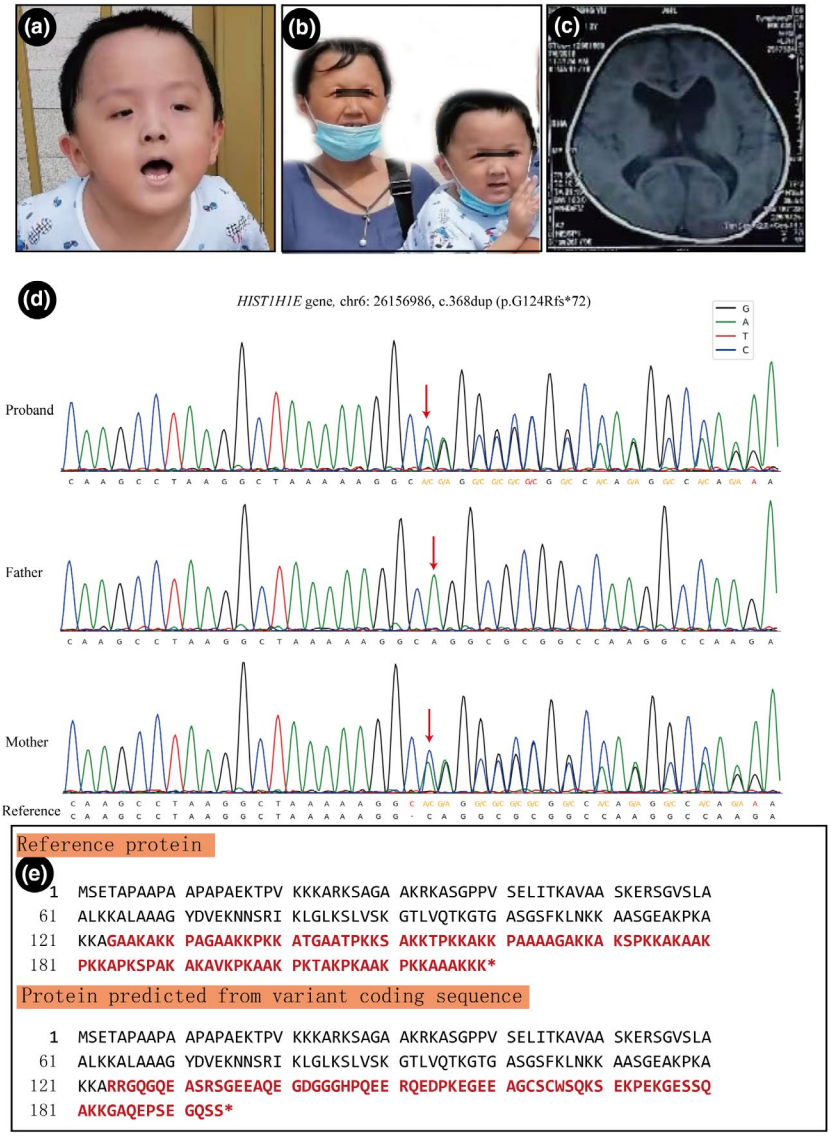

FIGURE 1 The *HIST1H1E* gene mutation and peculiar facial features. (a) Facial photographs. Note the full cheeks, broad forehead, high hairline, slightly wide-spaced eyes, narrow eyelid fissures, low flat nasal bridge, upturned broad nose, slightly low-set ear, sparse eyebrows, short neck, and uneven teeth. (b) Facial features of the proband and his parents. (c) Brain magnetic resonance imaging (MRI) results obtained for the patient in this case and revealed ventricular enlargement and Chiari malformation. (d) Sanger sequencing confirmed the *HIST1H1E* mutation is heterozygous maternal. (e) The amino acid changes of *HIST1H1E* gene mutation, c.368dup (p.G124Rfs*72), were predicted online (https://www.mutalyzer.nl/). Normal amino acids of HIST1H1E (TOP): The sequence has A C-terminal (red), which is mainly composed of lysine, alanine, and proline residues. Predicted amino acid change of HIST1H1E (bottom): The protein sequence is expected to change after c.368 has undergone a nucleotide "A C" repeat, significantly reducing the number of lysine, alanine, and proline residues (underlined) found at the C-terminal (red)

a written informed consent form. Genomic DNA was extracted from peripheral blood using the HiPure Blood DNA Maxi Kit (Magen), and was sequenced after using the Q800R Sonicator (Qsonica) to fragment the genomic DNA to 300–500 bp inserts. The xGen® Exome Research Panel v1.0 (Integrated DNA Technologies) was used for in-solution hybridization to enrich for 19,396 genes of the human exome. Enriched DNA samples were indexed and sequenced on an Illumina NextSeq 500 sequencer (Illumina) with a 150 bp single-end read length. Image processing was performed using an Illumina software and the raw data were presented as a FASTQ file. The data were filtered by quality control analysis to produce "clean data" (Q20).

Sequences were compared to the human reference genome (GRCh37/hg19, http://genome.ucsc.edu/) using the NextGENe software (SoftGenetics) for true and false variants identification. Single nucleotide variants (SNVs/indels) were called and annotated by filtering high-frequency variants in population frequency databases

(dbSNP, http://www.ncbi.nlm.nih.gov/snp; ExAC, https://ncbiinsights.ncbi.nlm.nih.gov/tag/exac/; and gnomAD, https://gnomad.broadinstitute.org/), and literature databases (OMIM, https://www.omim.org/; HGMD, ClinVar, https://www.ncbi.nlm.nih.gov/clinvar/; and MasterMind, https://mastermind.genomenon.com/). Multiple software (SIFT, http://sift.jcvi.org; Polyphen2, http://genetics.bwh.harvard.edu/pph2; MutationTaster http://www.mutationtaster.org; and AlamutVisual, https://www.interactive-biosoftware.com/alamut-visual/) predicted that the mutation may cause harmful effects on gene products, including conservative prediction, evolutionary predictions, and splicing site effects. An in-house bioinformatics pipeline based on read counts and Z-scores (AmCare Genomics Lab) was used to detect copy number variations (CNVs; Qi et al., 2020). The pathogenicity of CNVs was assessed utilizing various databases such as DGV (http://dgv.tcag.ca/dgv/app/home), DECIPHER (https://decipher.sanger.ac.uk/), and OMIM and published literature (Qi et al., 2020). SNVs and CNVs variants were classified according to the American College of Medical Genetics (ACMG) guidelines (Richards et al., 2015). Sanger sequencing was used to verify the potential mutation in the child and his parents.

3 | RESULT

3.1 | Whole exome sequencing and mutation annotation

The whole exome sequencing trio analysis was performed on the proband, father, and mother simultaneously. The gene panel included 19,293 related genes with 204,866 coding regions containing a total of 38,957,069 bases, with an average coverage depth of 146 ± 206X, 99.9% regions with >10X coverage depth, and 99.7% regions with >20X coverage depth. Validation by WES and Sanger sequencing confirmed that the proband had a heterozygous frameshift mutation, c.368dup (p.G124Rfs*72), in the *HIST1H1E* (NM_005321, GRCh37/hg19) gene and that this mutation was inherited from his mother (Figure 1d). Frameshift mutation, clear evidence that LOF of this gene is associated with disease (HI score = 3), and protein truncation >10%, since the gene has only one exon, the mutation is not considered in the case of last exon degradation (Figure 1e, PVS1_strong). To date, this novel mutation has not been reported in relevant clinical cases and has not been reported in population databases (PM2_supporting). The proband and his mother had clinical manifestations of intellectual disability and peculiar facial features that were highly consistent with a certain monogenic genetic disorder (PP4). In summary, this variant is classified as "likely pathogenic" according to the ACMG guidelines based on clinical information and pedigree analysis (Richards et al., 2015; Riggs et al., 2020).

3.2 | Patient management

The patient was admitted in August 2020 and consulted the doctor online in October 2020. As the child had speech delay and severe intellectual disability, only advice was given to speech rehabilitation, which was relatively short-lived and not particularly effective. Furthermore, we reminded his parents to pay attention to the child's ophthalmologic abnormalities, hearing, skeletal abnormalities, abnormal echocardiogram, behavior, and timely symptomatic treatment. In addition, this family was given reproductive guidance, prenatal diagnosis, and preimplantation genetic diagnosis was required for further pregnancy.

4 | DISCUSSION

In this case, a male child aged 4 years and 4 months presented to the hospital with speech delay and intellectual disability. We ruled out metabolic disorders through laboratory tests and MRI suggesting ventricular enlargement and Chiari malformation (Figure 1c). However, the exact etiology was not determined based on these findings alone. In this study, using trio WES and Sanger sequencing, we identified a novel heterozygous maternal *HIST1H1E* mutation, c.368dup (p.G124Rfs*72), in a 4-year-old boy with peculiar facial features (Figure 1). Due to concerns of the relatives concerned, the corresponding mutation was not detected to assess the source of the mutation, disease association, and genetic risk. Of note, in our retrospective cohort study, 97.2% (35/36) patients were reported with a de novo mutation (Table 1). All 48 patients were described as having intellectual disability, but only in 40 patients their degree of cognition and motor development was determined. From the 40 patients, 12.5% (5/40) patients were reported with severe intellectual disability, 65% (26/40) patients were reported with moderate intellectual disability, 17.5% (7/40) patients were reported with mild intellectual disability, and 5% (2/40) patients were reported with a normal intellectual disability (Table 1). Of note, many patients reported a particular facial appearance: high hairline and full cheeks, 100% (48/48). In addition, teeth, hearing, skin, hypotonia, cryptorchidism, sleep disturbances, and behavioral issues (including anxiety and autism) were common (Table 1).

The hot spot mutation region of *HIST1H1E* gene was located at the C-terminal tail (NO. 108–219 amino acids, Table

TABLE 1 Clinical and genetic findings in patients with *HIST1H1E* mutations

Patient ID	Sex	Ethic origin	Years	Intellectual disability	Facial appearance	Additional clinical features	Inheritance and *HIST1H1E* mutations	Publications
Patient #1	F	Japanese, Asian	3	Severe	Wide nasal bridge; prominent cheek bones; telecanthus; short palpebral fissures; high hairline; and long philtrum	Speech delay; strabismus; a high-arched palate; wide uvula; strabismus; epicanthal folds; simple auricles; auditory hypersensitivity; high-pitched voice; skin with hyperkeratosis; and multiple lentigines	De novo, c.433dup, (p.Ala145Glyfs*51)	Takenouchi et al. (2018)
COG0405	F	Caucasian	13	Mild	Full cheeks; had a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Head over growth; hypotonia; strabismus; advanced bone age; mild ventricular enlargement; severe kyphoscoliosis	De novo, c.430dupG, (p.Ala144Glyfs*52)	Tatton-Brown et al. (2017)
COG0412	M	Caucasian	15.5	Moderate	Full cheeks and had a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures, hypertelorism; premature aging	Head + height over growth; hypotonia; cryptorchidism; multiple nevi; redundant skin on palm of hands; major dental problems with crumbling teeth; flaky nails; anxiety disorder refractory to medical treatment; developed phobias	De novo, c.441dupC, (p.Lys148Glnfs*48)	Tatton-Brown et al. (2017)
COG1832	M	Caucasian	8.5	Severe	Full cheeks; high hairline; and telecanthus	Head over growth; speech delay; left amblyopia and astigmatism; constipation; a slender corpus callosum; unusual ventricular outline; very controlling; wants to be the center of attention; four teeth at the back with no enamel; baby teeth were peg shaped and adult teeth are serrated; talipes; delayed visual maturation; astigmatism; amblyopia; BrMRI- slender corpus callosum; abnormal ventricular outline	De novo, c.430dupG, (p.Ala144Glyfs*52)	Tatton-Brown et al. (2017)
COG1739	F	unknown	1.9	Moderate	Full cheeks; high hairline; telecanthus	Head over growth; hypoglycemia; increased muscle; camptodactyly	De novo, c.436_458del23, (p.Thr146Aspfs*42)	Tatton-Brown et al. (2017)

(Continues)

TABLE 1 (Continued)

Patient ID	Sex	Ethic origin	Years	Intellectual disability	Facial appearance	Additional clinical features	Inheritance and *HIST1H1E* mutations	Publications
COG0552	F	unknown	4	Unspecified	Full cheeks; high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures; hypertelorism; premature aging	Head over growth	Unknown, c.441dupC, (p.Lys148Glnfs*48)	Tatton-Brown et al. (2017)
Patient #2	M	American	10	Moderate	Downward-slanting palpebral fissures; hypertelorism; light eyebrows; micro retrognathia; wide philtrum	Motor delay; speech delay; single childhood seizure; strabismus; astigmatism; bilateral fifth finger clinodactyly; inverted nipples; pes planus; autism; restricted and repetitive behaviors or interests; sleep disturbances; arachnoid cyst and mild hydrocephalus	De novo, c.435dupC, (p.Thr146Hisfs*50)	Duffney et al (2018)
Patient 1	M	White race	15.2	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Autistic spectrum disorder; Crumbling dentition with missing adult teeth; hypothyroidism; small anterior pituitary; psoriasis; BrMRI- small pituitary	De novo, c.360_361insA, (p.Ala123Glyfs*73)	Burkardt et al. (2019)
Patient 2	F	White race	nk	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Hypotonia; ASD; craniosynostosis; generalized microdontia; class II malocclusion; BrMRI- possible Chiari malformation	De novo, c.406_407insT, (p.Lys136Ilefs*60)	Burkardt et al. (2019)
Patient 3	F	White race	2.3	Mild	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Kyphoscoliosis; small teeth; seizures	De novo, c.407dupA, (p.Lys137Glufs*59)	Burkardt et al. (2019)
Patient 4	M	White race	19	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Nervous personality; camptodactyly; weak teeth that need painting every year	De novo, c.416dupA, (p.Lys140Glufs*56)	Burkardt et al. (2019)

TABLE 1 (Continued)

Patient ID	Sex	Ethic origin	Years	Intellectual disability	Facial appearance	Additional clinical features	Inheritance and *HIST1H1E* mutations	Publications
Patient 5	M	White race	30	Moderate	High hairline; prominent forehead; alopecia totalis (sparse); low set ear; small, poorly enameled teeth; sparse eyelashes since age 10y; delayed hair growth as child; no eyebrows until about age 4; downward slant palpebral fissures; deep set eyes; ptosis	Speech delay; motor delay; hypotonia; strabismus; hearing loss; head over growth; febrile seizures; myopia; cryptorchidism; small; poorly enameled teeth; distal brachydactyly; alopecia totalis; fetal finger pads	De novo, c.425_431del7ins8, (p.Thr142Lysfs*54)	Burkardt et al. (2019)
Patient 8	M	White race	1.9	Severe	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Anxiety; needs routine; hand flapping; repetitive behaviors; hypotonia; VSD; PDA; hypothyroidism; chronic lung disease requiring oxygen; BrMRI - choroid plexus cyst	De novo, c.430dupG, (p.Ala144Glyfs*52)	Burkardt et al. (2019)
Patient 9	F	White race	7	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Anxiety; autistic spectrum disorder traits; hypotonia; hypothyroidism; SNHL	De novo, c.430dupG, (p.Ala144Glyfs*52)	Burkardt et al. (2019)
Patient 10	F	White race	2	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Anxiety; autistic spectrum disorder traits; hypotonia; ASD; preference to using left side over right; strabismus; slow-growing hair; BrMRI- slender corpus callosum and relative paucity of white matter	De novo, c.430dupG, (p.Ala144Glyfs*52)	Burkardt et al. (2019)
Patient 11	F	White race	1.2	Unspecified	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	ASD; glasses for intermittent alternating esotropia; orthotic sure step braces; 1 febrile seizure	De novo, c.430dupG, (p.Ala144Glyfs*52)	Burkardt et al. (2019)
Patient 12	M	White race	10.5	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Hand flaps; obsessions; hypotonia; multiple fractures; crumbling teeth; thin hair; SNHL; cortical visual impairment; seizures	Unknown, c.430dupG, (p.Ala144Glyfs*52)	Burkardt et al. (2019)

(Continues)

TABLE 1 (Continued)

Patient ID	Sex	Ethic origin	Years	Intellectual disability	Facial appearance	Additional clinical features	Inheritance and *HIST1H1E* mutations	Publications
Patient 13	F	White race	18	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Autistic spectrum disorder; Hypotonia; ASD; contractures right hip; camptodactyly; kyphoscoliosis; advanced dental age; small gappy teeth; hypothyroidism; virtually no body hair; thin nails; BrMRI- Chiari 1 malformation	De novo, c.430dupG, (p.Ala144Glyfs*52)	Burkardt et al. (2019)
Patient 14	M	White race	0.8	Unspecified	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Hypotonia; excessive perspiration; seizures	Unknown, c.430dupG, (p.Ala144Glyfs*52)	Burkardt et al. (2019)
Patient 15	M	White race	7.7	Moderate	Full cheek; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Anxiety; aggression; hypotonia; lower limb asymmetry; progressive pes cavus and cavovarus	De novo, c.430dupG, (p.Ala144Glyfs*52)	Burkardt et al. (2019)
Patient 16	F	White race	1.4	Unspecified	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Anxiety; hypotonia; VSD; philum terminalis lipoma; BrMRI- corpus callosum abnormality	Unknown, c.430dupG, (p.Ala144Glyfs*52)	Burkardt et al. (2019)
Patient 17	F	White race	5.1	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Hypotonia; persistent upper vena cava; BrMRI- asymmetric ventriculomegaly	unknown, c.430dupG, (p.Ala144Glyfs*52)	Burkardt et al. (2019)
Patient 18	F	White race	0.8	Unspecified	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Hypotonia	De novo, c.431dupC, (p.Ala145Glyfs*51)	Burkardt et al. (2019)

TABLE 1 (Continued)

Patient ID	Sex	Ethic origin	Years	Intellectual disability	Facial appearance	Additional clinical features	Inheritance and *HIST1H1E* mutations	Publications
Patient 19	M	White race	0.9	Unspecified	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	ASD; scoliosis; small teeth; hydrocephalus; BrMRI- severe hydrocephalus; slender corpus callosum	De novo, c.433dupG, (p.Ala145Glyfs*51)	Burkardt et al. (2019)
Patient 20	M	White race	9	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	ADHD; hypotonia; ASD; small temporary teeth; bad enamel; permanent teeth enamel is better but lower incisors are serrated; hypothyroidism; chronic constipation; GOR; BrMRI- small post fossa; partial decent of cerebellar tonsils	Unknown, c.435dupC, (p.Thr146Hisfs*50)	Burkardt et al. (2019)
Patient 21	F	White race	3	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Autistic spectrum disorder; hypotonia	De novo, c.435dupC, (p.Thr146Hisfs*50)	Burkardt et al. (2019)
Patient 23	M	White race	3.4	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Hypotonia; ASD; widely spaced teeth; BrMRI- ventriculomegaly	De novo, c.436_458del23, (p.Thr146Aspfs*42)	Burkardt et al. (2019)
Patient 24	F	White race	6.1	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Poor attention; frustration and anger; hypotonia; mulitple PFOs; lower limb asymmetry; many dental caries; astigmatism; divergent strabismus; myopia; high pain threshold; palmoplantar pustulosis; tracheomalacia; fine hair; thin nails; seizures; BrMRI- slender corpus callosum and prominent ventricles; small pons	De novo, c.437_438del, (p.Pro147Glnfs*48)	Burkardt et al. (2019)

(Continues)

TABLE 1 (Continued)

Patient ID	Sex	Ethic origin	Years	Intellectual disability	Facial appearance	Additional clinical features	Inheritance and *HIST1H1E* mutations	Publications
Patient 27	F	White race	nk	Severe	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Head bangs; cataracts; diabetes mellitus	Unknown, c.441dupC, (p.Lys148Glnfs*48)	Burkardt et al. (2019)
Patient 28	F	White race	12	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Hypotonia; ASD; multiple caries; hair and nails grow very slowly; strabismus; BrMRI- hypoplastic corpus callosum; delayed myelination;	De novo, c.441dupC, (p.Lys148Glnfs*48)	Burkardt et al. (2019)
Patient 29	F	White race	1.5	Unspecified	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	ASD; astigmatism; cutis aplasia; chronic discoloration of distal extremities exacerbated by cold temperature	De novo, c.444_466del23, (p.Lys149Glufs*39)	Burkardt et al. (2019)
Patient 30	M	White race	3.6	Moderate	Full cheeks; a high hairline; bitemporal narrowing; deep set eyes; downslanting palpebral fissures and hypertelorism; premature aging	Unknown	De novo, c.454_455insT, (p.Lys152Ilefs*44)	Burkardt et al. (2019)
S1	M	Caucasian	49	Moderate	High hairline; prominent forehead; sparse hair; hypotrichosis; bitemporal narrowing; ptosis; ear low set	Speech delay; motor delay; hearing loss; abnormal behavior; psychotic episodes; multiple nevi; skin hyperpigmentation; cutis laxa; abnormal behavior; psychotic episodes	De novo, c.441dupC, (p.Lys148Glnfs*48)	Flex et al. (2019)
S2	F	Caucasian	4.5	Mild	High hairline; prominent forehead; frontal upsweep; thin; sparse hair; downward slant palpebral fissures; small/pointed chin; dolichocephaly; early loss of primary teeth/delayed permanent teeth	Speech delay; motor delay; head + height + weight over growth; childhood focal seizures; early loss of primary teeth/delayed permanent teeth; sleep problems; mild ventricular enlargement; autism spectrum disorder	De novo, c.464dupC, (p.Lys157Glufs*39)	Flex et al. (2019)

TABLE 1 (Continued)

Patient ID	Sex	Ethic origin	Years	Intellectual disability	Facial appearance	Additional clinical features	Inheritance and *HIST1H1E* mutations	Publications
S4	F	Caucasian	1.2	Normal	High hairline; prominent forehead; sparse hair; small/pointed chin; pointed teeth	Head + weight over growth; motor seems late but still within range; hypotonia; small 'atrial septum defect; pointed teeth	De novo, c.414dupC, (p Lys139Glnfs*57)	Flex et al. (2019
S5	F	Caucasian	12	Mild	High hairline; prominent forehead; thin hair; Widow's peak (like father); downward slant palpebral fissures; hypertelorism; ear low set small and pointed teeth; some permanent teeth missing; short roots	Speech delay; motor delay; head over growth; hypermetropia; astigmatism and strabismus; mild cutis marmorata; dry skin; multiple lentigines solaris in face; sleep problems; diminished eye contact in childhood and socialization anomalies	De novo, c.441dupC, (p.Lys148Glnfs*48)	Flex et al. (2019)
S6	F	African American	3	Moderate	High hairline; prominent forehead; downward slant palpebral fissures; wide nasal bridge	Speech delay; motor delay; mild inferior vermian hypoplasia; hypotonia	Unknown, c.414dupC, (p.Lys139Glnfs*57)	Flex et al. (2019)
S7	M	Caucasian	11.9	Moderate	High hairline; prominent forehead; hypertelorism; ear low set	Head + height over growth; speech delay; motor delay; speech delay; hypotonia; single childhood seizure; astigmatism; hypermetropia; cryptorchidism; crowded teeth; partial agenesis of corpus callosum; ADHD	De novo, c.447dupG, (p.Ser150Glufs*46)	Flex et al. (2019)
S8	M	Asian	4.8	Normal	High hairline; prominent forehead; downward slant palpebral fissures; wide nasal bridge	Head + weight over growth; speech delay; motor delay; speech delay; hypotonia; strabismus; flat hyperpigmented patches on abdomen and thighs; periventricular white matter abnormality	Unknown, c.430dupG, (p.Ala144Glyfs*52)	Flex et al. (2019
S9	F	Caucasian	2	Unspecified	Prominent forehead; wide nasal bridge; ear low set	Head + weight over growth; febrile seizures; hearing loss	Unknown, c.425delinsAG, (p.Thr142Lysfs*54)	Flex et al. (2019)

(Continues)

TABLE 1 (Continued)

Patient ID	Sex	Ethic origin	Years	Intellectual disability	Facial appearance	Additional clinical features	Inheritance and *HIST1H1E* mutations	Publications
S10	M	Caucasian	1.6	Moderate	Coarse face; high hairline; prominent forehead; downward slant palpebral fissures; hypertelorism; wide nasal bridge; ear low set	Weight + height over growth; speech delay; motor delay; speech delay; febrile; cryptorchidism; small teeth; widely spaced; arachnoid cyst; behavioral problems (stereotypic movements with hands; rolls with eyes when tired)	De novo, c.441dupC, (p.Lys148Glnfs*48)	Flex et al. (2019)
S11	F	Caucasian	6	Moderate	Coarse face; high hairline; prominent forehead; thin hair; hypertelorism; wide nasal bridge	Head + weight over growth; speech delay; motor delay; speech delay; hypotonia; recurrent status epilepticus; hypermetropia; strabismus; mild cutis laxa in abdominal area; tooth dysgenesia with extreme short radices of milk molars with four elements missing; early eruption of teeth; high arched palate; cavum septum pellucidum	De novo, c.441dupC, (p.Lys148Glnfs*48)	Flex et al. (2019)
S12	M	Caucasian	4	Mild	Coarse face; high hairline; prominent forehead; deep set eyes; hypertelorism; wide nasal bridge; ear low set	Head + weight over growth; speech delay; motor delay; speech delay; hypotonia; cryptorchidism; atrial septum defect	De novo, c.408dupG, (p.Lys137Glufs*59)	Flex et al. (2019
S13	F	Caucasian	1.4	Moderate	Coarse face; high hairline; prominent forehead; bitemporal narrowing; downward slant palpebral fissures; hypertelorism; ear low set	Head over growth; speech delay; motor delay; speech delay; hypotonia; bilateral mild to moderate sensorineural hearing loss; astigmatism; hypermetropia; small atrial septum defect; mild prominence of the subarachnoid fluid spaces	De novo,c.430dupG, (p.Ala144Glyfs*53)	Flex et al. (2019)
Patient #3	M	Chinese	2.7	Moderate	Full cheeks; high hairline; widened canthus; narrow eyelid fissure); severe dental caries	Cryptorchidism; head over growth; advanced bone age	De novo, c.446dupA, (p.Serl 50Glufs*46)	Li et al. (2020)

TABLE 1 (Continued)

Patient ID	Sex	Ethic origin	Years	Intellectual disability	Facial appearance	Additional clinical features	Inheritance and *HIST1H1E* mutations	Publications
Our Patient #4	M	Chinese	4.3	Severe	Large head; full cheeks; high hairline; wide eye distance; narrow eyelid fissure; low and flat bridge of nose; upturned nose; wide nose; slightly low-set ear; sparse eyebrows; short neck	Head over growth; uneven teeth; speech delay; ventricular enlargement	Maternal, c.368dup, (p.Gly124Argfs*72)	This report
Our Patient #5	F	Chinese	unknown	Mild	Wide; protruding forehead; high hairline; shallow eyebrows; narrow eyelid fissure; deep-set-eyes	Premature aging	Unknown, c.368dup, (p.Gly124Argfs*72)	This report
Patient 8	F	Caucasian	7	Mild	Scaphocephaly; a high hairline with frontal upsweep of the hair; mild downslant of the palpebral fissures; small teeth	Global developmental delay at 14 months; head over growth; inverted nipples and a pectus excavatum; fingers tapering and there is significant generalized pitting edema of the lower limbs; an advanced bone age	Unknown, c.441dupC, (p.Lys148Glnfs*48)	Helsmoortel et al (2015)

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, atrial septal defect; GOR, gastro-oesophagela reflux; PDA, patent ductus arteriosus; SNHL, Sensori-neural hearing loss; VSD, ventricular septal defect.

1), which is normally rich in lysine residues and almost completely free of acidic and highly hydrophobic amino acids (Kasinsky et al., 2001), generating 30–50 net positive charges (Subirana, 1990). The C-terminal tail of HIST1H1E protein is important for chromatin stable folding (Allan et al., 1986) and is also required for high-affinity binding to chromatin in vivo (Michael et al., 2004). However, the mutation in the *HIST1H1E* gene, c.368dup (p.G124Rfs*72), caused a decrease in lysine number (Figure 1e). The mutated protein net charge calculation using the peptide property calculator (http://pepcalc.com/protein-calculator.php) (Tatton-Brown et al., 2017) produces only 13 net charges, disrupting the normal binding between positively charged *HIST1H1E* and negatively charged DNA, affecting the structure and function of chromatin, leading to the eventual clinical manifestation of the HIST1H1E syndrome.

Previous HIST1H1E syndrome patients were reported to have overgrowth with intellectual disability. Consistently, the patients reported in this study exhibited overgrowth in both head circumference and weight. In this case, as it was with an outpatient case, the patient was subsequently seen by the telemedicine service and no bone age test was performed. There is only one case reported in China, a 2-year-old and 8-month-old Uyghur boy with delayed speech and motor development, 98 cm (+1 SD) in height, 19 kg (+3 SD) in body mass, 54 cm (+3 SD) in head circumference, with a bone age consistent with 5.5 years of age, and showing overgrowth of the trunk. His face was peculiar, with plump cheeks, high hairline, widened canthal spacing, narrow eyelid fissures, pale eyebrows, deep-set eyes, severe dental caries, and cryptorchidism. The child was diagnosed with RMNS after WES revealed a de novo heterozygous mutation, c.446dupA (p.ser150Glufs*46), in the *HIST1H1E* gene. After 1 year of follow-up, the child underwent bilateral high cryptorchidism reduction and fixation and has recovered after surgery (Li et al., 2020). However, Takenouchi et al. (2018) suggested that skeletal overgrowth may not be an essential feature of HIST1H1E-related disorders. In their cohort study that included five subjects with de novo heterozygous frameshift mutations in the *HIST1H1E* gene associated with overgrowth syndrome with intellectual disability, 4 of 5 of the patients' height percentages decreased over time, with three of them starting out above average height but decreasing to average or below average height as they aged and did not have skeletal overgrowth features. In this study, 37.5% (18/48) of patients were reported with over growth features (Table 1). This suggests that overgrowth is not the main clinical manifestation of HIST1H1E syndrome.

The premature senescence phenotype is a previously unrecognized feature of HIST1H1E syndrome. Flex's findings identified an aberrant function of the C-terminal tail of *HIST1H1E* gene that is a direct link between abnormal chromatin remodeling, cellular senescence, and accelerated senescence (Flex et al., 2019). To date, patients with the HIST1H1E syndrome phenotype have frameshift mutations and no other variant types have been reported (Tatton-Brown et al., 2017). These frameshift mutations result in unstable proteins residing in the nucleus (Flex et al., 2019), binding to chromatin, disrupting chromatin structure and nuclear lamina organization, and associated with specific hypomethylation signatures (Ciolfi et al., 2020). Genomic instability, epigenetic modifications, poor DNA repair, improper chromosome compression and segregation, and nucleolus breakage ultimately lead to cellular senescence, and replicative stalemate (Flex et al., 2019). In our case, the mother of the proband showed signs of premature aging such as saggy skin (Figure 1). Additionally, in our retrospective cohort study, 62.5% (30/48) of the patients were reported to have premature aging (Table 1). This suggests that premature aging is one of the main clinical manifestations of HIST1H1E syndrome.

There is no evidence that life expectancy was reduced in individuals with HIST1H1E syndrome. The oldest individual reported was 49 years old (Flex et al., 2019). The mother of the proband in our case was also a patient with HIST1H1E syndrome and had mild intellectual impairment. Her disease was not recognized early on and no genetic testing was performed. Therefore, adults with HIST1H1E syndrome are likely to be underrecognized and underreported. Additionally, no significant thyroid, cryptorchid, cardiac, or skeletal abnormalities have been found in this child and regular follow-up is required. As HIST1H1E syndrome involves multiple systemic issues, management by multidisciplinary specialists is recommended, including, but not limited to developmental pediatrics/behavioral psychology, neurosurgery/neurology, urology, cardiology, endocrinology, ophthalmology, orthopedics, and dentistry. HIST1H1E syndrome patients need multidisciplinary consultation for their management.

The limitations of this study include the following two aspects: (a) Because of the limitations of sequencing methods, certain mutation types such as genomic structural reorganization (e.g., inversion and translocation), large segmental insertional mutations (e.g., ALU-mediated insertion), promoters, deep introns, and variants in GC-rich regions cannot be reliably detected. (b) The interpretation of variants is based on our current knowledge of these genes. As we gain more information about these genes over time, our interpretation readings are likely to change.

5 | CONCLUSION

It is required to consider HIST1H1E syndrome in patients with intellectual disability with particular facial features.

Prenatal testing and preimplantation genetic testing are required for offspring with HIST1H1E syndrome. In general, WES may be indicated for children with intellectual disability, speech delay, particular facial features, and suspected genetic disease. It is critical to reach a diagnosis for treatment and family planning.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

Jianbo Zhao created the research design, patients' selection, performed data collection, and submitted the paper. Guizhen Lyu wrote the manuscript and formulated the paper. Victor Wei Zhang reviewed the manuscript. Changhong Ding, Xiaohui Wang, Jiuwei Li, Weihua Zhang, and Xinying Yang participated in patients' recruitment, clinical assessment, and shared in data collection and reviewed the manuscript.

ETHICAL COMPLIANCE

The study was approved by the ethics committee of the Beijing Children's Hospital (No. [2021]-E-068-R, 7 May 2021). The genetic testing and published ultrasound images were provided by the parents of the proband after a signed consent. The study was performed in accordance with the principles of the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the corresponding author.

ORCID

Jianbo Zhao https://orcid.org/0000-0003-2407-6264

REFERENCES

Allan, J., Mitchell, T., Harborne, N., Bohm, L., & Crane-Robinson, C. (1986). Roles of H1 domains in determining higher order chromatin structure and H1 location. *Journal of Molecular Biology*, *187*(4), 591–601. https://doi.org/10.1016/0022-2836(86)90337-2

Burkardt, D. D. C., Zachariou, A., Loveday, C., Allen, C. L., Amor, D. J., Ardissone, A., & Cytrynbaum, C. (2019). *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. *American Journal of Medical Genetics Part A*, *179*(10), 2049–2055.

Ciolfi, A., Aref-Eshghi, E., Pizzi, S., Pedace, L., Miele, E., Kerkhof, J., Flex, E., Martinelli, S., Radio, F. C., Ruivenkamp, C. A. L., Santen, G. W. E., Bijlsma, E., Barge-Schaapveld, D., Ounap, K., Siu, V. M., Kooy, R. F., Dallapiccola, B., Sadikovic, B., & Tartaglia, M. (2020). Frameshift mutations at the C-terminus of HIST1H1E result in a specific DNA hypomethylation signature. *Clinical Epigenetics*, *12*(1), 1–11. https://doi.org/10.1186/s13148-019-0804-0

Duffney, L. J., Valdez, P., Tremblay, M. W., Cao, X., Montgomery, S., McConkie-Rosell, A., & Jiang, Yh (2018). Epigenetics and autism spectrum disorder: A report of an autism case with mutation in H1 linker histone HIST1H1E and literature review. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *177*(4), 426–433.

Flex, E., Martinelli, S., Van Dijck, A., Ciolfi, A., Cecchetti, S., Coluzzi, E., Pannone, L., Andreoli, C., Radio, F. C., Pizzi, S., Carpentieri, G., Bruselles, A., Catanzaro, G., Pedace, L., Miele, E., Carcarino, E., Ge, X., Chijiwa, C., Lewis, M. E. S., … Tartaglia, M. (2019). Aberrant function of the C-terminal tail of HIST1H1E accelerates cellular senescence and causes premature aging. *The American Journal of Human Genetics*, *105*(3), 493–508. https://doi.org/10.1016/j.ajhg.2019.07.007

Hergeth, S. P., & Schneider, R. (2015). The H1 linker histones: Multifunctional proteins beyond the nucleosomal core particle. *EMBO Reports*, *16*(11), 1439–1453. https://doi.org/10.15252/embr.201540749

Kasinsky, H. E., Lewis, J. D., Dacks, J. B., & Ausió, J. (2001). Origin of H1 linker histones. *FThe FASEB Journal*, *15*(1), 34. https://doi.org/10.1096/fj.00-0237rev

Li, Y., Luo, Y. F., Sun, G. H., Baoerhan, R., Dilihuma, J., & Mireguli, M. (2020). Rahman syndrome caused by *HIST1H1E* gene mutation: a case report and literature review (in Chinese with English abstract). *Journal of Clinical Pediatrics*, *5*, 347–350.

Hendzel, M. J., Lever, M. A., Crawford, E., & Thng, J. P. H. (2004). The C-terminal Domain Is the Primary Determinant of Histone H1 Binding to Chromatinin Vivo. *Journal of Biological Chemistry*, *279*(19):20028–20034.

Qi, Q., Jiang, Y., Zhou, X., Meng, H., Hao, N. A., Chang, J., Bai, J., Wang, C., Wang, M., Guo, J., Ouyang, Y., Xu, Z., Xiao, M., Zhang, V. W., & Liu, J. (2020). Simultaneous detection of CNVs and SNVs improves the diagnostic yield of fetuses with ultrasound anomalies and normal karyotypes. *Genes*, *11*(12), 1397. https://doi.org/10.3390/genes11121397

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., & Rehm, H. L. (2015). 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. *Genetics in Medicine*, *17*(5), 405–423. https://doi.org/10.1038/gim.2015.30

Riggs, E. R., Andersen, E. F., Cherry, A. M., Kantarci, S., Kearney, H., Patel, A., Raca, G., Ritter, D. I., South, S. T., Thorland, E. C., Pineda-Alvarez, D., Aradhya, S., & Martin, C. L. (2020). Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). *Genetics in Medicine*, *22*(2), 245–257. https://doi.org/10.1038/s41436-019-0686-8

Subirana, J. A. (1990). Analysis of the charge distribution in the C-terminal region of histone H1 as related to its interaction with DNA. *Biopolymers: Original Research on Biomolecules*, *29*(10–11), 1351–1357. https://doi.org/10.1002/bip.360291003

Takenouchi, T., Uehara, T., Kosaki, K., & Mizuno, S. (2018). Growth pattern of Rahman syndrome. *American Journal of Medical*

Genetics Part A, *176*(3), 712–714. https://doi.org/10.1002/ajmg.a.38616

Tatton-Brown, K., Loveday, C., Yost, S., Clarke, M., Ramsay, E., Zachariou, A., Elliott, A., Wylie, H., Ardissone, A., Rittinger, O., Stewart, F., Temple, I. K., Cole, T., Mahamdallie, S., Seal, S., Ruark, E., & Rahman, N. (2017). Mutations in epigenetic regulation genes are a major cause of overgrowth with intellectual disability. *The American Journal of Human Genetics*, *100*(5), 725–736. https://doi.org/10.1016/j.ajhg.2017.03.010

How to cite this article: Zhao, J., Lyu, G., Ding, C., Wangi, X., Li, J., Zhang, W., Yang, X., & Zhang, V.W. (2022). Expanding the mutational spectrum of Rahman syndrome: A rare disorder with severe intellectual disability and particular facial features in two Chinese patients. *Molecular Genetics & Genomic Medicine*, 10, e1825. https://doi.org/10.1002/mgg3.1825