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The phenotype of Sotos syndrome in adulthood: a review of 44 individuals

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ABSTRACT

Sotos syndrome is an overgrowth-intellectual disability (OGID) syndrome caused by *NSD1* pathogenic variants and characterized by a distinctive facial appearance, an intellectual disability, tall stature and/or macrocephaly. Other associated clinical features include scoliosis, seizures, renal anomalies and cardiac anomalies. However, many of the published Sotos syndrome clinical descriptions are based on studies of children; the phenotype in adults with Sotos syndrome is not yet well described. Given that it is now 17 years since disruption of *NSD1* was shown to cause Sotos syndrome, many of the children first reported are now adults. It is therefore timely to investigate the phenotype of 44 adults with Sotos syndrome and *NSD1* pathogenic variants. We have shown that adults with Sotos syndrome display a wide spectrum of intellectual ability with functioning ranging from fully independent to fully dependent. Reproductive rates are low. In our cohort, median height in adult women is +1.9 SD and men +0.5 SD. There is a distinctive facial appearance in adults with a tall, square, prominent chin. Reassuringly, adults with Sotos syndrome are generally healthy with few new medical issues; however, lymphedema, poor dentition, hearing loss, contractures and tremor have developed in a small number of individuals.

Keywords

Overgrowth-intellectual disability syndrome; Sotos syndrome; adult phenotype

1. Introduction

Sotos syndrome (OMIM #117550) was first described in 1964 by Dr Juan Sotos (Sotos, Dodge, Muirhead, Crawford, & Talbot, 1964) and has an estimated incidence of 1 in 14,000 live births (Tatton-Brown, Cole, & Rahman, 2015). The cardinal clinical features of Sotos syndrome include a characteristic facial appearance, an intellectual disability and

overgrowth (defined as height and/or head circumference at least two standard deviations above the mean, ≥ +2.0 SD) (Cole & Hughes, 1994; Tatton-Brown et al., 2005). Most easily recognized in early childhood, the classical facial appearance consists of a tall forehead, frontal-temporal balding, downslanting palpebral fissures, malar flushing, long and narrow face, narrow jaw and a tall, broad chin (Allanson & Cole, 1996). Other major clinical associations, reported in at least 15% of individuals, include scoliosis, seizures, renal anomalies and cardiac anomalies (Tatton-Brown et al., 2005). The majority of individuals have advanced bone age (Cole & Hughes, 1994). Abnormalities on brain MRI scan, most frequently ventriculomegaly, are common (Schaefer, Bodensteiner, Buehler, Lin, & Cole, 1997).

Sotos syndrome is caused by *NSD1* heterozygous pathogenic variants (Kurotaki et al., 2002). *NSD1* is located at chromosome region 5q35 and encodes a histone methyltransferase that catalyzes the transfer of methyl groups to lysine residues of histone tails: more specifically lysine residue 36 of histone H3 (H3K36) and less frequently lysine reside 20 of histone H4 (H4K20) (Rayasam et al., 2003). These methylation marks are most frequently associated with transcriptional activation but can be associated with repression depending on the cellular context (Cao et al., 2002; Huang et al., 1998).

Although Sotos syndrome is a well-characterized overgrowth-intellectual disability (OGID) syndrome, the vast majority of studies have focused on the childhood clinical presentation and there are limited data on the evolution of the phenotype into adulthood (Fickie et al., 2011). In particular, there is debate around the final adult height and concerns about reproductive outcomes, new or progressive health problems in adulthood and experiences of day to day living. As it is 17 years since *NSD1* haploinsufficiency was shown to cause Sotos syndrome, many children diagnosed through genetic testing have now reached adulthood. It is therefore timely to undertake a study on 44 adults to clarify the adult presentation and optimize individual care for Sotos syndrome.

2. Methods

Editorial Policies and Ethical Considerations

The study was approved by the London Multicenter Ethics Committee (MREC01/02/44 and 05/MRE02/17). Informed consent for participating in the study was obtained for all participants.

Case series

44 adults with Sotos syndrome and a confirmed *NSD1* pathogenic variant were recruited including 17 males and 27 females. The age range of study participants was 18-48 years with a mean age of 30 years (supplementary table 1).

26 of the 44 individuals had previously been included, as children, in a study to clarify genotype-phenotype relationships in Sotos syndrome (Tatton-Brown et al., 2005). These individuals, now older than 18 years, were re-contacted to ask for their continued participation in the adult Sotos study. 18 individuals were identified through testing in the diagnostic laboratories within and outside of the UK.

Phenotype data were obtained through a clinic meeting (23 individuals) or a standardized clinical proforma- completed either by their Clinical Geneticist or individual/family member respectively (21 individuals). Clinical photographs with accompanying consent for publication were requested from all individuals and received from 17 families.

3. Results

The majority of study participants enjoyed good health. However, notable themes in adulthood included a variable intellectual disability; specific behavioral issues; differences in male and female growth patterns; puberty and reproduction and new and evolving medical problems. The full range of adult and childhood-onset clinical issues, growth and spectrum of intellectual disability is detailed in supplementary table 1.

Intellectual disability

The degree of intellectual disability was variable within the cohort, with eight individuals (18%) reported to have normal learning whilst 17 (39%) had a mild intellectual disability, 12 (27%) a moderate intellectual disability and seven (16%) a severe intellectual disability (table 1, figure 1).

All individuals reported to have normal learning were employed in a range of jobs including as a carer, barber and sales clerk or in vocational training courses including information technology, nursing and business studies (figure 1).

Nearly all (15/17, 88%) individuals with a mild intellectual disability were completely independent in self-caring (washing, brushing teeth and dressing, figure 1). 59% (10/17) felt unable or did not want to live away from the support of their families. Managing money and finances was an area of difficulty mentioned by 24% (4/17). Most (14/17, 82%) individuals with a mild intellectual disability were employed or engaged in vocational training in diverse fields including retail, painting/decorating, waitressing, health and social care, air stewarding and cleaning.

Only five (5/12, 42%) individuals with a moderate intellectual disability were independent in self-caring (figure 1) and two were in supported employment (shop assistant and office assistant). None of the adults with severe intellectual disability were self-caring or in employment; seven attended special educational needs colleges or day care and one was receiving 24 hour care.

Behavior

Nine adults (20%), all with a moderate or severe intellectual disability, had a diagnosis of autistic spectrum disorder. Other adult-onset behavioral/psychiatric issues included anger/aggression (seven individuals) and anxiety (manifesting as panic attacks and/or social avoidance (six individuals)). One adult with anxiety had co-existing depression and continued to take anti-psychotic medication commenced for an episode of psychosis at the age of 13.

Growth

Female adult growth

Female adult height ranged from -0.1 SD to +6.0 SD, with a median of +1.9 SD; weight ranged from -1.4 SD to +3.8 SD with a median of +1.7 SD and BMI ranged from -1.1 SD to +3.8 SD with a median of +1.2 SD. The head circumference ranged from +0.8 SD to +6.1 SD with a median of +2.7 SD (figure 2)..

Male adult growth

Male adult height ranged from –1.5 SD to +3.2 SD, with a median +0.5 SD; weight ranged from -1.3 SD to +3.1 SD with a median +1.0 SD and BMI ranged from -1.0 SD to +2.6 SD with a median of +1.2 SD (height and BMI data excluded one adult male with severe progressive scoliosis awaiting surgery (height –3.0 SD)). The head circumference ranged from +0.7 SD to +3.9 SD with a median of +2.4 SD (figure 2). .

Facial appearance

The facial appearance in adults with Sotos syndrome remained distinctive with downslanting palpebral fissures, high hairline and tall, broad chin (figure 3b). However, characteristic facial features of children with Sotos syndrome such as malar flushing and narrow jaw line were not evident in adulthood (figure 3a).

Puberty and reproductive issues

Menarche ranged from 7 years to 16 years with a median age of 13 years, comparable to the median age of 12.9 years in girls in the general UK population (Whincup, Gilg, Odoki, Taylor, & Cook, 2001). One girl required hormonal treatment to initiate puberty at the age of 14 years. Given that the onset of male puberty is harder to define, we used the age at which the voice broke as a proxy: this ranged from 11 to 17 years with a median age of 14 years. This is similar to the UK population, with the change in male voice in puberty occurring between Tanner stage 3 at a mean age of 12.9 years and Tanner stage 4 at mean

age of 13.8 years (Harries, Walker, Williams, Hawkins, & Hughes, 1997; Marshall & Tanner, 1970).

Four women in our cohort had children. The first had two children, neither of whom had Sotos syndrome. The second was diagnosed with Sotos syndrome in adulthood following the diagnosis in her monozygotic twins. She also had an unaffected child. The third conceived an affected child through in vitro fertilization for prolonged infertility and the fourth had four children, one of whom had inherited the *NSD1* alteration.

One man was known to have a low sperm count and did not have children. No other individuals reported planning to have children or infertility issues.

Associated medical problems

a) New medical problems

In general, adults with Sotos syndrome were healthy with few new medical issues. New medical problems reported in at least two adults included dental problems, hearing loss, aortic dilatation, contractures, lymphedema and tremor.

Dental problems

Dental problems were reported in seven adults (7/44, 16%): soft, worn or crumbling teeth (three individuals); absent and/or abnormal secondary dentition (four individuals) (table 1).

Hearing loss

Seven adults (7/44, 16%) had hearing loss, two of whom had recurrent ear infections, one with a cholesteatoma diagnosed age 25, one with degenerative changes of the eardrum and three with hearing loss of unspecified cause. Four individuals wore hearing aids.

Aortic dilatation

Four individuals had dilatation of the aortic root or ascending aorta (table 1). However, in two of these individuals (COG1878 and COG1918) the dilatation had resolved by their 30s/40s and the third individual (COG0622, previously reported by Robertson and Bankier

1999 and Hood et al. 2016) had a mild diffuse non-progressive dilatation of the ascending aorta for which he was treated with prophylactic beta blocker therapy (Hood et al., 2016). The fourth individual (COG2057) was diagnosed with borderline enlargement of the aortic sinus at the age of 47 that was not present on transthoracic echocardiogram at the age of 39. A repeat echocardiogram is planned in five years' time to assess for progression.

Contractures

Contractures affected four adults: one individual developed mild contractures of both elbows in adulthood, with no prior history of hypermobility (COG0030); a second developed hip and ankle contractures (with tight tendo-Achilles and hamstrings, COG0588) and two individuals developed bilateral camptodactyly (COG0045 and COG0254, table 1).

Lymphedema

Three individuals developed lower limb lymphedema in adulthood. One individual (COG2026) initially developed right leg swelling at the age of 32, shortly followed by swelling in the left. On examination, both legs were Stemmers positive and bilateral lymphedema was confirmed by lymphoscintogram. Testing of *FLT4* did not identify a gene variant causative of the lymphedema. The second patient (COG2057) developed bilateral lower limb lymphedema at the age of 21. This was treated with compression stockings and a lymphedema pump three hours per day. Whole exome sequencing did not identify a gene variant causative of the lymphedema. The third patient (COG) developed bilateral lymphoedema of the feet age 16. Of note, two of the individuals with lymphoedema (COG2057 and COG0721) also developed pericarditis: COG2057 developed pericarditis complicated by pericardial effusion at the age of 21. No specific cause was identified. She required admission to critical care for five days and subsequently developed lymphedema. COG0721 had myopericarditis at the age of 20, four years after the onset of lymphedema.

Tremor

Two of the individuals described with camptodactyly (COG0045 and COG0254) also developed progressive essential tremor (table 1). This impacted their ability to undertake everyday tasks such as eating, drinking, and dressing. One of these individuals was receiving symptomatic treatment with propranolol and clonidine. A third individual (COG2057) developed a progressive tremor in her early 30s with no current impact on function.

b) New complications of known Sotos syndrome medical associations

Scoliosis

Scoliosis is one of the most common Sotos syndrome medical problems, previously reported in one third of individuals (Tatton-Brown et al., 2005). Over half the adults (24/44, 55%) had scoliosis and/or kyphosis. All except one individual were diagnosed before age 16. Eleven individuals with scoliosis (11/24, 46%) required surgery. Three adults with surgically treated scoliosis developed severe chronic pain: the first needed a wheelchair to walk more than 100 meters and was being managed by orthopedics with joint injections; the second was receiving treatment with amitriptyline and the third adult had chronic leg pain, paresthesia, and breathlessness and was being managed by the neurosurgeons and pain team (table 1). All three had normal intellect or a mild intellectual disability and had left employment or training due to chronic pain.

Renal anomalies

A minority of individuals (8/44, 18%) had congenital renal anomalies, including combinations of hydronephrosis, pelvi-ureteric junction (PUJ) obstruction, hydroureters, renal agenesis, duplicated ureter, and/or posterior urethral valves. Two individuals with congenital renal anomalies developed hypertension: one in his early 20s with an absent right kidney and left sided hydronephrosis and hydroureter, and the other in her late 40s with a duplicated left ureter (surgically repaired) and recurrent urinary tract infections). In addition, one individual with posterior urethral valves required a long-term indwelling catheter (table 1). No individuals in the current study had chronic renal impairment.

4. Discussion

The results of this study describe important outcomes for adults with Sotos syndrome with regards to features of adult life including employment, independent living and reproductive status as well as growth parameters, long-term medical problems and any evolving medical issues.

There was a wide spectrum of independence, ability to self-care and employment status in our series. Of particular note, eight individuals were reported to have normal intellect, broadening our perception of the potential achievements of a small proportion of individuals with Sotos syndrome. Two of these individuals, including one adult who lived abroad for two years to attend a business course in a second language, had struggled academically in mainstream school. Autistic spectrum disorder was present in over 20% of adults with Sotos syndrome and may represent an area where additional support would be of benefit. Anxiety was also a key issue for some adults and increased recognition and support in this area may improve quality of life and independence for these individuals.

In contrast to childhood data but consistent with another study on adult Sotos syndrome (Fickie et al., 2011), our study identified a difference in the final height attained by men and women, with women frequently remaining tall (median height +1.9 SD) in adulthood whilst men are more likely to have a height within the normal range (median height +0.5 SD). One explanation for this male/female discrepancy would be if puberty were delayed in girls and/or early in boys. There was no evidence for this in the current series where puberty occurred within the normal range in both sexes. We also did not identify a difference in the incidence of untreated scoliosis between men and women which might explain the discrepancy in excess height. However, we must consider that data on parental heights are not available which would enable a more accurate assessment of excessive height for each individual. It is possible that by chance female individuals had taller than average parents and/or male individuals had shorter than average parents, influencing their target height.

Reproductive rates in our study were low. However, as this was a cohort of young adults with an average age of 30, it is possible that other individuals will go on to have children in the future. Fertility issues were reported in two individuals.

Reassuringly, this study did not highlight many new or evolving Sotos syndrome medical problems. Primary bilateral lower limb lymphedema developed in three individuals in our study, two of whom interestingly also developed pericarditis (chylous pericardial effusion is a known association of lymphedema). An additional adult with primary lymphedema has been reported in the literature (McClelland, Burgess, Crock, & Goel, 2016). In two of our cases and the case in the literature, sequencing of primary lymphedema genes did not identify causative gene alterations. It has been postulated that dysregulation of the MAPK/ERK signaling cascade is responsible for both Sotos syndrome and primary lymphedema (McClelland, Burgess, Crock, & Goel, 2016). However, until further functional studies and/or individuals with both diagnoses are identified, we will remain uncertain whether lymphedema is rare association of Sotos syndrome or a coincidental finding.

Of note, four study participants were reported to have a non-progressive aortic dilatation. In two of these individuals the dilatation appeared to resolve. In addition, as there are no published reports of morbidity or mortality related to aortic dilatation in individuals with Sotos syndrome, we therefore do not recommend routine echocardiograms screening for aortic dilatation.

One potentially new and important finding is that two adults had very similar patterns of progressive camptodactyly developing in teenage years followed by the appearance of a progressive bilateral tremor at the age of 20. Both affected individuals were unable to perform fine motor tasks important for activities of daily living. As only two adults had these symptoms it is not possible to be certain whether these findings were related to Sotos syndrome, but it is a distinctive and rare pattern that may constitute a new complication of this condition in adulthood. Another individual in our study, and another adult with Sotos in the literature (McClelland, Burgess, Crock & Goel 2016) developed a

tremor without camptodactyly, suggesting that tremor may be an independent association of Sotos syndrome in adulthood.

Scoliosis remained an issue for a small number of individuals who had chronic pain. The development of a cholesteatoma in one individual and degenerative changes of the ear drum in another suggests that specific enquiry should be made about new onset hearing loss when reviewing adults with Sotos syndrome in the clinic. Attendance at routine dental check-ups is advised as is regular blood pressure measurement to monitor for hypertension, particularly if an individual has had a congenital renal anomaly.

Of note and given previous suggestions that Sotos syndrome may be associated with an increased tumor susceptibility (Lapunzina 2005), none of the individuals developed tumors in adulthood. Taken together with the now widely reported very low absolute risk of tumors in childhood, we conclude that there is little evidence to support increased tumor surveillance in Sotos syndrome.

The current study has helped to clarify the clinical presentation of Sotos syndrome in adulthood. However, there remain unanswered questions. For instance, it is still not clear whether there are infertility/reproductive issues in Sotos syndrome that may account for so few families familial cases. In addition, there are limited data on the natural history of the aortic dilatation. Finally, whilst this is a study into adulthood, only 19 individuals were > 30 years old and only seven were > 40 years old. We therefore still do not know whether additional clinical problems develop in late adulthood. We will continue to follow the current cohort of individuals as they grow older to address these queries and provide information for individual and families as well as the health care professionals who are involved in transition care of individuals with Sotos syndrome.

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Conflicts of Interest

The authors declare that they have no conflict of interest

Web Resources

Mendelian Inheritance In Man, www.omim.org

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Tables

Table 1 Learning, behavior, new medical issues and complications of known Sotos syndrome clinical associations described in at least two adults with Sotos syndrome

Clinical Feature	Number of affected patients	Percentage of affected patients
Intellectual disability		
None	8	18%
Mild	17	39%
Moderate	12	27%
Severe	7	16%
Behavior		
Autistic spectrum disorder	9	20%
Anger/aggression	7	16%
Anxiety	6	14%
New medical issues		
Aortic dilatation	4	9%
Contractures	4	9%
Tremor	3	7%
Lymphedema	3	7%
Dental issues	7	16%
New complications of known medical associations		
Chronic pain following scoliosis surgery	3	7%
Long term complications of congenital renal anomalies	3	7%

Figure legends:

Figure 1 The range of Intellectual disability related to ability to self-care in adults with Sotos syndrome

Figure 2 The range of height and head circumference in standard deviation (SD) in women and men with Sotos syndrome

Figure 3 A) The evolving facial appearance from childhood to adulthood and **B)** the adult facial appearance in Sotos syndrome

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Consent for Publication or Presentation of Photographs

Patient's full name: THOMAS WHITE	ICR Reference: COG 0030
Address: FLAT 6, FANAD HOUSE, 85 GRAVELLY HILL NORTH, ERDINGTON, BIRMINGHAM	Date of Birth: 9/2/85
Hospital Reference Number: CGH 913.0	

☐ Adult, capable ☐ Minor ☑ Incapable of giving consent (**Stop, seek guidance**)
Verbal agreement from Thomas. His mother and care worker both agreed Thomas would be happy for his photograph (face only) to be published.

Name of Guardian: MOTHER – DENISE WHITE	Contact details: 07964 573 719

Name and Title of Clinician Requesting Consent:
DR AWON FOSTER, ST5 CLINICAL GENETICS

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: ..... Print name: DENISE WHITE Date: 20.2.15

CONSULTEE (CARE WORKER) AGREEMENT:

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

Signed: ..... Print name: MICHELLE FLYNN Date: 20.2.15

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Consent for Publication or Presentation of Photographs

Patient's full name: RYAN BENNETT	ICR Reference:
Address: 86a School Rd Wales Sheffield S26 5QJ	Date of Birth: 3.10.84
Hospital Reference Number:	

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

Name of Guardian: Sharon Harrold.	Contact details: 01909 771402
Name and Title of Clinician Requesting Consent: Alison Fosker. SpR.	

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: S.G. Harrold Print name: S.G. Harrold Date: 24.10.15

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

Signed: A.K. Print name: Alison Fosker Date: 24.10.15

Division of Genetics & Epidemiology
The Institute of Cancer Research
15 Cotswold Road
Sutton, SM1 2TD
UNITED KINGDOM

Telephone: +44 (0)20 8722 4155
Email: grs@icr.ac.uk

ICR

Consent for Publication or Presentation of Photographs

Patient's full name: MIMI WASSELL	ICR Reference: COG 0079
Address: 2 SION HILL, KIDDERMINSTER, WORCS DY10 2XS	Date of Birth: 8/12/93
Hospital Reference Number: CGH 7890.0	

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

Name of Guardian: MARIA WASSELL	Contact details: 2 SION HILL, KIDDERMINSTER, DY10 2XS
Name and Title of Clinician Requesting Consent: DR ANSON POSTER	

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: M Wassell ..... Print name: M. WASSELL Date: 26-2-15.

Verbal consent given by Mimi Wassell. Written consent from her mother.

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: CLARE EDWARDS	ICR Reference: COG0082
Address: 27 PATTERDALE STREET, BURSLEM, STOKE ON TRENT	Date of Birth: 14/09/1989
Hospital Reference Number: 4464.0	

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

Name of Guardian: NEIL EDWARDS	Contact details: 01782 824054

Name and Title of Clinician Requesting Consent:
DR ALISON FOSTER, REGISTRAR CLINICAL GENETICS

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: NEIL EDWARDS

Signed: C. Edwards Print name: ..... Date: 29/4/15

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

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

8943

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ICR

Consent for Publication or Presentation of Photographs

Patient's full name: TAYLOR BURGESS	ICR Reference:
Address: 30 Mitchell Place Falkirk.	Date of Birth: 17/4/80.
Hospital Reference Number:	

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

Name of Guardian: Ann Morrow.	Contact details:

Name and Title of Clinician Requesting Consent: SHOLAH TOSS.

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: T. BURGESS Print name: TAYLOR BURGESS Date: 15/8/14.

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

Signed: A.M.Morrow Print name: Ann M. Morrow Date: 15/8/14.

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

Hospital Reference Number:

ICR

The Childhood Overgrowth Study
ADULT CONSENT FORM

REFERRING CENTRE BIRMINGHAM

PATIENT / FAMILY REF NUMBER .....

I, JANE BRUSSALIS (name)

Of 67 STELVIO PARK ROAD, NEWPORT, GWENT, NP20 3ES (address)

1. confirm that I have read the information sheet dated .....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.

JBRUSSALIS	24-2-16	J Brussalis
Name of Parent / ~~Guardian~~	Date	Signature
ALISON FOSTER	29.2.16	A. Foster
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

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: ETHAN BRUSSALLS	ICR Reference:
Address: 67 STELVIO PARK ROAD, NEWPORT, GWENT, NP20 3RS	Date of Birth: 26.01.95
Hospital Reference Number:	
☐ Adult, capable ☐ Minor ☑ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: JANE BRUSSALLS	Contact details: 07720777758
Name and Title of Clinician Requesting Consent: DR ALISON FOSTER STS	

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: ..... Print name: J BRUSSALLS Date: 24-2-16.

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: Lukasz Wojniak	ICR Reference:
Address:	Date of Birth: 1/4/81
Hospital Reference Number: CF 10982	

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

Name of Guardian:	Contact details:

Name and Title of Clinician Requesting Consent: E. Thompson (A/ Prof ; clinical geneticist)

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: ..... Print name: LUKASZ WOJNIAK Date: 24/11/1(

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

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

SA Clinical Genetics Service

THIS FORM IS TO BE USED ONLY BY STAFF & CLIENTS OF THE SACGS IN THE COURSE OF CARE PROVIDED BY THIS SERVICE.

SA PATHOLOGY

Consent for Medical Photography and Publication

In reply, please quote GF 11498

Patient name: Katelynn Meagher DOB: 9/2/99 Date: 24.4.17

☐ Tick here if patient is a minor or unable to provide consent for themselves, and complete the shaded box below

By signing this form below I confirm that this consent form has been explained to me in terms which I understand.

1) I consent for medical photographs to be made of my child and stored in my child's medical record.

Yes ☒ No ☐ (please tick to indicate your choice) ..... (Signature)

2) I consent to my child's photographs and relevant medical information being shown to health professionals for the purpose of assisting in my child's medical care.

Yes ☒ No ☐ (please tick to indicate your choice) ..... (Signature)

3) I consent to my child's photographs and relevant medical information being shown to doctors and other health professionals for teaching purposes.

Yes ☒ No ☐ (please tick to indicate your choice) ..... (Signature)

4) I consent to my child's photographs and relevant medical information being used in medical publications, including medical journals, textbooks, and electronic publications. I understand that the main purpose of publication is professional education, to share information and experience with health care professionals, and to stimulate research. I understand that the photographs and information may be seen by members of the general public. I also understand that although the photographs and information will be used without identifying information such as my child's name, it is possible that someone may recognise my child.

Yes ☒ No ☐ (please tick to indicate your choice) ..... (Signature)

5) I understand that declining to consent to publication will not affect the medical care my child receive(s). I understand that I will not receive payment for the photographs. I am aware that if I have any questions or wish to withdraw my consent in the future I may contact the SA Clinical Genetics Service (phone numbers below).

..... (Signature)

FOR PATIENTS UNDER 16 OR UNABLE TO PROVIDE CONSENT

Please complete as appropriate (A for all patients where proxy- consent is given and B if patient is able to assent)

A) Full name of person giving proxy-consent ..... Susan A Meagher

Relationship to patient ..... mother

B) **Statement of assent:** the signature below indicates that the information in this consent form has been explained to me, and that I agree to my photos and information being used as outlined above:

..... (Patient's signature) 24.4.17 date

Full name and signature of witness ..... Patrick Meagher .....

If you have further questions, please contact us on the relevant telephone number below.

Paediatric and Reproductive Genetics Unit	Adult Genetic Unit	Metabolic Clinic
08 8161 7375	08 8161 6995	08 8161 7295

FOR-3520a; version date 01 May 2013

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ICR

Consent for Publication or Presentation of Photographs

Patient's full name: MR STEPHEN THOMPSON	ICR Reference: CGS 0255
Address: 27 MERRITTS BROOK LANE	Date of Birth: 15. 01. 1997
Hospital Reference Number: CGU 20060.0	

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

Name of Guardian: CELIA THOMPSON	Contact details: 27 MERRITS BROOK LANE NORTHFIELD, BIRMINGHAM B31 2LUH
Name and Title of Clinician Requesting Consent: DR ALISON FOSTER	

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: Mrs C Thompson .... Print name: MRS CELIA THOMPSON Date: 26.2.2015

Both parents agree to consent to publication of photographs.

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

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

In partnership with:
The ROYAL MARSDEN
NHS Foundation Trust

Division of Genetics & Epidemiology
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UNITED KINGDOM

Telephone: +44 (0)20 8722 4155
Email: grs@icr.ac.uk

ICR

Consent for Publication or Presentation of Photographs

Patient's full name: AARON INGLES	ICR Reference:
Address: 2 OFFENHAM ROAD, EVESHAM WORCESTERSHIRE WR11 5DY	Date of Birth: 7/7/99
Hospital Reference Number: CGU 32295.0	

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

Name of Guardian: KAREN INGLES, SCOTT INGLES	Contact details: tel 01386 40733
Name and Title of Clinician Requesting Consent: AARON FOSTER REGISTRAR CLINICAL GENETICS	

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: ..... Print name: KAREN INGLES Date: 24/8/15

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: MARK HEATH	ICR Reference: 4
Address: 212 WHITCHURCH RD	Date of Birth: 13/03/1989
Hospital Reference Number: 20780.0	

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

Name of Guardian:	Contact details:

Name and Title of Clinician Requesting Consent: DR ANSON FOSTER REGISTRAR CLINICAL GENETICS

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: M Heagh Print name: M Heagh Date: 24/4/15

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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ICR

Consent for Publication or Presentation of Photographs

Patient's full name: JILL CRAMMAN	ICR Reference:
Address: 91, GROSVENOR ROAD SOUTH SHIELDS Tyne Wear	Date of Birth: 30.3.83
Hospital Reference Number:	
☐ Adult, capable ☐ Minor ☑ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: M. I. CRAMMAN	Contact details: 07905269572
Name and Title of Clinician Requesting Consent: ALISON FOSTER REGISTRAR	

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: ....M. J. Cramman.... Print name: ....M. I. CRAMMAN.... Date: ..6/11/15..

A translator or witness may sign here if a patient cannot read this form but indicates consent.
Signed: ....[signature].... Print name: ....ALISON FOSTER.... Date: ..6.11.15..

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UNITED KINGDOM

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ICR

Consent for Publication or Presentation of Photographs

Patient's full name: KATE LIDDLE	ICR Reference:
Address: 64 INVERNESS STREET	Date of Birth: 6.7.99
Hospital Reference Number:	

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

Name of Guardian: MRS. SONIA LIDDLE	Contact details: 07840968695 01915498334

Name and Title of Clinician Requesting Consent: ALISON FOSTER REGISTRAR

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: S. Liddle K. Liddle Print name: S. LIDDLE Date: 6/11/15

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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UNITED KINGDOM

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ICR

Consent for Publication or Presentation of Photographs

Patient's full name: LAWRENCE OWEN HAGUE	ICR Reference: ?
Address: FLAT 2, JAMES WALKER MEWS WITNEY, OXFORDSHIRE	Date of Birth: 19 MARCH 1979
Hospital Reference Number: CASE NO. 2643 DEPT OF CLINICAL GENETICS, CHURCHILL HOSPITAL, OXFORD	
☑ Adult, capable ☐ Minor ☐ Incapable of giving consent (Stop, seek guidance)	
Name of Guardian:	Contact details:
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.

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

Patient ~~or Guardian's~~ Consent:

Signed: ..... Print name: LAWRENCE OWEN HAGUE Date: 21 JUNE 2016

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: Helen Maher	ICR Reference:
Address: 47, Wheeler Rd.	Date of Birth: 16.8.73.
Hospital Reference Number: G 108439.	
☐ Adult, capable ☐ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Gillian Maher.	Contact details:
Name and Title of Clinician Requesting Consent: Dr Kate Tutton-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: Gillian Maher Print name: GILLIAN MAHER Date: 20 Jul 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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UNITED KINGDOM

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Consent for Publication or Presentation of Photographs

Patient's full name: Milo Balk	ICR Reference:
233 Villeneuve W Montreal Quebec H2T 2R8	24 aug 2001
Hospital Reference Number:	
☐ Adult, capable ☐X Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Pamela Reimer	see address reip@videotron.ca
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:……..Pamela Reimer…….
Date:..……18 Feb 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: Kelsey Ann Weick	ICR Reference:
Address: 22141 W. Vernon Ridge Drive Mundelein, IL 60060 USA	Date of Birth 06-17-1991
Hospital Reference Number:	
☐ Adult, capable ☐ Minor ☐ Incapable of giving consent (**Stop, seek guidance**)	
Name of Guardian: Joanne Weick	Contact details: JoanneWeick59@gmail.com Cell 1(630)240-9742
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.

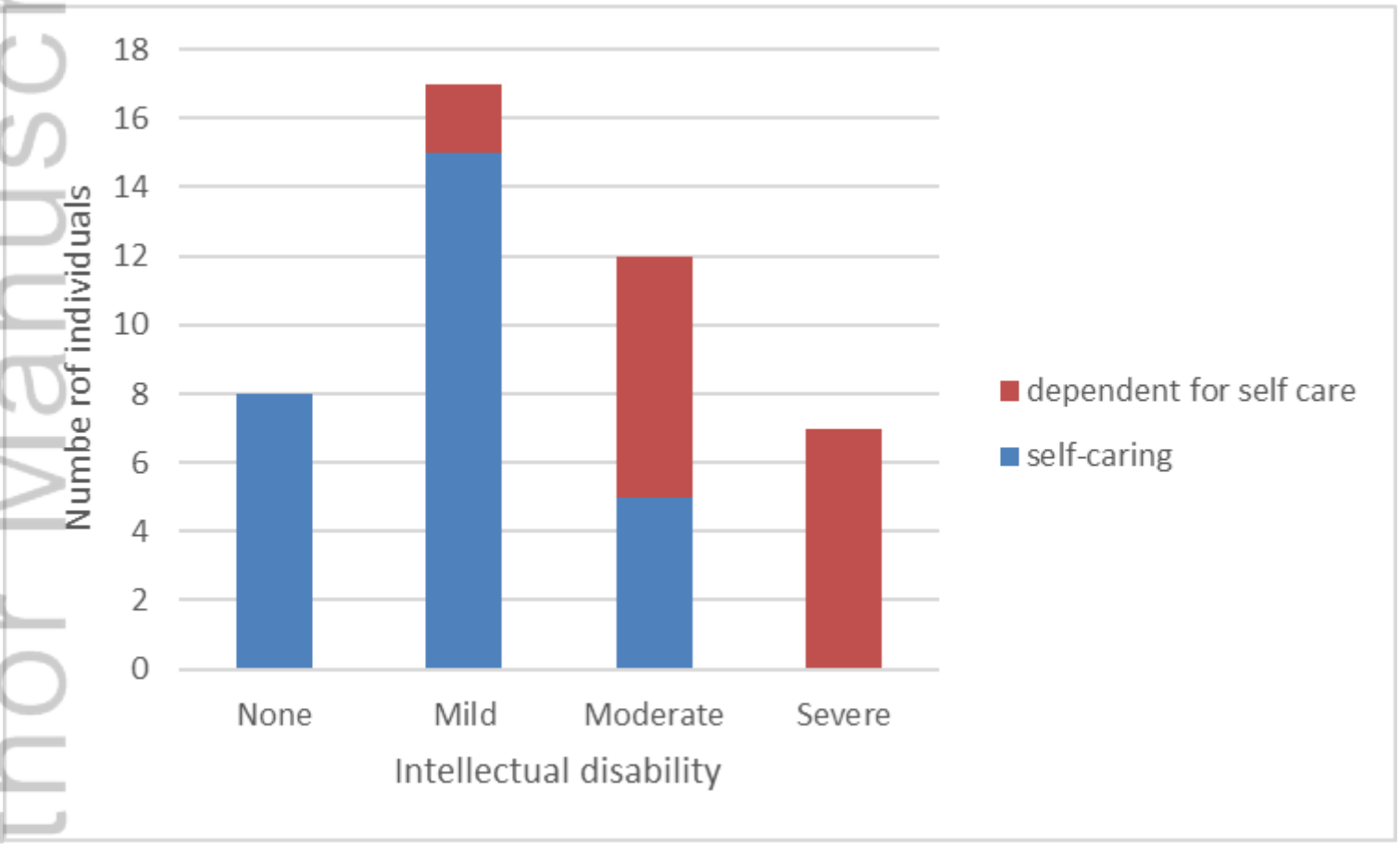
I understand that my name will NOT be published under any circumstances.

Patient or Guardian's Consent:

Signed: Joanne Weick Print name: Joanne Weick Date: 3-3-2019

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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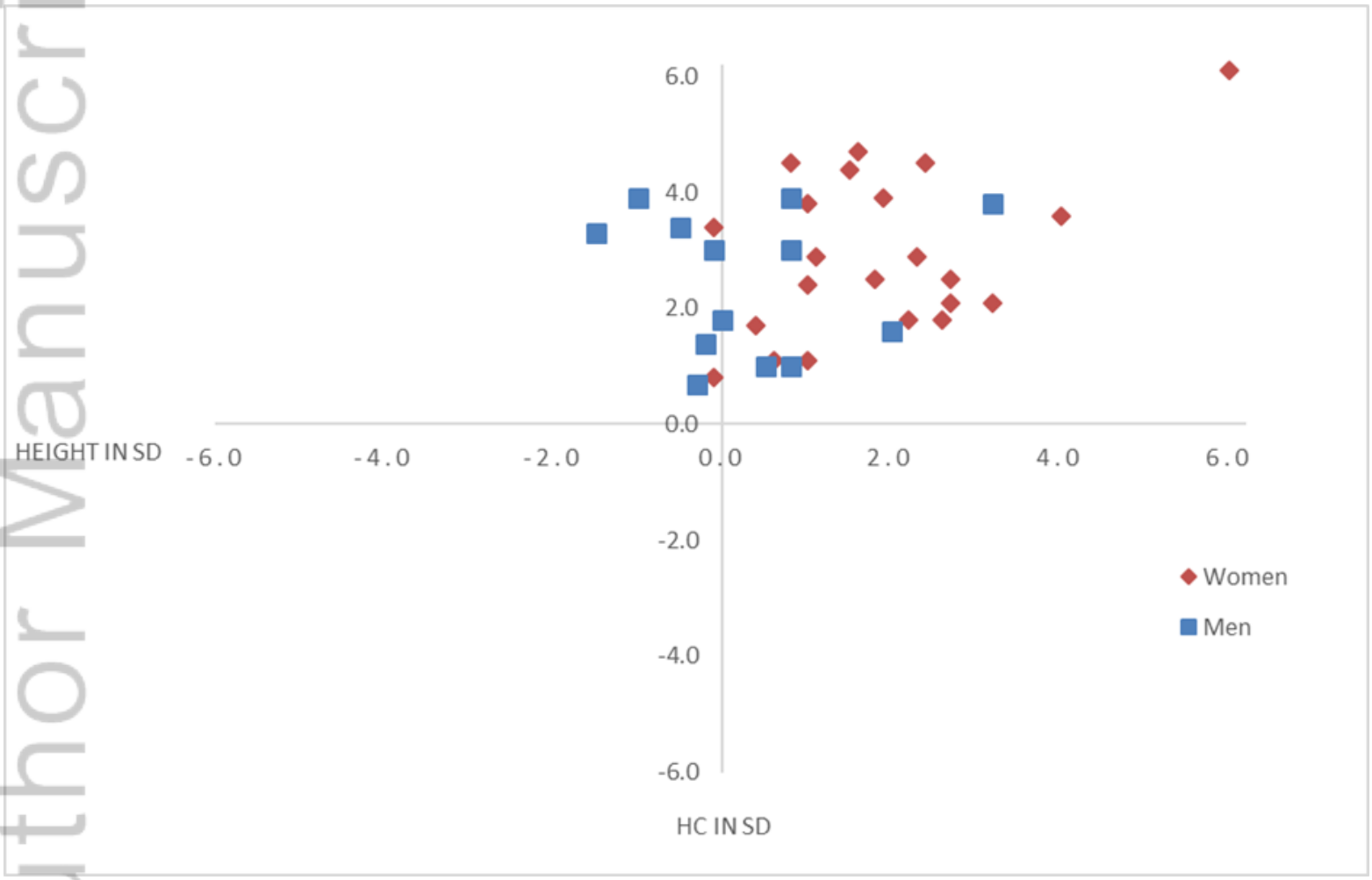

AJMGC_31738_Figure 2 TIFF.tiff

AJMGC_31738_Figure 3 TIFF.tiff

Author/s:
Foster, A; Zachariou, A; Loveday, C; Ashraf, T; Blair, E; Clayton-Smith, J; Dorkins, H; Fryer, A; Gener, B; Goudie, D; Henderson, A; Irving, M; Joss, S; Keeley, V; Lahiri, N; Lynch, SA; Mansour, S; McCann, E; Morton, J; Motton, N; Murray, A; Riches, K; Shears, D; Stark, Z; Thompson, E; Vogt, J; Wright, M; Cole, T; Tatton-Brown, K

Title:
The phenotype of Sotos syndrome in adulthood: A review of 44 individuals

Date:
2019-12-01

Citation:
Foster, A., Zachariou, A., Loveday, C., Ashraf, T., Blair, E., Clayton-Smith, J., Dorkins, H., Fryer, A., Gener, B., Goudie, D., Henderson, A., Irving, M., Joss, S., Keeley, V., Lahiri, N., Lynch, S. A., Mansour, S., McCann, E., Morton, J. ,... Tatton-Brown, K. (2019). The phenotype of Sotos syndrome in adulthood: A review of 44 individuals. AMERICAN JOURNAL OF MEDICAL GENETICS PART C-SEMINARS IN MEDICAL GENETICS, 181 (4), pp.502-508. https://doi.org/10.1002/ajmg.c.31738.