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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.

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Abstract

Histone Gene Cluster 1, Member E, HIST1H1E, encodes histone H1.4 and is one of a family of epigenetic regulator genes that acts as a linker histone protein and is responsible for higher order chromatin structure. HIST1H1E syndrome (also known as Rahman syndrome, OMIM #617537) is a recently described intellectual disability syndrome. Since the initial description of five unrelated individuals with three different heterozygous protein truncating variants (PTVs) in the *HIST1H1E* gene in 2017, we have recruited 30 patients, all with *HIST1H1E* PTVs that result in the same shift in frame and that cluster to a 94 base pair region in the *HIST1H1E* carboxy terminal domain (CTD). The identification of 30 patients with *HIST1H1E* variants has allowed the clarification of the HIST1H1E syndrome phenotype. Major findings include an intellectual disability and a recognizable facial appearance. Intellectual disability was reported in all patients and is most frequently of moderate severity. The facial gestalt consists of a high frontal hairline and full lower cheeks in early childhood and, in later childhood and adulthood, affected individuals have a strikingly high frontal hairline, frontal bossing and deep-set eyes. Other associated clinical features include hypothyroidism, abnormal dentition, behavioral issues, cryptorchidism and cardiac anomalies. Brain MRI imaging is frequently abnormal with a slender corpus callosum a frequent finding.

Keywords: *HIST1H1E*, intellectual disability, Epigenetic regulator gene, Rahman Syndrome

Introduction

HIST1H1E syndrome (also known as Rahman syndrome, OMIM #617537) is a recently described intellectual disability syndrome caused by protein truncating variants (PTVs) in the *Histone Gene Cluster 1, Member E, HIST1H1E* (Tatton-Brown et al., 2017). *HIST1H1E*, is located at chromosome 6p22.2 and encodes the ubiquitously expressed human linker Histone H1.4, one of a family of linker histones that has historically been thought to determine higher order chromatin structure facilitating DNA replication, DNA repair and genome stability (Fyodorov et al., 2018). More specifically, Histone H1.4 is preferentially sequestered to heterochromatin regions: in the presence of Histone H1.4, nucleosome arrays arrange into a twisted left-hand double helix with a zig-zag two-start tetranucleosome (Roque et al., 2016, Song et al., 2014, Ponte et al., 2017, McGinty et al., 2015).

Since the HIST1H1E syndrome was first described as an intellectual disability syndrome (in association with increased growth) in 2017, a total of seven patients have been reported (Tatton-Brown et al. 2017; Takenouchi et al., 2018; Duffney et al., 2018). Here we describe 30 patients with HIST1H1E syndrome with 14 different pathogenic variants, all PTVs causing the same shift in frame and clustering to a 94 base pair region in the *HIST1H1E* carboxy terminal domain. Through a detailed clinical evaluation of these 30 patients, we describe a recurrent and recognizable HIST1H1E syndrome phenotype characterized by a distinctive facial appearance and moderate intellectual disability in association with a range of medical problems.

Subjects and Methods

The study was approved by the UK Research Ethics Committee (10/H0305/83), granted by the Cambridge South Research Ethics Committee and the London Multicentre Research Ethics Committee (MREC MREC/01/2/44). Thirty patients with *HIST1H1E* variants, identified through exome sequencing in the diagnostic and research environments, were recruited through clinical genetics services worldwide and family support groups (https://www.facebook.com/hist1h1e/) (including five previously reported patients, Tatton-Brown et al., 2017, and one patient included in a paper submitted for publication, details in supplementary table 1). The *HIST1H1E* variants were reported with reference to the canonical transcript (NM_005321.2). Informed consent was obtained from all participants and/or parents. Photographs, with accompanying written informed consent to publish, were requested from all participants and received from 21.

Detailed phenotype data were collected through clinic evaluation by at least one of the authors (all experienced dysmorphologists) and standardized clinical proformas. Growth parameter standard deviations were calculated with reference to UK90 growth data (Cole et al., 2012). Intellectual disability was classified by the recruiting clinician as mild, moderate, or severe and unclassified where a child was demonstrating developmental delay but was judged by the clinician as being too young to determine the severity of the intellectual disability. For the purposes of our study the following working definitions were used: mild intellectual disability typically described where an individual had delayed milestones but would attend a mainstream school with some support and live independently, with support, as an adult; moderate intellectual

disability typically described where an individual required high-level support in a mainstream school or special educational needs schooling and would live with support as an adult; severe intellectual disability typically described where an individual required special educational needs schooling, had limited speech, and would not live independently as an adult.

Protein net charge calculations were undertaken for the wild type and mutant carboxy terminal domain (from p.Lys110 onward) at neutral pH using the Peptide Property Calculator at the Innovagen website and methods as previously described (Tatton-Brown et al., 2017).

Results

Spectrum of HIST1H1E variants

Thirty unrelated individuals with 14 frameshift *HIST1H1E* variants were identified (Figure 1, Supplementary Table 1). Recurrent variants occurred at c.430dupG_p.(Ala144Glyfs*52) (12 patients); c.441dupC_p.(Lys148Glnfs*48) (four patients); c.435dupC_p.(Thr146Hisfs*50) (two patients) and c.436_458del23_p.(Thr146Aspfs*42) (two patients).

All variants were absent from the gnomAD database, clustered to a 94 base pair region in the carboxy terminal domain (CTD) and were predicted to result in the same shift in the reading frame (Figure 1, Supplementary Figure 1). The predicted mutant proteins shared the same 38 amino acid carboxy terminal motif and all were predicted to have a reduced net positive charge

at pH 7 of -6 to 10.9 compared to the predicted wild type protein charge of 41 (Supplementary Figure 1).

HIST1H1E phenotype

Phenotype data for the 30 patients, including 13 males and 17 females with ages ranging from nine months to 30 years, are detailed in Supplementary Table 1. Notable themes included a recognizable facial gestalt with abnormal dentition, a consistent intellectual disability often with behavioral problems and associated medical problems including hypotonia, cryptorchidism in boys, congenital cardiac anomalies, hypothyroidism, a range of skeletal anomalies and brain MRI abnormalities (Figure 2).

Facial Gestalt

There were shared facial features amongst children and adults with HIST1H1E syndrome (Figure 3). In early childhood, patients had full cheeks and at all ages patients frequently had a high hairline, bi-temporal narrowing, deep set eyes, downslanting palpebral fissures and hypertelorism and often appeared older than their chronological age (Figure 3A and 3B).

Learning and Behavior

All 30 patients were described as having an intellectual disability but only 24 patients were old enough to determine their degree of cognitive impairment: 17% (4/24) patients were reported with a severe intellectual disability, 79% (19/24) patients were reported with a moderate

intellectual disability and 4% (1/24) patients were reported with a mild intellectual disability. Of note, many families report a particular deficit in expressive language acquisition, discrepant with other cognitive skills such as understanding. In addition, behavioral issues were common (50%; 15/30) and included combinations of anxiety; attention deficit hyperactivity disorder; autistic spectrum disorder/traits; head banging and aggression (Figure 2, Supplementary Table 1).

Associated Clinical Features

Hypotonia was a common feature 63% (19/30), frequently presenting in the neonatal period. Brain MRI imaging had been undertaken in 15 patients and was reported abnormal in 13 (86%) with corpus callosum abnormalities the most frequent finding (Figure 2).

Cryptorchidism was reported in in 69% (9/13) of boys. Abnormal dentition including dental erosions, thin enamel, crumbling teeth and multiple dental caries was reported in 43% (13/30) patients (Figure 3C).

Cardiac abnormalities were reported in 43% (13/30) patients, and included combinations of atrial septal defect (nine patients), ventricular septal defect (three patients), patent foramen ovale (one patient), patent ductus arteriosus (one patient) and persistent superior vena cava (one patient). Skeletal anomalies were reported in 40% (12/30) and included combinations of kypho/scoliosis (four patients), camptodactyly (three patients), lower limb asymmetry (two patients) and craniosynostosis, distal brachydactyly, multiple fractures and overlapping toes (one patient each). Hypothyroidism had been diagnosed in five patients (29%, where 17 patients had been

tested). Ectodermal abnormalities were reported in six patients including thin and/or brittle, slow growing hair, lack of body hair and thin nails.

Growth

The mean birth weight was 0.2 standard deviations above the mean (0.2SD), mean birth length was 0.3SD and the mean birth head circumference was 1.4SD. Postnatally, the mean height was 0.4SD (range of -1.8SD to 8.3SD); the mean weight was 1.1 SD (range of -1.8SD to 4.6SD) and the mean head circumference was 1.1SD (range of -1.7 to 3.7SD) (Figure 4).

Discussion

The aim of this study was to define the HIST1H1E syndrome phenotype in order to propose evidence-based management guidance. Through the detailed clinical evaluation of 30 patients with likely/pathogenic *HIST1H1E* variants, we have shown that an intellectual disability (most frequently moderate) and a characteristic facial gestalt are consistent HIST1H1E associations. Other frequent clinical findings include behavioral issues (especially anxiety); cryptorchidism; hypotonia; abnormal dentition; congenital cardiac anomalies; hypothyroidism; ectodermal findings and brain MRI findings (most frequently corpus callosum abnormalities). Contrary to the initial report, height and/or head circumference were not consistently increased >2SD. We propose the name **HIST1H1E** syndrome as an acronym to help remember the characteristic features of this emerging, recognizable phenotype: **H** for Hypotonia, **I** for Intellectual Disability

(ID) with behavioral Issues, **S** for Skeletal, **T** for Testes (undescended) and Thyroid, **H** for Heart anomalies and **E** for Ectodermal issues (including sparse hair and abnormal dentition).

Based upon the current phenotypic evaluation, we suggest children with *HIST1H1E* variants are regularly reviewed by a pediatrician to assess development and determine appropriate referral to speech and language therapy and physical therapy; that children have a regular (at least six monthly) dental review to mitigate potentially preventable issues arising from abnormal dentition and that annual thyroid function tests are undertaken. Given the association with congenital cardiac anomalies, we propose a baseline echocardiogram investigation is undertaken with cardiology follow up dependent upon findings. Although *HIST1H1E* somatic variants have been associated with chronic lymphocytic leukemia as well as diffuse large B-cell lymphoma and hepatocellular carcinoma, these are more usually nonsynonymous variants distributed throughout the gene (Chang et al., 2019). None of the patients in this current clinical series developed cancer. We do not therefore currently advocate specific tumor surveillance but any possible tumor related symptoms should be investigated.

The 14 *HIST1H1E* variants identified in the 30 patients, all cluster to 94 base pair region in the CTD tail of HIST1H1E. This replicates our initial finding that HIST1H1E syndrome variants are frameshift variants that generate a mutant protein with the same 38 amino acid tail, the result of the same shift in the reading frame (Tatton-Brown et al., 2017). To date, no patient with the HIST1H1E syndrome phenotype has been described with a *HIST1H1E* whole gene deletion, stop gain variant or frameshift variant that results in an alternate shift in reading frame (the latter is

not predicted to be associated with a net reduction in charge, Tatton-Brown et al., 2017). In addition, none *HIST1H1E* frameshift variants reported in gnomAD cluster to the same 94 base pair region, nor do they result in the same shift in frame and the generation of a mutant protein with the common 38 amino acid tail. This suggests that the HIST1H1E syndrome phenotype is attributable to a specific set of variants with a defined effect on the protein. Our current working hypothesis is that, because *HIST1H1E* is a single exon, intronless gene, the *HIST1H1E* variants escape nonsense-mediated RNA decay and the resultant mutant HIST1H1E proteins are characterized by a reduced net positive charge compared to wild type proteins, potentially disrupting the normal binding between positively charged HIST1H1E and negatively charged DNA (Tatton-Brown et al., 2017). Further work is required to investigate this.

An important remaining question that our current study has not been able to answer is whether the underlying *HIST1H1E* genetic variant determines the range and severity of clinical features. Currently too few patients have been identified to perform robust genotype-phenotype analyses. However, as greater numbers of patients with the HIST1H1E syndrome are identified it will be interesting to further clarify the HIST1H1E phenotype, better delineate the spectrum of causative *HIST1H1E* variants and investigate the relationship between genetic variant and clinical presentation.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

URLs

Uniprot: https://www.uniprot.org/

Facebook Parent Support Group: https://www.facebook.com/hist1h1e/

Genome Aggregation Database (gnomAD), https://gnomad.broadinstitute.org/

HIST1H1E reference transcript, https://www.ncbi.nlm.nih.gov/nuccore/NM_005321

OMIM, https://www.omim.org/

Protein calculator, http://pepcalc.com/protein-calculator.php

SMART: https://smart.embl.de

Protein Atlas (HIST1H1E): https://www.proteinatlas.org/ENSG00000168298-HIST1H1E/tissue

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Figure Legends

Figure 1. Protein schematic showing the 94 base pair clustering of the 14 different protein truncating variants (each variant is designated by a red circle)

Figure 2. The key clinical features that characterize the HIST1H1E syndrome.

Figure 3. A) The facial gestalt consists of a high frontal hairline and full lower cheeks in early childhood and, in later childhood and adulthood, affected individuals have a strikingly high frontal hairline, bi-temporal narrowing, frontal bossing and deep-set eyes.

B) The evolving facial gestalt in three individuals at ages stated.

C) The dental phenotype includes erosions, thin enamel, crumbling teeth and multiple dental caries. Dental X-rays of an adolescent patient demonstrate thin enamel and short dental roots.

Figure 4. Growth parameters (with height on x axis and head circumference on y axis) plotted by standard deviation, calculated with reference to UK90 growth data. Although in individual patients, the height and/or head circumference might be increased above two standard deviations, in most patients the growth parameters cluster around the mean.

Supplementary Figure 1: Wild type and mutant HIST1H1E (generated by the 14 different *HIST1H1E* frameshift variants) showing the reduction in net charge of the carboxy

terminal domain motif (from Lys110) at neutral pH7. Mutant proteins share a common 38 amino acid tail.

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ICR

Consent for Publication or Presentation of Photographs

Patient's full name: PETROVIC Pamela Stone	ICR Reference: COGO405
Address: A-5020 Salzburg, Goethestraße 13	Date of Birth: 19-03-02
Hospital Reference Number:	

☐ Adult, capable ☐ Minor ☒ Incapable of giving consent (**Stop, seek guidance**)

Name of Guardian: Petrovic Bronislaw (father)	Contact details:

Name and Title of Clinician Requesting Consent:

Univ.-Doz. Dr. Olaf Rittinger

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: Petrovic Bronislaw Print name: PETROVIC Bronislaw (father) Date: 31-03-15

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

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Patient's full name:	ICR Reference:
RONAN CLEARY	COG0412
Address: [illegible]	Date of Birth [illegible]
Hospital Reference Number: [illegible]	
☐ Adult, capable ☒ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Mrs Helen Cleary	Contact details: [illegible]
Name and Title of Clinician Requesting Consent: Dr Nora Stewart	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: [signature] Print name: [illegible] Cleary Date: 7.12.16

A translator or witness may sign here if a patient cannot read this form but indicates consent.
Signed: ..... Print name: ..... Date: .. ..

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WESSEX CLINICAL GENETICS SERVICE

CONSENT FOR PUBLICATION

I give permission for clinical details of me/my child to be used for publication by the Clinical Genetics team and I understand that the clinical details will be used for publication in a specialist genetics journal. I understand that most genetics journals are available to professionals in paper and electronic versions. The details used in genetics articles are anonymous.

Name of Person: Frederick Bull.

X **Your name:** Julia Mary Bull

X **Relationship to child:** Mother
(If applicable)

X **Signature:** Julia Bull

Consent explained by: I Karen Temple

Job Title: Prof Medical Genetics

Date: 5/12/16

Consent for Publication or Presentation of Photographs

Patient's full name: Bryce Robert Kennedy	ICR Reference:
Address: (Parents/Guardians) 5637 Clearwater Rd Baxter, MN 56425 USA	Date of Birth 10/6/1984
Hospital Reference Number:	
☒ Adult, capable ☐ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Mary Rumpho-Kennedy & Robert Kennedy	Contact details: (USA) 207-944-0469 mrumpho@gmail.com
Name and Title of Clinician Requesting Consent:	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: MEKennedy Print name: Mary E. Rumpho-Kennedy, guardian Date: 5/2/2017

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

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Consent for Publication or Presentation of Photographs

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Hospital Reference Number: GF 55174	
☐ Adult, capable ☑ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Rebecca Kitchin	Contact details: 22 Elizabeth St Scottsdale Tasmania 7260 Australia
Name and Title of Clinician Requesting Consent: Prof. David Amor	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: RKitchin ..... Print name: Rebecca Kitchin. Date: 19/7/2017

A translator or witness may sign here if a patient cannot read this form but indicates consent.
Signed: ..... Print name: ..... Date: .. ..

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Address: Carpinteria, CA	Date of Birth 09-09-2010
Hospital Reference Number:	
☐ Adult, capable X Minor ☐ Incapable of giving consent **(Stop, seek guidance)**	
Name of Guardian: Anna-Lisa and Scott Odgers	Contact details: 818-434-4556 cell phone
Name and Title of Clinician Requesting Consent:	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed Anna Lisa Odgers Print name:Anna-Lisa Odgers Date 11-27-17

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Division of Genetics & Epidemiology
The Institute of Cancer Research
15 Cotswold Road
Sutton, SM2 5NG
UNITED KINGDOM

Telephone: +44 (0)20 8722 4099
Email: grs@icr.ac.uk

ICR

Consent for Publication or Presentation of Photographs

Patient's full name: Parker Greenberg	ICR Reference:
Address: 87 Cross Hwy Westport, CT 06880	Date of Birth 1/2/2016
Hospital Reference Number:	
☐ Adult, capable ☒ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Kimberly Greenberg	Contact details: 203-214-6877
Name and Title of Clinician Requesting Consent:	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: Kimberly Greenberg Date: 2/27/18

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

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Email: grs@icr.ac.uk

ICR

Consent for Publication or Presentation of Photographs

Patient's full name: Maren Eileen Nikkel	ICR Reference:
Address: 123 Windrush Lane Durham NC 27703	Date of Birth 02·02·2017
Hospital Reference Number:	
☐ Adult, capable ☒ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Julie C. Nikkel	Contact details: mother
Name and Title of Clinician Requesting Consent:	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: Julie C Nikkel Print name: Julie C Nikkel Date: 4/14/18

A translator or witness may sign here if a patient cannot read this form but indicates consent.
Signed: ..... Print name: ..... Date: .. ..

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ICR

Consent for Publication or Presentation of Photographs

Patient's full name: Ho SZE MAN	ICR Reference:
Address: G/F. Ho Pui Chuen. Tsuen Wan Hong Kong	Date of Birth: 30 June 1981
Hospital Reference Number: C 6123	
☐ Adult, capable ☑ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: SIN SO CHUN	Contact details: 852 90759101
Name and Title of Clinician Requesting Consent: Luk Ho MING	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: SIN SO CHUN Date: 4 May 2018

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: Luk Ho Ming Date: 4 May 2018

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Email: grs@icr.ac.uk

ICR

Consent for Publication or Presentation of Photographs

Patient STMH T7701306 BARRETT Angel Honey Blossom 44 Salcombe Road Knowle BRISTOL BS4 1AQ NHS 654 095 8722 DOB: 01 May 2012 Cons ..... Female	ICR Reference:
Addres	Date of Birth 1/5/12
Hospital Reference Number:	

☐ Adult, capable ☑ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)

Name of Guardian: Lesley Laughlin	Contact details: as above address
Name and Title of Clinician Requesting Consent: Karen Low, Clinical Geneticist Bristol	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

X Signed: ..... Print name: LESLEY LOUGHLIN Date: 8/6/18

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

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UNITED KINGDOM

Telephone: +44 (0)20 8722 4099
Email: grs@icr.ac.uk

G9 4744
To be SB

ICR

Consent for Publication or Presentation of Photographs

Patient's full name: BEN ALAN COLLINS	ICR Reference:
Address: 57 LOWTHER CRESCENT LEYLAND LANCS PR26 6QA	Date of Birth 22 DEC 1998
Hospital Reference Number: SB/SH/G9474431	
☐ Adult, capable ☐ Minor ☒ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: JUDITH COLLINS ALAN COLLINS	Contact details: 01772 465377 07779191858
Name and Title of Clinician Requesting Consent:	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: JACollins AR COLLINS Print name: JUDITH COLLINS ALAN COLLINS Date: 18/6/18

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

VUmc

Stichting Spaarne Gasthuis
Kindergeneeskunde
Dr. J. Goede
Spaarnepoort 1
2134 TM Hoofddorp

VUMC POLI KLINISCHE GENETICA
SPAARNE HOOFDDORP
Geen informatie opgeslagen.
Geen informatie opgeslagen.

Datum
29-05-18

Ons kenmerk

Betreft:
M. Suler, geb. 12-7-2006, gesl. vrouw, patnr. 6419109, BSN 262092839,
adres SEOELLN 6 2152 KK NIEUW VENNEP

Geachte collega,

Bovengenoemde patiënte zag ik op 17-5-2018 op VUMC POLI KLINISCHE GENETICA SPAARNE HOOFDDORP.

Reden van verwijzing
Herbeoordeling ontwikkelingsachterstand zonder diagnose.

Voorgeschiedenis
- Partus 41 wkn, GG 3635 gram (p50). Lengte 52 cm.
- Ontwikkelingsachterstand vastgesteld op 4-5 maanden. Lopen op 2,5 jaar. Spreekt woordjes.
- Hypotonie als baby met vaak verslikken en veel broncho-obstructieve klachten en luchtweginfecties in eerste 2,5 jaar.
- MRI hersenen (2010): vertraagde myelinisatie, atypische frontaal hoorn laterale ventrikels en lichte hypoplasie rostrum corpus callosum
- ASD II, spontaan gesloten bij cardiologische controle in 2012
- Periode van gewichtstoename en veel eten (2012). Nu gewicht genormaliseerd
- Strabisme operatie bdz, +8 afwijking.
- Veel caries
- Chronische buikpijn, obstipatie. Nu niet meer, geen forlax meer.
- Condylomata accuminata perianaal

Eerder verricht genetisch onderzoek (2007-2014):
Chromosomen onderzoek: 46,XX
Metabool onderzoek (AMC): geen afwijkingen.
Array 105k, array CGH 180k, SNP array: geen afwijkingen
FISH onderzoek naar Pallister-Killian op wangslijmvlies: geen afwijkingen.
DNA onderzoek naar Prader Willi syndroom (AMC): geen afwijkingen.
Whole exome sequencing (trio analyse gehele exoom) (2014): geen afwijkingen.

VUMC Boelelaan 1118 Postbus 7057 1007 MB Amsterdam Telefoon 020-4444444

Anamnese
Melissa zit nu op het ZMLK. Recente IQ test (SON 2,5-7 jaar) toonde nivo 4;6 en IQ<50. Ze is makkelijk, vrolijk en slaapt goed. Melissa heeft opvallende tanden, extreem wit en kegelvormige hoektanden, brokkelig. Ze heeft (bijna) alles gewisseld, het melkgebit is deels getrokken vw caries. Ze heeft dunne nagels die nauwelijks groeien. Ook het haar groeit bijna niet. Ze heeft snel ontstekingen van de huid (bij muggenbult, wondjes, oorbellen). Nadat de keelamandelen zijn verwijderd heeft ze geen (lage) luchtweginfecties meer gehad. Ze wel vaker en heftiger ziek dan anderen.

Familie anamnese
Tweede kind niet-consanguine ouders. Moeder heeft eenmaal een miskraam gehad.

Lichamelijk onderzoek
Lengte 147,6 cm (-1 SD). Schedelomtrek 56 cm (+1,4 SD).
Metingen op 14-3 -2018: Gewicht 47 kg (+0,9 SD); Lengte 146 cm (-1 SD); BMI 22 (+1,7 SD)
Craniofaciaal: hoge voorste haargrens, kleine ooglidspleten, diepliggende ogen, brede neusbrug, lichte wenkbrauwen, volle wangen.
Extremiteiten: tapering vingers, camptodactylie 3e vinger links (rechts status na correctieve operatie), dunne nagels (mn op tenen).

Aanvullend onderzoek
Herbeoordeling whole exome sequencin: de novo c.441dup; p.(Lys148Glnfs*48) (Chr6(GRCh37):g.26157059dup in HIST1H1E gen: in 2014 niet gemeld omdat onbekend gen. Inmiddels bekend gen, beschreven mutatie (Tatton-Brown et al 2017).

Bespreking
Melisa is bekend met een ontwikkelingsachterstand. Bij eerder genetisch onderzoek was er geen oorzaak gevonden. Herbeoordeling van de WES (uit 2014) toonde nu een mutatie in het HIST1H1E gen en hiermee is nu toch een diagnose gesteld bij Melissa.

<u>Diagnose Rahman syndroom</u>
Mutaties in het HIST1H1E gen zijn in 2017 voor het eerst beschreven en veroorzaken het Rahman syndroom. Er zijn nu wereldwijd 8 patiënten (oudste 21 jaar) met deze aandoening beschreven met de volgende kenmerken:

- Milde tot ernstige ontwikkelingsachterstand: lage spierspanning in eerste jaren, later lopen, beperkte spraak, verstandelijke beperking.
- Variabele overgroei (lengte, gewicht en/of schedelomtrek boven normaal) maar meestal na aantal jaar normale lengte.
- Gelaatskenmerken: hoge voorste haargrens, volle wangen, ogen ver uit elkaar (telecanthus/hypertelorisme), lichte wenkbrauwen.
- Sommige verschijnselen worden een enkele keer genoemd: strabisme (3 kinderen), milde afwijkingen op MRI hersenen (3), camptodactylie of clinodactylie (2), tapering van de vingers (1), (milde) scoliose (2), kwetsbaar gebit en dunne nagels (1), obstipatie (1), moeilijk gedrag (1), angsten (2), autisme (1).

De verschijnselen van Melissa passen goed bij deze diagnose. Melissa heeft ook afwijkende tanden, dunne nagels en langzaam groeiend haar (passend bij een ectodermale dysplasie). Dit is nog niet als duidelijk kenmerk beschreven bij Rahman syndroom maar hoort er waarschijnlijk wel bij.

<u>Overerving Rahman syndroom</u>
De HIST1H1E mutaties die Rahman syndroom veroorzaken zijn *autosomaal dominant*. Dat betekent dat één mutatie leidt tot de aandoening. De mutatie werd niet terug gevonden bij de ouders van

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Melissa en is dus nieuw (*de novo*) ontstaan. Daarom is de kans op dezelfde aandoening bij andere kinderen van ouders heel klein (1-2%)*. Ouders hebben geen verdere kinderwens.
Melissa's broer heeft de aandoening niet. Voor zijn kinderen is er daarom GEEN verhoogde kans op de aandoening van Melissa. Voor kinderen van Melissa zelf is er wel een kans van 50% op de aandoening.

Conclusie
Diagnose: Rahman syndroom ten gevolge van een *de novo* mutatie in het HIST1H1E gen.

Bij verdere vragen kan altijd contact worden opgenomen. Omdat er nu nog weinig bekend is over de aandoening, zie ik Melissa graag terug over 2-3 jaar om verdere ontwikkelingen in de kennis te bespreken.

** Meestal ontstaat een nieuwe mutatie in een van de geslachtscellen (zaadcel of eicel) waaruit het kind is gegroeid en is er geen kans op een volgend kind met dezelfde aandoening. Heel soms is de mutatie ontstaan in een voorloper cel van de zaadcellen of eicellen bij één van de ouders en dan kan er een volgend kind worden geboren met dezelfde aandoening. De kans op een volgend aangedaan kind is daarom 1-2% (1-2 op de 100).*

Met collegiale hoogachting,

Dr. J.M. Van de Kamp,
Klinisch geneticus

Cc:
B. BERNDSEN
Hugo De Vriesstraat 17
2152 CT Nieuw-Vennep
VIA Zorgmail

Ouders/verzorgers van M. Suler
Seoelln 6
2152 KK Nieuw Vennep
VIA Post

MREC 01/2/44
(Version 3, dated January 2018)

ICR

THE CHILDHOOD OVERGROWTH (COG) STUDY

ADULT/CHILD CONSENT FORM

Referring Hospital/Centre VUmc Dr van der kamp (clinical genetist)

Patient/Family Reference Number .....

Patient's name Melisa Suler

Name of legal guardian/next of kin Esther Suler

1. I confirm that I have read **and understand** the information sheet dated..... **(Version.....)** for the above study and have had the opportunity to ask questions.

2. I understand that my/**my child's** participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my/**my child's** medical care or legal rights being affected.

3. I understand **and give permission for** my/**my child's** medical records, photographs and/**or** pathology specimens **to** be looked at by responsible members of the research team **and their research collaborators. I have been assured that strict confidentiality will be maintained.**

4. I understand that information that might have implications for the medical care of my family may become available as a result of this research. I understand that any such information will be sent to the Doctor that referred **me/my child** to the study to be managed in accordance with standard medical practice. I understand that no results from the study will be sent directly to myself.

5. I agree to **my/my child's participation** in the above study.

Esther Suler	01-08-2018	Esther
Name of **Patient / Parent**	Date	Signature
Name of **Clinician obtaining** consent	Date	Signature

ENQUIRIES:
COG Team
phone: 020 8722 4099
fax: 020 8722 4359
email: grs@icr.ac.uk

Principal Investigator
Prof Nazneen Rahman
Institute of Cancer Research
15 Cotswold Road
Sutton, Surrey
SM2 5NG

1 copy for Patient, 1 for Principal Investigator, 1 for Hospital Notes

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UNITED KINGDOM

Telephone: +44 (0)20 8722 4099
Email: grs@icr.ac.uk

ICR

Consent for Publication or Presentation of Photographs

Patient's full name: Melisa Süler	ICR Reference:
Address: Seeellaan 6 2152 kk nieuw-vennep nederland	Date of Birth 12-07-2006
Hospital Reference Number:	
☐ Adult, capable ☒ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Esther Süler	Contact details: esther.suler@live.nl 06-25143882
Name and Title of Clinician Requesting Consent: Dr van der kamp → VU mc 020-4444444 (telephone number)	Hospital:

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: Esther Süler Date: 12-07-2006 01-08-ug 2018

A translator or witness may sign here if a patient cannot read this form but indicates consent.
Signed: ..... Print name: ..... Date: .. ..

ICR

ADDITIONAL CLINICAL INFORMATION
HIST1H1E STUDY

COG ID

THIS FORM IS TO BE USED IN ADDITION TO THE STANDARD OVERGROWTH PROFORMA

(If you have not completed the standard overgrowth proforma, I would be grateful if you could complete and return this with the supplementary questionnaire).

PATIENT INFORMATION

Name..Melisa Siles.....dob..12-07-2006..~~male~~/female

CLINICAL INFORMATION

Please include additional clinical information that you consider relevant at the bottom of this questionnaire.

Most recent growth parameters

Measured 27-07-2018

Height..154..cm 12 year ~~0 months~~ age (months)

OFC..54..cm 12 age (months)

Weight..50,2 kg..cm 12 age (months)

Learning and behaviour

(melisa her iq is 50)

Current Learning disability Severe ☐ Moderate ☒ Mild ☐ None ☐

Autistic spectrum disorder Yes ☐ No ☒ Unknown ☐ Details.....

Any other behavioural/psychiatric problems including anxiety..no.....

Associated Clinical Features

Scoliosis Yes ☐ No ☒ Unknown ☐ Details.....

Joint laxity Yes ☐ No ☒ Unknown ☐ Details.....

Hypotonia Yes ☒ No ☐ Unknown ☐ Details.....

Seizures Yes ☐ No ☒ Unknown ☐ Details.....

Tumour Yes ☐ No ☒ Unknown ☐ Details.....

Loose, redundant skin Yes ☐ No ☒ Unknown ☐ Details.....

Thyroid disease Yes ☐ No ☒ Unknown ☐ Details.....

Dental problems Yes ☒ No ☐ Unknown ☐ Details.....

Puberty Early ☐ Late ☒ Average ☐ Not known ☐ melisa is 12 now and she has no physical development yet

Other clinical details .....

.....

Facial gestalt. Please describe your patient's facial features and send photos at different ages if possible/available.

eyes far apart, round face,.....

Investigations

Advanced bone age Yes ☐ No ☐ Unknown ☒ Details.....

MRI abnormalities Yes ☒ No ☐ Unknown ☐ Details..sorry I can't translate it in English

Form completed by.....**Date**.....

Other clinical details:

x hair hardly grows
x nails hardly grows
x skin is always very dry
x lazy eye
x crooked fingers (middle)
x toes are over each other
x poor visibility

Childhood Overgrowth (COG) Study
CLINICAL PROFORMA

PATIENT INFORMATION

Name Melisa Suler dob 12-07-2006 ~~male~~/female

Likely Diagnosis Hist1H1E

Consultant in charge of care Dr van der kamp – VU mc

GROWTH

Height 154 cm (age 12 yrs 0 months) (..... centile)

Head circumference 54 cm (age 12 yrs 0 months) (..... centile)

Weight 50,2 kg (age 12 yrs 0 months) (..... centile)

Mother's height 180 cm Father's height 183 cm

Mother's head circumference ~~57~~ 57,5 cm Father's head circumference 57 cm

ASYMMETRIC GROWTH

Is there asymmetry/hemihypertrophy?	Yes ☐	No ☐	Unknown ☒	
Which body parts are affected	Face ☐	Arm ☐	Leg ☐	Trunk ☐
Which side is bigger	Right ☐	Left ☐	Both ☐	Crossed ☐
What is the approximate size difference between the two sides	..... cm			
Is the asymmetry	Static ☐	Increasing ☐	Decreasing ☐	
Is the asymmetry	Mild ☐	Moderate ☐	Severe ☐	
Has debulking surgery been required?	Yes ☐	No ☐	Planned ☐	

Does the individual have learning difficulties? No ☐ Mild ☐ Moderate ☒ Severe ☐

Does the individual have behavioural problems? Yes ☐ No ☒ Unknown ☐

Please give details of behavioural problems.....

Is the individual dysmorphic? Yes ☐ No ☒ Unknown ☐

BIRTH, PREGNANCY AND NEWBORN PERIOD

Was the conception Natural ☒ Assisted ☐ Details.....

Duration of pregnancy 41 weeks Details of any complications no

Birth weight 3400 g (.....centile) Birth length 52 cm (.....centile)

Birth OFC ? cm (.....centile)

Were any of the following present in the neonatal period? The first year she choked a lot

Jaundice ☐ Hypoglycaemia ☐ Poor feeding ☒ Hypotonia ☒

Other ☒ please give details..... a lot of pneumonia the first year (and bronchitis)

OTHER CLINICAL FEATURES

Tumours Yes ☐ No ☒ Unknown ☐ Details.....

Cardiac anomalies Yes ☒ No ☐ Unknown ☐ Details..... ASD II (little hole in heart)

Genito-urinary anomalies Yes ☐ No ☐ Unknown ☒ Details.....

Neurological problems Yes ☐ No ☐ Unknown ☒ Details.....

Skeletal problems Yes ☐ No ☐ Unknown ☒ Details.....

Pigmentary abnormalities Yes ☐ No ☒ Unknown ☐ Details.....

Vascular abnormalities Yes ☐ No ☐ Unknown ☒ Details.....

Lumps (inc lipomata) Yes ☐ No ☐ Unknown ☒ Details.....

Other ☒ please give details..... x many caries in teeth
x squint eyes
x constipation (the first 4 years)

Please indicate if any of the following are present:

Macroglossia ☐ Omphalocoele ☐ Umbilical hernia ☐ Diastasis recti ☐

Nevus flammeus ☐ Ear creases/pits ☐

FAMILY HISTORY

Mother's name..... Esther Süler .....Mother's dob..... 13-09-1977

Father's name..... Koray Süler .....Father's dob..... 02-11-1975

Family History of				
	Learning difficulties	Yes ☐	No ☒	Unknown ☐
	Overgrowth	Yes ☐	No ☒	Unknown ☐
	Hemihypertrophy	Yes ☐	No ☐	Unknown ☐
	Cancer	Yes ☒	No ☐	Unknown ☐

If yes, please give details..... in both of the familys there has been cancer

INVESTIGATIONS. Please indicate the following results. If not performed, please leave blank. :

NSD1.....11p15.....

PTEN.....GPC3.....

Karyotype.....Array CGH.....

Telomeres.....**Other (inc bone age)**.....

?

Form completed by..... Esther Süler .....(please print name)

Contact details: telephone..... 06-25143282 ...email..... esther_suler@live.nl

Please include relevant clinic letters and laboratory reports

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The Institute of Cancer Research
15 Cotswold Road
Sutton, SM2 5NG
UNITED KINGDOM

Telephone: +44 (0)20 8722 4099
Email: grs@icr.ac.uk

ICR

Consent for Publication or Presentation of Photographs

Patient's full name: Alexander Jason LeBlanc	ICR Reference:
Address: 3 Dorothy E. Lucey Dr., Newburyport, MA 01950, U.S.A.	Date of Birth 05/30/08
Hospital Reference Number:	
☐ Adult, capable ☑ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Jason LeBlanc	Contact details: 978-473-9595 jleblanc234@yahoo.com
Name and Title of Clinician Requesting Consent: Tatton-Brown	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: Jason LeBlanc Date: 9/22/18

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

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Email: grs@icr.ac.uk

ICR

Consent for Publication or Presentation of Photographs

Patient's full name: Anne Shirley Howlet	ICR Reference:
Address: 217 4th Avenue West, Owen Sound, ON N4K 4V1 CANADA	Date of Birth 14 September 200
Hospital Reference Number:	
☐ Adult, capable ☐ Minor X Incapable of giving consent (**Stop, seek guidance**) Andrew & Laura Howlett have P.O.A for Anne Howlett	
Name of Guardian: Laura Howlett	Contact details: 01(519)378-4161 laura@howlett.net
Name and Title of Clinician Requesting Consent:	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed:..... Print name:...Dr. Laura A Howlett.... Date:.....Sept 16, 2018.

A translator or witness may sign here if a patient cannot read this form but indicates consent. Signed: ..... Print name: ..... Date: .. ..

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Telephone: +44 (0)20 8722 4099
Email: grs@icr.ac.uk

ICR

Consent for Publication or Presentation of Photographs

Patient's full name: Matthew Eli Grushka	ICR Reference:
Address: 44 Ravenglass Crescent London, Ontario, Canada N6G4K1	Date of Birth July 25, 2015
Hospital Reference Number: London Health Sciences (London, Ontario, Canada): 11989378	
X Adult, capable ☐ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Daniel Grushka (Father)	Contact details: Email: dgrushk@uwo.ca Telephone: 519-673-8519
Name and Title of Clinician Requesting Consent: Dr. Kate Tatton-Brown	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: Daniel Grushka Date: Jan 31/2019

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

Consent for Publication or Presentation of Photographs

Patient's full name:	ICR Reference:
Corke Scarlett (Ms) 2 Whiting Close,Warren Row Reading Berks RG10 8ER Mob: 07756067543 Case #: **68462** PAS #: **4747735** Sex: F DoB: 28-Jul-04 NHS #: 706 068 0527 Pt # **133391** Tel: 01628316623	Date of Birth

☐ Adult, capable ☐ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)

Name of Guardian:	Contact details:
DAVID CORKE	07871 457791

Name and Title of Clinician Requesting Consent:

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: DAVID CORKE Date: 27/10/18

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

Division of Genetics & Epidemiology
The Institute of Cancer Research
15 Cotswold Road
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Email: grs@icr.ac.uk

1159.17 ref

ICR

Consent for Publication or Presentation of Photographs

Patient's full name: BROHON LORENZO	ICR Reference:
Address: 9 LOTISSEMENT LA SOURCE 71470 MONTPONT EN BRESSE FRANCE	Date of Birth: 14 JUNE 2016.
Hospital Reference Number: CHU DIJON 21000	
☐ Adult, capable ☒ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: FONTANY SANDRA. BROHON NICOLAS.	Contact details: Mother and Father
Name and Title of Clinician Requesting Consent: Pr. Laurence OLIVIER-FAIVRE CHU DIJON FRANCE	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: FONTANY SANDRA Date: 02.01.2019

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: Dr POIGNAND PATRICIA Date: 2.01.2019

MREC/01/2/44
(version 2, dated March 2005)

ICR

The Childhood Overgrowth Study
ADULT CONSENT FORM

REFERRING CENTRE .....

PATIENT / FAMILY REF NUMBER .....

I, FONTANY Sandra IN NAME OF MY SON BROHON LORENZO (name)

Of 9 LOTISSEMENT LA SOURCE (address)
71470 MONTPONT EN BRESSE FRANCE

1. confirm that I have read the information sheet dated 02.01.2019 for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that my medical records, photographs and pathology specimens may be looked at by responsible individuals from the research team. I give permission for these individuals to have access to these records.
4. I understand that information that might have implications for the medical care of my family may become available as a result of this research. I understand that any such information will be sent to the Doctor that referred my family to the study to be managed in accordance with standard medical practice. I understand that no results from the study will be sent directly to myself.
5. I agree to take part in the above study.

FONTANY SANDRA	02.01.2019	
Name of Parent / Guardian	Date	Signature
BROHON LORENZO (CHILD)	X	X
Name of Person taking consent	Date	Signature

ENQUIRIES:
COG Team
phone: 020 8722 4099
fax: 020 8722 4359
email: grs@icr.ac.uk

Principal Investigator
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Sutton, Surrey
SM2 5NG

Our Ref ID

1 copy for Patient, 1 for Principal Investigator, 1 for Hospital Notes

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ICR

Consent for Publication or Presentation of Photographs

Patient's full name: Isabella Wright	ICR Reference:
Address: 3549 Cast Palm Dr Buford, GA 30519	Date of Birth 07/29/2019
Hospital Reference Number:	
☐ Adult, capable ☑ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Madison Prickett	Contact details: phone: 678-775-9503 email: mprickett7010@gmail.com
Name and Title of Clinician Requesting Consent: Dr. Kate Tatton Brown	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: Madison Prickett Print name: Madison Prickett Date: may 2, 2019

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

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ICR

Consent for Publication or Presentation of Photographs

Patient's full name: Chaney Eleanor Ford	ICR Reference:
Address: 1695 Bogey St., Batesville, AR 72501	Date of Birth 11/26/16
Hospital Reference Number: White River Medical Center, Batesville, AR	
☒ Adult, capable ☐ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Georgeanne Ford	Contact details: 501-425-2942 ganneford@gmail.com
Name and Title of Clinician Requesting Consent: Kate Tatton-Brown	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

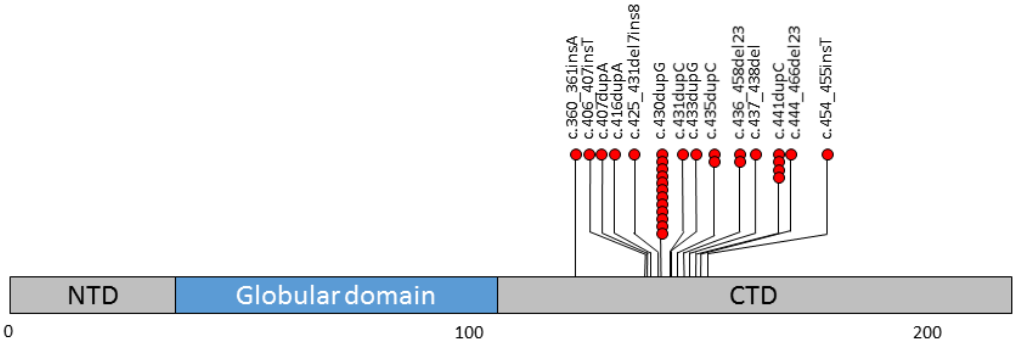
I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: Georgeanne Ford Print name: Georgeanne Ford Date: 2/6/19

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..



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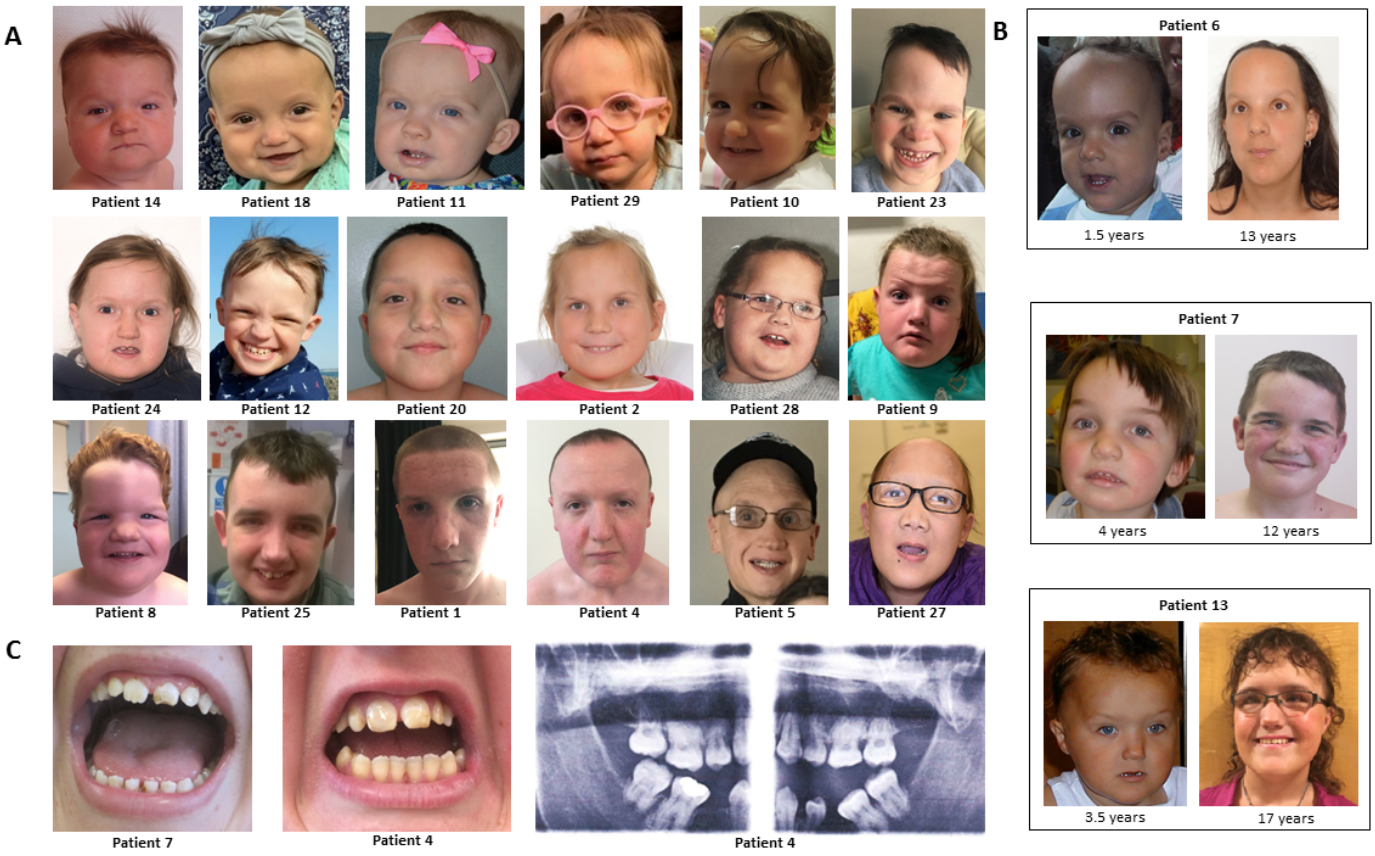
Patient Number	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16	Patient 17	Patient 18	Patient 19	Patient 20	Patient 21	Patient 22	Patient 23	Patient 24	Patient 25	Patient 26	Patient 27	Patient 28	Patient 29	Patient 30	Incidence
Gender	M	F	F	M	M	F	M	M	F	F	F	M	F	M	M	F	F	F	M	M	F	F	M	F	M	F	F	F	F	M	
Age (years)	15.2	nk	2.3	19.0	30.0	13.0	8.5	1.9	7.0	2.0	1.2	10.5	18.0	0.8	7.7	1.4	5.1	0.8	0.9	9.0	3.0	1.9	3.4	6.1	1.5	4.2	nk	12.0	1.5	3.6	
Facial gestalt	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	100%
Intellectual disability	Mo	Mo	Mi	Mo	Mo	S	S	S	Mo	Mo	U	Mo	Mo	U	Mo	U	Mo	U	U	Mo	Mo	Mo	Mo	Mo	Mo	Mo	S	Mo	U	Mo	100%
Abnormal Brain MRI	■	■	nk	nk	nk	nk	■	■	nk	■	nk	nk	■		nk	■	■	nk	■	■	nk	nk	■	■	nk	nk	nk	■	nk		87%
Cryptorchidism	■	/	/	■	■	/		■	/	/	/	■	/	■		/	/	/		■	/	/	■	/	■	/	/	/	/		69% ♂
Hypotonia		■			■	■	■	■	■	■		■	■	■	■	■	■	■		■	■		■	■				■			63%
Behavioral issues	■			■			■	■	■	■		■	■		■	■				■	■			■	■		■				50%
Abnormal dentition	■	■	■	■	■	nk	■		nk	nk	nk	■	■						nk	nk	■	nk	■	■	■	nk		■			43%
Cardiac anomalies			■					■		■	■		■			■	■		■	■			■	■				■	■		43%
Skeletal anomalies		■	■	■	■	■						■	■		■				■			■		■	■						40%
Hypothyroidism	■			nk		nk		■	■	nk	nk	nk	■						nk	■	nk	nk	nk		nk	nk					25%

Key: Squares are shaded when feature is present. Squares are unshaded when feature is absent. Unshaded squares with oblique line represents female where cryptorchidism is not relevant.
Abbreviations: M=male, F=female; Mi, mild; Mo, moderate; S, severe; U, unclassified; nk, not known

AJMGA_61321_AJMGA_61321_Figure 2_revision.tif



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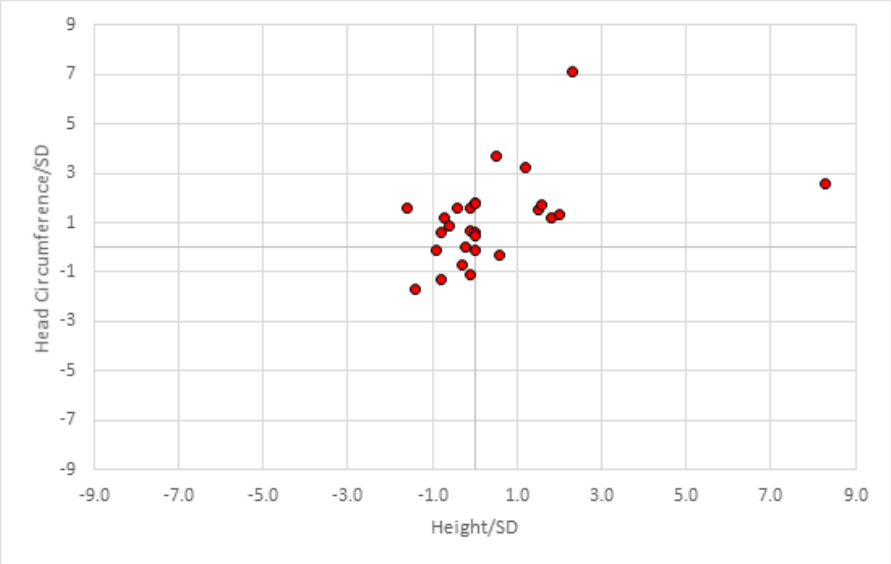

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HIST1H1E Heterozygous Protein Truncating Variants Cause a Recognizable Syndrome with Intellectual Disability and Distinctive Facial Gestalt: A Study to Clarify the HIST1H1E Syndrome Phenotype in 30 individuals.

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Abstract

Histone Gene Cluster 1, Member E, HIST1H1E, encodes histone H1.4 and is one of a family of epigenetic regulator genes that acts as a linker histone protein and is responsible for higher order chromatin structure. HIST1H1E syndrome (also known as Rahman syndrome, OMIM #617537) is a recently described intellectual disability syndrome. Since the initial description of five unrelated individuals with three different heterozygous protein truncating variants (PTVs) in the *HIST1H1E* gene in 2017, we have recruited 30 patients, all with *HIST1H1E* PTVs that result in the same shift in frame and that cluster to a 94 base pair region in the *HIST1H1E* carboxy terminal domain (CTD). The identification of 30 patients with *HIST1H1E* variants has allowed the clarification of the HIST1H1E syndrome phenotype. Major findings include an intellectual disability and a recognizable facial appearance. Intellectual disability was reported in all patients and is most frequently of moderate severity. The facial gestalt consists of a high frontal hairline and full lower cheeks in early childhood and, in later childhood and adulthood, affected individuals have a strikingly high frontal hairline, frontal bossing and deep-set eyes. Other associated clinical features include hypothyroidism, abnormal dentition, behavioral issues, cryptorchidism and cardiac anomalies. Brain MRI imaging is frequently abnormal with a slender corpus callosum a frequent finding.

Keywords: *HIST1H1E*, intellectual disability, Epigenetic regulator gene, Rahman Syndrome

Introduction

HIST1H1E syndrome (also known as Rahman syndrome, OMIM #617537) is a recently described intellectual disability syndrome caused by protein truncating variants (PTVs) in the *Histone Gene Cluster 1, Member E, HIST1H1E* (Tatton-Brown et al., 2017). *HIST1H1E*, is located at chromosome 6p22.2 and encodes the ubiquitously expressed human linker Histone H1.4, one of a family of linker histones that has historically been thought to determine higher order chromatin structure facilitating DNA replication, DNA repair and genome stability (Fyodorov et al., 2018). More specifically, Histone H1.4 is preferentially sequestered to heterochromatin regions: in the presence of Histone H1.4, nucleosome arrays arrange into a twisted left-hand double helix with a zig-zag two-start tetranucleosome (Roque et al., 2016, Song et al., 2014, Ponte et al., 2017, McGinty et al., 2015).

Since the HIST1H1E syndrome was first described as an intellectual disability syndrome (in association with increased growth) in 2017, a total of seven patients have been reported (Tatton-Brown et al. 2017; Takenouchi et al., 2018; Duffney et al., 2018). Here we describe 30 patients with HIST1H1E syndrome with 14 different pathogenic variants, all PTVs causing the same shift in frame and clustering to a 94 base pair region in the *HIST1H1E* carboxy terminal domain. Through a detailed clinical evaluation of these 30 patients, we describe a recurrent and recognizable HIST1H1E syndrome phenotype characterized by a distinctive facial appearance and moderate intellectual disability in association with a range of medical problems.

Subjects and Methods

The study was approved by the UK Research Ethics Committee (10/H0305/83), granted by the Cambridge South Research Ethics Committee and the London Multicentre Research Ethics Committee (MREC MREC/01/2/44). Thirty patients with *HIST1H1E* variants, identified through exome sequencing in the diagnostic and research environments, were recruited through clinical genetics services worldwide and family support groups (https://www.facebook.com/hist1h1e/) (including five previously reported patients, Tatton-Brown et al., 2017, and one patient included in a paper submitted for publication, details in supplementary table 1). The *HIST1H1E* variants were reported with reference to the canonical transcript (NM_005321.2). Informed consent was obtained from all participants and/or parents. Photographs, with accompanying written informed consent to publish, were requested from all participants and received from 21.

Detailed phenotype data were collected through clinic evaluation by at least one of the authors (all experienced dysmorphologists) and standardized clinical proformas. Growth parameter standard deviations were calculated with reference to UK90 growth data (Cole et al., 2012). Intellectual disability was classified by the recruiting clinician as mild, moderate, or severe and unclassified where a child was demonstrating developmental delay but was judged by the clinician as being too young to determine the severity of the intellectual disability. For the purposes of our study the following working definitions were used: mild intellectual disability typically described where an individual had delayed milestones but would attend a mainstream school with some support and live independently, with support, as an adult; moderate intellectual disability typically described where an individual required high-level support in a mainstream school or special educational needs schooling and would live with support as an adult; severe

intellectual disability typically described where an individual required special educational needs schooling, had limited speech, and would not live independently as an adult.

Protein net charge calculations were undertaken for the wild type and mutant carboxy terminal domain (from p.Lys110 onward) at neutral pH using the Peptide Property Calculator at the Innovagen website and methods as previously described (Tatton-Brown et al., 2017).

Results

Spectrum of HIST1H1E variants

Thirty unrelated individuals with 14 frameshift *HIST1H1E* variants were identified (Figure 1, Supplementary Table 1). Recurrent variants occurred at c.430dupG_p.(Ala144Glyfs*52) (12 patients); c.441dupC_p.(Lys148Glnfs*48) (four patients); c.435dupC_p.(Thr146Hisfs*50) (two patients) and c.436_458del23_p.(Thr146Aspfs*42) (two patients).

All variants were absent from the gnomAD database, clustered to a 94 base pair region in the carboxy terminal domain (CTD) and were predicted to result in the same shift in the reading frame (Figure 1, Supplementary Figure 1). The predicted mutant proteins shared the same 38 amino acid carboxy terminal motif and all were predicted to have a reduced net positive charge at pH 7 of -6 to 10.9 compared to the predicted wild type protein charge of 41 (Supplementary Figure 1).

HIST1H1E phenotype

Phenotype data for the 30 patients, including 13 males and 17 females with ages ranging from nine months to 30 years, are detailed in Supplementary Table 1. Notable themes included a

recognizable facial gestalt with abnormal dentition, a consistent intellectual disability often with behavioral problems and associated medical problems including hypotonia, cryptorchidism in boys, congenital cardiac anomalies, hypothyroidism, a range of skeletal anomalies and brain MRI abnormalities (Figure 2).

Facial Gestalt

There were shared facial features amongst children and adults with HIST1H1E syndrome (Figure 3). In early childhood, patients had full cheeks and at all ages patients frequently had a high hairline, bi-temporal narrowing, deep set eyes, downslanting palpebral fissures and hypertelorism and often appeared older than their chronological age (Figure 3A and 3B).

Learning and Behavior

All 30 patients were described as having an intellectual disability but only 24 patients were old enough to determine their degree of cognitive impairment: 17% (4/24) patients were reported with a severe intellectual disability, 79% (19/24) patients were reported with a moderate intellectual disability and 4% (1/24) patients were reported with a mild intellectual disability. Of note, many families report a particular deficit in expressive language acquisition, discrepant with other cognitive skills such as understanding. In addition, behavioral issues were common (50%; 15/30) and included combinations of anxiety; attention deficit hyperactivity disorder; autistic spectrum disorder/traits; head banging and aggression (Figure 2, Supplementary Table 1).

Associated Clinical Features

Hypotonia was a common feature 63% (19/30), frequently presenting in the neonatal period. Brain MRI imaging had been undertaken in 15 patients and was reported abnormal in 13 (86%) with corpus callosum abnormalities the most frequent finding (Figure 2).

Cryptorchidism was reported in in 69% (9/13) of boys. Abnormal dentition including dental erosions, thin enamel, crumbling teeth and multiple dental caries was reported in 43% (13/30) patients (Figure 3C).

Cardiac abnormalities were reported in 43% (13/30) patients, and included combinations of atrial septal defect (nine patients), ventricular septal defect (three patients), patent foramen ovale (one patient), patent ductus arteriosus (one patient) and persistent superior vena cava (one patient). Skeletal anomalies were reported in 40% (12/30) and included combinations of kypho/scoliosis (four patients), camptodactyly (three patients), lower limb asymmetry (two patients) and craniosynostosis, distal brachydactyly, multiple fractures and overlapping toes (one patient each). Hypothyroidism had been diagnosed in five patients (29%, where 17 patients had been tested). Ectodermal abnormalities were reported in six patients including thin and/or brittle, slow growing hair, lack of body hair and thin nails.

Growth

The mean birth weight was 0.2 standard deviations above the mean (0.2SD), mean birth length was 0.3SD and the mean birth head circumference was 1.4SD. Postnatally, the mean height was 0.4SD (range of -1.8SD to 8.3SD); the mean weight was 1.1 SD (range of -1.8SD to 4.6SD) and the mean head circumference was 1.1SD (range of -1.7 to 3.7SD) (Figure 4).

Discussion

The aim of this study was to define the HIST1H1E syndrome phenotype in order to propose evidence-based management guidance. Through the detailed clinical evaluation of 30 patients with likely/pathogenic *HIST1H1E* variants, we have shown that an intellectual disability (most frequently moderate) and a characteristic facial gestalt are consistent HIST1H1E associations. Other frequent clinical findings include behavioral issues (especially anxiety); cryptorchidism; hypotonia; abnormal dentition; congenital cardiac anomalies; hypothyroidism; ectodermal findings and brain MRI findings (most frequently corpus callosum abnormalities). Contrary to the initial report, height and/or head circumference were not consistently increased >2SD. We propose the name **HIST1H1E** syndrome as an acronym to help remember the characteristic features of this emerging, recognizable phenotype: **H** for Hypotonia, **I** for Intellectual Disability (ID) with behavioral Issues, **S** for Skeletal, **T** for Testes (undescended) and Thyroid, **H** for Heart anomalies and **E** for Ectodermal issues (including sparse hair and abnormal dentition).

Based upon the current phenotypic evaluation, we suggest children with *HIST1H1E* variants are regularly reviewed by a pediatrician to assess development and determine appropriate referral to speech and language therapy and physical therapy; that children have a regular (at least six monthly) dental review to mitigate potentially preventable issues arising from abnormal dentition and that annual thyroid function tests are undertaken. Given the association with congenital cardiac anomalies, we propose a baseline echocardiogram investigation is undertaken with cardiology follow up dependent upon findings. Although *HIST1H1E* somatic variants have been associated with chronic lymphocytic leukemia as well as diffuse large B-cell lymphoma and hepatocellular carcinoma, these are more usually nonsynonymous variants distributed throughout the gene (Chang et al., 2019). None of the patients in this current clinical series developed

cancer. We do not therefore currently advocate specific tumor surveillance but any possible tumor related symptoms should be investigated.

The 14 *HIST1H1E* variants identified in the 30 patients, all cluster to 94 base pair region in the CTD tail of HIST1H1E. This replicates our initial finding that HIST1H1E syndrome variants are frameshift variants that generate a mutant protein with the same 38 amino acid tail, the result of the same shift in the reading frame (Tatton-Brown et al., 2017). To date, no patient with the HIST1H1E syndrome phenotype has been described with a *HIST1H1E* whole gene deletion, stop gain variant or frameshift variant that results in an alternate shift in reading frame (the latter is not predicted to be associated with a net reduction in charge, Tatton-Brown et al., 2017). In addition, none *HIST1H1E* frameshift variants reported in gnomAD cluster to the same 94 base pair region, nor do they result in the same shift in frame and the generation of a mutant protein with the common 38 amino acid tail. This suggests that the HIST1H1E syndrome phenotype is attributable to a specific set of variants with a defined effect on the protein. Our current working hypothesis is that, because *HIST1H1E* is a single exon, intronless gene, the *HIST1H1E* variants escape nonsense-mediated RNA decay and the resultant mutant HIST1H1E proteins are characterized by a reduced net positive charge compared to wild type proteins, potentially disrupting the normal binding between positively charged HIST1H1E and negatively charged DNA (Tatton-Brown et al., 2017). Further work is required to investigate this.

An important remaining question that our current study has not been able to answer is whether the underlying *HIST1H1E* genetic variant determines the range and severity of clinical features. Currently too few patients have been identified to perform robust genotype-phenotype analyses. However, as greater numbers of patients with the HIST1H1E syndrome are identified it will be interesting to further clarify the HIST1H1E phenotype, better delineate the spectrum of causative

HIST1H1E variants and investigate the relationship between genetic variant and clinical presentation.

Acknowledgements:

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Conflicts of Interest

The authors declare that they have no conflict of interest.

URLs

Uniprot: https://www.uniprot.org/

Facebook Parent Support Group: https://www.facebook.com/hist1h1e/

Genome Aggregation Database (gnomAD), https://gnomad.broadinstitute.org/

HIST1H1E reference transcript, https://www.ncbi.nlm.nih.gov/nuccore/NM_005321

OMIM, https://www.omim.org/

Protein calculator, http://pepcalc.com/protein-calculator.php

SMART: https://smart.embl.de

Protein Atlas (HIST1H1E): https://www.proteinatlas.org/ENSG00000168298-HIST1H1E/tissue

References

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 May 4;100(5):725-736. doi: 10.1016/j.ajhg.2017.03.010. PubMed PMID: 28475857; PubMed Central PMCID: PMC5420355.

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Figure Legends

Figure 1. Protein schematic showing the 94 base pair clustering of the 14 different protein truncating variants (each variant is designated by a red circle)

Figure 2. The key clinical features that characterize the HIST1H1E syndrome.

Figure 3. A) The facial gestalt consists of a high frontal hairline and full lower cheeks in early childhood and, in later childhood and adulthood, affected individuals have a strikingly high frontal hairline, bi-temporal narrowing, frontal bossing and deep-set eyes.

B) The evolving facial gestalt in three individuals at ages stated.

C) The dental phenotype includes erosions, thin enamel, crumbling teeth and multiple dental caries. Dental X-rays of an adolescent patient demonstrate thin enamel and short dental roots.

Figure 4. Growth parameters (with height on x axis and head circumference on y axis) plotted by standard deviation, calculated with reference to UK90 growth data. Although in individual patients, the height and/or head circumference might be increased above two standard deviations, in most patients the growth parameters cluster around the mean.

Supplementary Figure 1: Wild type and mutant HIST1H1E (generated by the 14 different *HIST1H1E* frameshift variants) showing the reduction in net charge of the carboxy terminal domain motif (from Lys110) at neutral pH7. Mutant proteins share a common 38 amino acid tail.

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ICR

Consent for Publication or Presentation of Photographs

Patient's full name: PETROVIC Pamela Stone	ICR Reference: COGO405
Address: A-5020 Salzburg, Goethestraße 13	Date of Birth: 19-03-02
Hospital Reference Number:	

☐ Adult, capable ☐ Minor ☒ Incapable of giving consent (**Stop, seek guidance**)

Name of Guardian: Petrovic Bronislaw (father)	Contact details:

Name and Title of Clinician Requesting Consent:

Univ.-Doz. Dr. Olaf Rittinger

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: Petrovic Bronislaw Print name: PETROVIC Bronislaw (father) Date: 31-03-15

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

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Consent for Publication or Presentation of Photographs

Patient's full name:	ICR Reference:
RONAN CLEARY	COG0412
Address: [illegible]	Date of Birth [illegible]
Hospital Reference Number: [illegible]	
☐ Adult, capable ☒ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Mrs Helen Cleary	Contact details: [illegible]
Name and Title of Clinician Requesting Consent: Dr Nora Stewart	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: [signature] Print name: [illegible] Cleary Date: 7.12.16

A translator or witness may sign here if a patient cannot read this form but indicates consent.
Signed: ..... Print name: ..... Date: .. ..

COG1832

Southampton NHS
University Hospitals NHS Trust

Wessex Clinical Genetics Service
G Level, Mailpoint 105
Princess Anne Hospital
Coxford Road
Southampton SO16 5YA

Tel: 023 8079 6170
Fax: 023 8079 4346
www.suht.nhs.uk/wcgs

WESSEX CLINICAL GENETICS SERVICE

CONSENT FOR PUBLICATION

I give permission for clinical details of me/my child to be used for publication by the Clinical Genetics team and I understand that the clinical details will be used for publication in a specialist genetics journal. I understand that most genetics journals are available to professionals in paper and electronic versions. The details used in genetics articles are anonymous.

Name of Person: Frederick Bull.

X **Your name:** Julia Mary Bull

X **Relationship to child:** Mother
(If applicable)

X **Signature:** Julia Bull

Consent explained by: I Karen Temple

Job Title: Prof Medical Genetics

Date: 5/12/16

Consent for Publication or Presentation of Photographs

Patient's full name: Bryce Robert Kennedy	ICR Reference:
Address: (Parents/Guardians) 5637 Clearwater Rd Baxter, MN 56425 USA	Date of Birth 10/6/1984
Hospital Reference Number:	
☒ Adult, capable ☐ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Mary Rumpho-Kennedy & Robert Kennedy	Contact details: (USA) 207-944-0469 mrumpho@gmail.com
Name and Title of Clinician Requesting Consent:	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: MEKennedy Print name: Mary E. Rumpho-Kennedy, guardian Date: 5/2/2017

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

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Consent for Publication or Presentation of Photographs

Patient's full name: **Xavier Jack Kitchin**	ICR Reference:
Address: 22 Elizabeth Street, Scottsdale Tas 7260	Date of Birth 28/4/2011
Hospital Reference Number: GF 55174	
☐ Adult, capable ☑ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Rebecca Kitchin	Contact details: 22 Elizabeth St Scottsdale Tasmania 7260 Australia
Name and Title of Clinician Requesting Consent: Prof. David Amor	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: RKitchin ..... Print name: Rebecca Kitchin. Date: 19/7/2017

A translator or witness may sign here if a patient cannot read this form but indicates consent.
Signed: ..... Print name: ..... Date: .. ..

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Consent for Publication or Presentation of Photographs

Patient's full name: Bonnie Bridget Odgers	ICR Reference:
Address: Carpinteria, CA	Date of Birth 09-09-2010
Hospital Reference Number:	
☐ Adult, capable X Minor ☐ Incapable of giving consent **(Stop, seek guidance)**	
Name of Guardian: Anna-Lisa and Scott Odgers	Contact details: 818-434-4556 cell phone
Name and Title of Clinician Requesting Consent:	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: Anna Lisa Odgers Print name: Anna-Lisa Odgers Date 11-27-17

A translator or witness may sign here if a patient cannot read this form but indicates consent.

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Patient's full name: Parker Greenberg	ICR Reference:
Address: 87 Cross Hwy Westport, CT 06880	Date of Birth 1/2/2016
Hospital Reference Number:	
☐ Adult, capable ☒ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Kimberly Greenberg	Contact details: 203-214-6877
Name and Title of Clinician Requesting Consent:	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: Kimberly Greenberg Date: 2/27/18

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Signed: ..... Print name: ..... Date: .. ..

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Patient's full name: Maren Eileen Nikkel	ICR Reference:
Address: 123 Windrush Lane Durham NC 27703	Date of Birth 02·02·2017
Hospital Reference Number:	
☐ Adult, capable ☒ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Julie C. Nikkel	Contact details: mother
Name and Title of Clinician Requesting Consent:	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: Julie C Nikkel Print name: Julie C Nikkel Date: 4/14/18

A translator or witness may sign here if a patient cannot read this form but indicates consent.
Signed: ..... Print name: ..... Date: .. ..

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Consent for Publication or Presentation of Photographs

Patient's full name: Ho SZE MAN	ICR Reference:
Address: G/F. Ho Pui Chuen. Tsuen Wan Hong Kong	Date of Birth: 30 June 1981
Hospital Reference Number: C 6123	
☐ Adult, capable ☑ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: SIN SO CHUN	Contact details: 852 90759101
Name and Title of Clinician Requesting Consent: Luk Ho MING	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: SIN SO CHUN Date: 4 May 2018

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: Luk Ho Ming Date: 4 May 2018

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Consent for Publication or Presentation of Photographs

Patient STMH T7701306 BARRETT Angel Honey Blossom 44 Salcombe Road Knowle BRISTOL BS4 1AQ NHS 654 095 8722 DOB: 01 May 2012 Cons ..... Female	ICR Reference:
Addres	Date of Birth 1/5/12
Hospital Reference Number:	

☐ Adult, capable ☑ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)

Name of Guardian: Lesley Laughlin	Contact details: as above address
Name and Title of Clinician Requesting Consent: Karen Low, Clinical Geneticist Bristol	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

X Signed: ..... Print name: LESLEY LOUGHLIN Date: 8/6/18

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

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G9 4744
To be SB

ICR

Consent for Publication or Presentation of Photographs

Patient's full name: BEN ALAN COLLINS	ICR Reference:
Address: 57 LOWTHER CRESCENT LEYLAND LANCS PR26 6QA	Date of Birth 22 DEC 1998
Hospital Reference Number: SB/SH/G9474431	
☐ Adult, capable ☐ Minor ☒ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: JUDITH COLLINS ALAN COLLINS	Contact details: 01772 465377 07779191858
Name and Title of Clinician Requesting Consent:	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: JACollins AR COLLINS Print name: JUDITH COLLINS ALAN COLLINS Date: 18/6/18

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

VUmc

Stichting Spaarne Gasthuis
Kindergeneeskunde
Dr. J. Goede
Spaarnepoort 1
2134 TM Hoofddorp

VUMC POLI KLINISCHE GENETICA
SPAARNE HOOFDDORP
Geen informatie opgeslagen.
Geen informatie opgeslagen.

Datum
29-05-18

Ons kenmerk

Betreft:
M. Suler, geb. 12-7-2006, gesl. vrouw, patnr. 6419109, BSN 262092839,
adres SEOELLN 6 2152 KK NIEUW VENNEP

Geachte collega,

Bovengenoemde patiënte zag ik op 17-5-2018 op VUMC POLI KLINISCHE GENETICA SPAARNE HOOFDDORP.

Reden van verwijzing
Herbeoordeling ontwikkelingsachterstand zonder diagnose.

Voorgeschiedenis
- Partus 41 wkn, GG 3635 gram (p50). Lengte 52 cm.
- Ontwikkelingsachterstand vastgesteld op 4-5 maanden. Lopen op 2,5 jaar. Spreekt woordjes.
- Hypotonie als baby met vaak verslikken en veel broncho-obstructieve klachten en luchtweginfecties in eerste 2,5 jaar.
- MRI hersenen (2010): vertraagde myelinisatie, atypische frontaal hoorn laterale ventrikels en lichte hypoplasie rostrum corpus callosum
- ASD II, spontaan gesloten bij cardiologische controle in 2012
- Periode van gewichtstoename en veel eten (2012). Nu gewicht genormaliseerd
- Strabisme operatie bdz, +8 afwijking.
- Veel caries
- Chronische buikpijn, obstipatie. Nu niet meer, geen forlax meer.
- Condylomata accuminata perianaal

Eerder verricht genetisch onderzoek (2007-2014):
Chromosomen onderzoek: 46,XX
Metabool onderzoek (AMC): geen afwijkingen.
Array 105k, array CGH 180k, SNP array: geen afwijkingen
FISH onderzoek naar Pallister-Killian op wangslijmvlies: geen afwijkingen.
DNA onderzoek naar Prader Willi syndroom (AMC): geen afwijkingen.
Whole exome sequencing (trio analyse gehele exoom) (2014): geen afwijkingen.

VUMC Boelelaan 1118 Postbus 7057 1007 MB Amsterdam Telefoon 020-4444444

Anamnese
Melissa zit nu op het ZMLK. Recente IQ test (SON 2,5-7 jaar) toonde nivo 4;6 en IQ<50. Ze is makkelijk, vrolijk en slaapt goed. Melissa heeft opvallende tanden, extreem wit en kegelvormige hoektanden, brokkelig. Ze heeft (bijna) alles gewisseld, het melkgebit is deels getrokken vw caries. Ze heeft dunne nagels die nauwelijks groeien. Ook het haar groeit bijna niet. Ze heeft snel ontstekingen van de huid (bij muggenbult, wondjes, oorbellen). Nadat de keelamandelen zijn verwijderd heeft ze geen (lage) luchtweginfecties meer gehad. Ze wel vaker en heftiger ziek dan anderen.

Familie anamnese
Tweede kind niet-consanguine ouders. Moeder heeft eenmaal een miskraam gehad.

Lichamelijk onderzoek
Lengte 147,6 cm (-1 SD). Schedelomtrek 56 cm (+1,4 SD).
Metingen op 14-3 -2018: Gewicht 47 kg (+0,9 SD); Lengte 146 cm (-1 SD); BMI 22 (+1,7 SD)
Craniofaciaal: hoge voorste haargrens, kleine ooglidspleten, diepliggende ogen, brede neusbrug, lichte wenkbrauwen, volle wangen.
Extremiteiten: tapering vingers, camptodactylie 3e vinger links (rechts status na correctieve operatie), dunne nagels (mn op tenen).

Aanvullend onderzoek
Herbeoordeling whole exome sequencin: de novo c.441dup; p.(Lys148Glnfs*48) (Chr6(GRCh37):g.26157059dup in HIST1H1E gen: in 2014 niet gemeld omdat onbekend gen. Inmiddels bekend gen, beschreven mutatie (Tatton-Brown et al 2017).

Bespreking
Melisa is bekend met een ontwikkelingsachterstand. Bij eerder genetisch onderzoek was er geen oorzaak gevonden. Herbeoordeling van de WES (uit 2014) toonde nu een mutatie in het HIST1H1E gen en hiermee is nu toch een diagnose gesteld bij Melissa.

<u>Diagnose Rahman syndroom</u>
Mutaties in het HIST1H1E gen zijn in 2017 voor het eerst beschreven en veroorzaken het Rahman syndroom. Er zijn nu wereldwijd 8 patiënten (oudste 21 jaar) met deze aandoening beschreven met de volgende kenmerken:

- Milde tot ernstige ontwikkelingsachterstand: lage spierspanning in eerste jaren, later lopen, beperkte spraak, verstandelijke beperking.
- Variabele overgroei (lengte, gewicht en/of schedelomtrek boven normaal) maar meestal na aantal jaar normale lengte.
- Gelaatskenmerken: hoge voorste haargrens, volle wangen, ogen ver uit elkaar (telecanthus/hypertelorisme), lichte wenkbrauwen.
- Sommige verschijnselen worden een enkele keer genoemd: strabisme (3 kinderen), milde afwijkingen op MRI hersenen (3), camptodactylie of clinodactylie (2), tapering van de vingers (1), (milde) scoliose (2), kwetsbaar gebit en dunne nagels (1), obstipatie (1), moeilijk gedrag (1), angsten (2), autisme (1).

De verschijnselen van Melissa passen goed bij deze diagnose. Melissa heeft ook afwijkende tanden, dunne nagels en langzaam groeiend haar (passend bij een ectodermale dysplasie). Dit is nog niet als duidelijk kenmerk beschreven bij Rahman syndroom maar hoort er waarschijnlijk wel bij.

<u>Overerving Rahman syndroom</u>
De HIST1H1E mutaties die Rahman syndroom veroorzaken zijn *autosomaal dominant*. Dat betekent dat één mutatie leidt tot de aandoening. De mutatie werd niet terug gevonden bij de ouders van

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Melissa en is dus nieuw (*de novo*) ontstaan. Daarom is de kans op dezelfde aandoening bij andere kinderen van ouders heel klein (1-2%)*. Ouders hebben geen verdere kinderwens.
Melissa's broer heeft de aandoening niet. Voor zijn kinderen is er daarom GEEN verhoogde kans op de aandoening van Melissa. Voor kinderen van Melissa zelf is er wel een kans van 50% op de aandoening.

Conclusie
Diagnose: Rahman syndroom ten gevolge van een *de novo* mutatie in het HIST1H1E gen.

Bij verdere vragen kan altijd contact worden opgenomen. Omdat er nu nog weinig bekend is over de aandoening, zie ik Melissa graag terug over 2-3 jaar om verdere ontwikkelingen in de kennis te bespreken.

** Meestal ontstaat een nieuwe mutatie in een van de geslachtscellen (zaadcel of eicel) waaruit het kind is gegroeid en is er geen kans op een volgend kind met dezelfde aandoening. Heel soms is de mutatie ontstaan in een voorloper cel van de zaadcellen of eicellen bij één van de ouders en dan kan er een volgend kind worden geboren met dezelfde aandoening. De kans op een volgend aangedaan kind is daarom 1-2% (1-2 op de 100).*

Met collegiale hoogachting,

Dr. J.M. Van de Kamp,
Klinisch geneticus

Cc:
B. BERNDSEN
Hugo De Vriesstraat 17
2152 CT Nieuw-Vennep
VIA Zorgmail

Ouders/verzorgers van M. Suler
Seoelln 6
2152 KK Nieuw Vennep
VIA Post

MREC 01/2/44
(Version 3, dated January 2018)

ICR

THE CHILDHOOD OVERGROWTH (COG) STUDY

ADULT/CHILD CONSENT FORM

Referring Hospital/Centre VUmc Dr van der kamp (clinical genetist)

Patient/Family Reference Number .....

Patient's name Melisa Suler

Name of legal guardian/next of kin Esther Suler

1. I confirm that I have read **and understand** the information sheet dated..... **(Version.....)** for the above study and have had the opportunity to ask questions.

2. I understand that my/**my child's** participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my/**my child's** medical care or legal rights being affected.

3. I understand **and give permission for** my/**my child's** medical records, photographs and/**or** pathology specimens **to** be looked at by responsible members of the research team **and their research collaborators. I have been assured that strict confidentiality will be maintained.**

4. I understand that information that might have implications for the medical care of my family may become available as a result of this research. I understand that any such information will be sent to the Doctor that referred **me/my child** to the study to be managed in accordance with standard medical practice. I understand that no results from the study will be sent directly to myself.

5. I agree to **my/my child's participation** in the above study.

Esther Suler	01-08-2018	Esther
Name of **Patient / Parent**	Date	Signature
Name of **Clinician obtaining** consent	Date	Signature

ENQUIRIES:
COG Team
phone: 020 8722 4099
fax: 020 8722 4359
email: grs@icr.ac.uk

Principal Investigator
Prof Nazneen Rahman
Institute of Cancer Research
15 Cotswold Road
Sutton, Surrey
SM2 5NG

1 copy for Patient, 1 for Principal Investigator, 1 for Hospital Notes

Division of Genetics & Epidemiology
The Institute of Cancer Research
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UNITED KINGDOM

Telephone: +44 (0)20 8722 4099
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ICR

Consent for Publication or Presentation of Photographs

Patient's full name: Melisa Süler	ICR Reference:
Address: Seeellaan 6 2152 kk nieuw-vennep nederland	Date of Birth 12-07-2006
Hospital Reference Number:	
☐ Adult, capable ☒ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Esther Süler	Contact details: esther.suler@live.nl 06-25143882
Name and Title of Clinician Requesting Consent: Dr van der kamp → VU mc 020-4444444 (telephone number)	Hospital:

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: Esther Süler Date: 12-07-2006 01-08-ug 2018

A translator or witness may sign here if a patient cannot read this form but indicates consent.
Signed: ..... Print name: ..... Date: .. ..

ICR

ADDITIONAL CLINICAL INFORMATION
HIST1H1E STUDY

COG ID

THIS FORM IS TO BE USED IN ADDITION TO THE STANDARD OVERGROWTH PROFORMA

(If you have not completed the standard overgrowth proforma, I would be grateful if you could complete and return this with the supplementary questionnaire).

PATIENT INFORMATION

Name..Melisa Siles.....dob..12-07-2006..~~male~~/female

CLINICAL INFORMATION

Please include additional clinical information that you consider relevant at the bottom of this questionnaire.

Most recent growth parameters

Measured 27-07-2018

Height..154..cm 12 year ~~0 months~~ age (months)

OFC..54..cm 12 age (months)

Weight..50,2 kg..cm 12 age (months)

Learning and behaviour

(melisa her iq is 50)

Current Learning disability Severe ☐ Moderate ☒ Mild ☐ None ☐

Autistic spectrum disorder Yes ☐ No ☒ Unknown ☐ Details.....

Any other behavioural/psychiatric problems including anxiety..no.....

Associated Clinical Features

Scoliosis Yes ☐ No ☒ Unknown ☐ Details.....

Joint laxity Yes ☐ No ☒ Unknown ☐ Details.....

Hypotonia Yes ☒ No ☐ Unknown ☐ Details.....

Seizures Yes ☐ No ☒ Unknown ☐ Details.....

Tumour Yes ☐ No ☒ Unknown ☐ Details.....

Loose, redundant skin Yes ☐ No ☒ Unknown ☐ Details.....

Thyroid disease Yes ☐ No ☒ Unknown ☐ Details.....

Dental problems Yes ☒ No ☐ Unknown ☐ Details.....

Puberty Early ☐ Late ☒ Average ☐ Not known ☐ melisa is 12 now and she has no physical development yet

Other clinical details .....

.....

Facial gestalt. Please describe your patient's facial features and send photos at different ages if possible/available.

eyes far apart, round face,.....

Investigations

Advanced bone age Yes ☐ No ☐ Unknown ☒ Details.....

MRI abnormalities Yes ☒ No ☐ Unknown ☐ Details..sorry I can't translate it in English

Form completed by.....**Date**.....

Other clinical details:

x hair hardly grows
x nails hardly grows
x skin is always very dry
x lazy eye
x crooked fingers (middle)
x toes are over each other
x poor visibility

Childhood Overgrowth (COG) Study
CLINICAL PROFORMA

PATIENT INFORMATION

Name Melisa Suler dob 12-07-2006 ~~male~~/female

Likely Diagnosis Hist1H1E

Consultant in charge of care Dr van der kamp – VU mc

GROWTH

Height 154 cm (age 12 yrs 0 months) (..... centile)

Head circumference 54 cm (age 12 yrs 0 months) (..... centile)

Weight 50,2 kg (age 12 yrs 0 months) (..... centile)

Mother's height 180 cm Father's height 183 cm

Mother's head circumference ~~57~~ 57,5 cm Father's head circumference 57 cm

ASYMMETRIC GROWTH

Is there asymmetry/hemihypertrophy?	Yes ☐	No ☐	Unknown ☒	
Which body parts are affected	Face ☐	Arm ☐	Leg ☐	Trunk ☐
Which side is bigger	Right ☐	Left ☐	Both ☐	Crossed ☐
What is the approximate size difference between the two sides	..... cm			
Is the asymmetry	Static ☐	Increasing ☐	Decreasing ☐	
Is the asymmetry	Mild ☐	Moderate ☐	Severe ☐	
Has debulking surgery been required?	Yes ☐	No ☐	Planned ☐	

Does the individual have learning difficulties? No ☐ Mild ☐ Moderate ☒ Severe ☐

Does the individual have behavioural problems? Yes ☐ No ☒ Unknown ☐

Please give details of behavioural problems.....

Is the individual dysmorphic? Yes ☐ No ☒ Unknown ☐

BIRTH, PREGNANCY AND NEWBORN PERIOD

Was the conception Natural ☒ Assisted ☐ Details.....

Duration of pregnancy 41 weeks Details of any complications no

Birth weight 3400 g (.....centile) Birth length 52 cm (.....centile)

Birth OFC ? cm (.....centile)

Were any of the following present in the neonatal period? The first year she choked a lot

Jaundice ☐ Hypoglycaemia ☐ Poor feeding ☒ Hypotonia ☒

Other ☒ please give details..... a lot of pneumonia the first year (and bronchitis)

OTHER CLINICAL FEATURES

Tumours Yes ☐ No ☒ Unknown ☐ Details.....

Cardiac anomalies Yes ☒ No ☐ Unknown ☐ Details..... ASD II (little hole in heart)

Genito-urinary anomalies Yes ☐ No ☐ Unknown ☒ Details.....

Neurological problems Yes ☐ No ☐ Unknown ☒ Details.....

Skeletal problems Yes ☐ No ☐ Unknown ☒ Details.....

Pigmentary abnormalities Yes ☐ No ☒ Unknown ☐ Details.....

Vascular abnormalities Yes ☐ No ☐ Unknown ☒ Details.....

Lumps (inc lipomata) Yes ☐ No ☐ Unknown ☒ Details.....

Other ☒ please give details..... x many caries in teeth
x squint eyes
x constipation (the first 4 years)

Please indicate if any of the following are present:

Macroglossia ☐ Omphalocoele ☐ Umbilical hernia ☐ Diastasis recti ☐

Nevus flammeus ☐ Ear creases/pits ☐

FAMILY HISTORY

Mother's name..... Esther Süler .....Mother's dob..... 13-09-1977

Father's name..... Koray Süler .....Father's dob..... 02-11-1975

Family History of				
	Learning difficulties	Yes ☐	No ☒	Unknown ☐
	Overgrowth	Yes ☐	No ☒	Unknown ☐
	Hemihypertrophy	Yes ☐	No ☐	Unknown ☐
	Cancer	Yes ☒	No ☐	Unknown ☐

If yes, please give details..... in both of the familys there has been cancer

INVESTIGATIONS. Please indicate the following results. If not performed, please leave blank. :

NSD1.....11p15.....

PTEN.....GPC3.....

Karyotype.....Array CGH.....

Telomeres.....**Other (inc bone age)**.....

?

Form completed by..... Esther Süler .....(please print name)

Contact details: telephone..... 06-25143282 ...email..... esther_suler@live.nl

Please include relevant clinic letters and laboratory reports

Division of Genetics & Epidemiology
The Institute of Cancer Research
15 Cotswold Road
Sutton, SM2 5NG
UNITED KINGDOM

Telephone: +44 (0)20 8722 4099
Email: grs@icr.ac.uk

ICR

Consent for Publication or Presentation of Photographs

Patient's full name: Alexander Jason LeBlanc	ICR Reference:
Address: 3 Dorothy E. Lucey Dr., Newburyport, MA 01950, U.S.A.	Date of Birth 05/30/08
Hospital Reference Number:	
☐ Adult, capable ☑ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Jason LeBlanc	Contact details: 978-473-9595 jleblanc234@yahoo.com
Name and Title of Clinician Requesting Consent: Tatton-Brown	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: Jason LeBlanc Date: 9/22/18

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

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Consent for Publication or Presentation of Photographs

Patient's full name: Anne Shirley Howlet	ICR Reference:
Address: 217 4th Avenue West, Owen Sound, ON N4K 4V1 CANADA	Date of Birth 14 September 200
Hospital Reference Number:	
☐ Adult, capable ☐ Minor X Incapable of giving consent (**Stop, seek guidance**) Andrew & Laura Howlett have P.O.A for Anne Howlett	
Name of Guardian: Laura Howlett	Contact details: 01(519)378-4161 laura@howlett.net
Name and Title of Clinician Requesting Consent:	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed:..... Print name:...Dr. Laura A Howlett.... Date:.....Sept 16, 2018.

A translator or witness may sign here if a patient cannot read this form but indicates consent. Signed: ..... Print name: ..... Date: .. ..

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Consent for Publication or Presentation of Photographs

Patient's full name: Matthew Eli Grushka	ICR Reference:
Address: 44 Ravenglass Crescent London, Ontario, Canada N6G4K1	Date of Birth July 25, 2015
Hospital Reference Number: London Health Sciences (London, Ontario, Canada): 11989378	
X Adult, capable ☐ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Daniel Grushka (Father)	Contact details: Email: dgrushk@uwo.ca Telephone: 519-673-8519
Name and Title of Clinician Requesting Consent: Dr. Kate Tatton-Brown	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: Daniel Grushka Date: Jan 31/2019

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

Consent for Publication or Presentation of Photographs

Patient's full name:	ICR Reference:
Corke Scarlett (Ms) 2 Whiting Close,Warren Row Reading Berks RG10 8ER Mob: 07756067543 Case #: **68462** PAS #: **4747735** Sex: F DoB: 28-Jul-04 NHS #: 706 068 0527 Pt # **133391** Tel: 01628316623	Date of Birth

☐ Adult, capable ☐ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)

Name of Guardian:	Contact details:
DAVID CORKE	07871 457791

Name and Title of Clinician Requesting Consent:

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: DAVID CORKE Date: 27/10/18

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

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UNITED KINGDOM

Telephone: +44 (0)20 8722 4099
Email: grs@icr.ac.uk

1159.17 ref

ICR

Consent for Publication or Presentation of Photographs

Patient's full name: BROHON LORENZO	ICR Reference:
Address: 9 LOTISSEMENT LA SOURCE 71470 MONTPONT EN BRESSE FRANCE	Date of Birth: 14 JUNE 2016.
Hospital Reference Number: CHU DIJON 21000	
☐ Adult, capable ☒ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: FONTANY SANDRA. BROHON NICOLAS.	Contact details: Mother and Father
Name and Title of Clinician Requesting Consent: Pr. Laurence OLIVIER-FAIVRE CHU DIJON FRANCE	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: ..... Print name: FONTANY SANDRA Date: 02.01.2019

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: Dr POIGNAND PATRICIA Date: 2.01.2019

MREC/01/2/44
(version 2, dated March 2005)

ICR

The Childhood Overgrowth Study
ADULT CONSENT FORM

REFERRING CENTRE .....

PATIENT / FAMILY REF NUMBER .....

I, FONTANY Sandra IN NAME OF MY SON BROHON LORENZO (name)

Of 9 LOTISSEMENT LA SOURCE (address)
71470 MONTPONT EN BRESSE FRANCE

1. confirm that I have read the information sheet dated 02.01.2019 for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that my medical records, photographs and pathology specimens may be looked at by responsible individuals from the research team. I give permission for these individuals to have access to these records.
4. I understand that information that might have implications for the medical care of my family may become available as a result of this research. I understand that any such information will be sent to the Doctor that referred my family to the study to be managed in accordance with standard medical practice. I understand that no results from the study will be sent directly to myself.
5. I agree to take part in the above study.

FONTANY SANDRA	02.01.2019	
Name of Parent / Guardian	Date	Signature
BROHON LORENZO (CHILD)	X	X
Name of Person taking consent	Date	Signature

ENQUIRIES:
COG Team
phone: 020 8722 4099
fax: 020 8722 4359
email: grs@icr.ac.uk

Principal Investigator
Prof Nazneen Rahman
Institute of Cancer Research
15 Cotswold Road
Sutton, Surrey
SM2 5NG

Our Ref ID

1 copy for Patient, 1 for Principal Investigator, 1 for Hospital Notes

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The Institute of Cancer Research
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ICR

Consent for Publication or Presentation of Photographs

Patient's full name: Isabella Wright	ICR Reference:
Address: 3549 Cast Palm Dr Buford, GA 30519	Date of Birth 07/29/2019
Hospital Reference Number:	
☐ Adult, capable ☑ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Madison Prickett	Contact details: phone: 678-775-9503 email: mprickett7010@gmail.com
Name and Title of Clinician Requesting Consent: Dr. Kate Tatton Brown	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: Madison Prickett Print name: Madison Prickett Date: may 2, 2019

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

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ICR

Consent for Publication or Presentation of Photographs

Patient's full name: Chaney Eleanor Ford	ICR Reference:
Address: 1695 Bogey St., Batesville, AR 72501	Date of Birth 11/26/16
Hospital Reference Number: White River Medical Center, Batesville, AR	
☒ Adult, capable ☐ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Georgeanne Ford	Contact details: 501-425-2942 ganneford@gmail.com
Name and Title of Clinician Requesting Consent: Kate Tatton-Brown	

For Patient or Guardian:

I have discussed the reason that photographs have been taken and have had a chance to see them and ask questions. I agree that clinical photographs and information related to my medical condition may be submitted and published in the medical literature. This may be in a printed or electronic format.

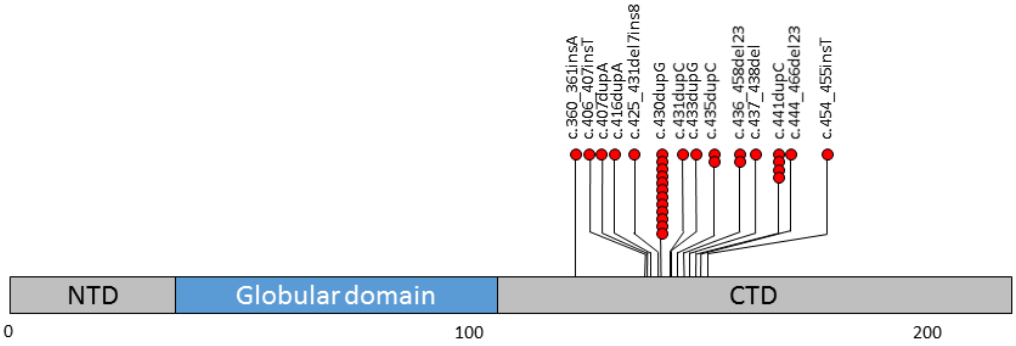
I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: Georgeanne Ford Print name: Georgeanne Ford Date: 2/6/19

A translator or witness may sign here if a patient cannot read this form but indicates consent.

Signed: ..... Print name: ..... Date: .. ..

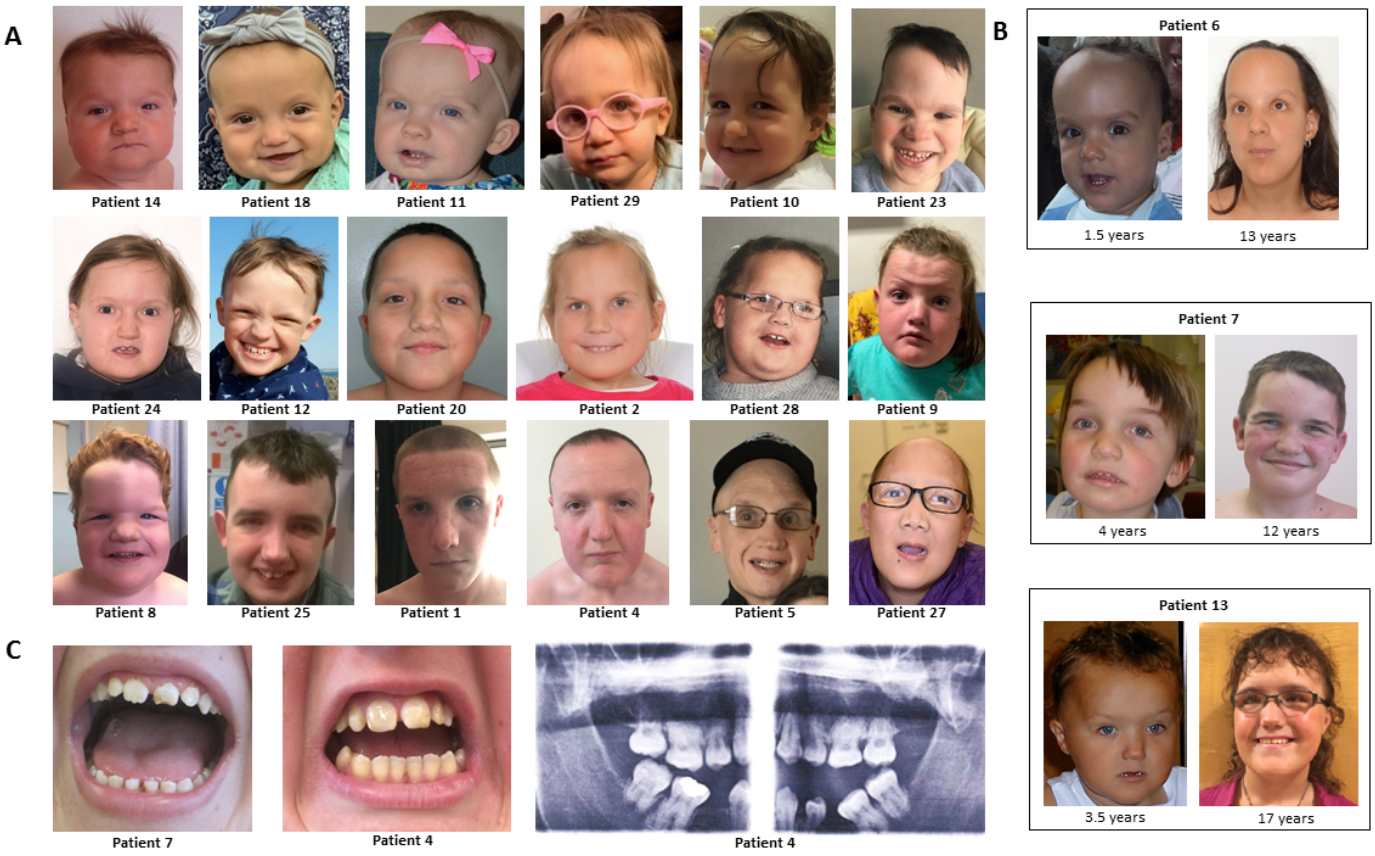


AJMGA_61321_Figure 1_revision.tif

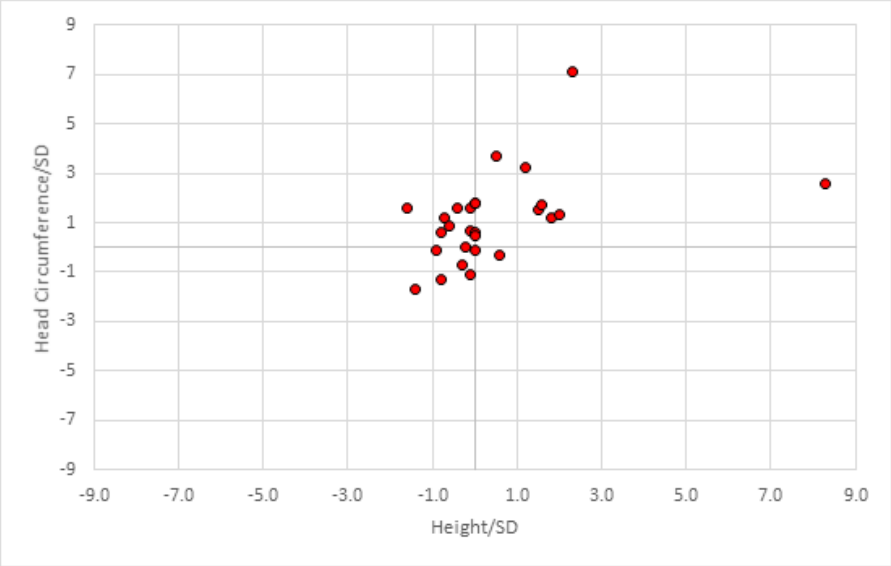
Patient Number	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16	Patient 17	Patient 18	Patient 19	Patient 20	Patient 21	Patient 22	Patient 23	Patient 24	Patient 25	Patient 26	Patient 27	Patient 28	Patient 29	Patient 30	Incidence
Gender	M	F	F	M	M	F	M	M	F	F	F	M	F	M	M	F	F	F	M	M	F	F	M	F	M	F	F	F	F	M	
Age (years)	15.2	nk	2.3	19.0	30.0	13.0	8.5	1.9	7.0	2.0	1.2	10.5	18.0	0.8	7.7	1.4	5.1	0.8	0.9	9.0	3.0	1.9	3.4	6.1	1.5	4.2	nk	12.0	1.5	3.6	
Facial gestalt																															100%
Intellectual disability	Mo	Mo	Mi	Mo	Mo	S	S	S	Mo	Mo	U	Mo	Mo	U	Mo	U	Mo	U	U	Mo	Mo	Mo	Mo	Mo	Mo	Mo	S	Mo	U	Mo	100%
Abnormal Brain MRI			nk	nk	nk	nk			nk		nk	nk			nk			nk			nk	nk			nk	nk	nk		nk		87%
Cryptorchidism		⁄	⁄			⁄			⁄	⁄	⁄		⁄			⁄	⁄	⁄			⁄	⁄		⁄		⁄	⁄	⁄	⁄		69% ♂
Hypotonia																															63%
Behavioral issues																															50%
Abnormal dentition						nk			nk	nk	nk								nk	nk		nk				nk					43%
Cardiac anomalies																															43%
Skeletal anomalies																															40%
Hypothyroidism				nk		nk				nk	nk	nk							nk		nk	nk	nk		nk	nk					25%

Key: Squares are shaded when feature is present. Squares are unshaded when feature is absent. Unshaded squares with oblique line represents female where cryptorchidism is not relevant.
Abbreviations: M=male, F=female; Mi, mild; Mo, moderate; S, severe; U, unclassified; nk, not known

AJMGA_61321_Figure 2_revision.tif



AJMGA_61321_Figure 3_revision.tif



AJMGA_61321_Figure 4_revision.tif