Manchester Rare Conditions Centre

MANCHESTER ESHG

SYNDROMOLOGY AND DYSMORPHOLOGY COURSE 2026

14–16 October 2026 • The Manchester Museum, Oxford Road, Manchester M13 9PL

ESHG The European Society of Human Genetics

Under-and overgrowth syndromes

Sofia Douzgou Houge

NORWEGIAN CENTRE FOR RARE DISEASES

HELSE BERGEN

Background – *the natural history of human growth*

- Infancy: predominantly regulated by nutrition
- Mid-childhood: growth hormone, IGF1 and thyroid hormones
- Pubertal growth: regulated by sex steroids (occurs only in humans)
- Adult height potential: mainly genetic determinants (70-90%) (modulated by nutrition, endocrine and metabolic factors) - sex adjusted mid-parental height

- Skeletal maturation (ossification): bone age (non-dominant hand)



Undergrowth

- **Definition**
  - An attained somatic size and/or growth rate below that expected for age, sex, gestational age, population and genetic potential
  - Undergrowth is broader than short stature

- **(Conventional) Standard**
  - Length/height and/or weight and/or (sometimes) head circumference < -2 SDS

- **Growth failure**
  - A progressive decline in height SDS or growth velocity
  - Crossing downward growth centiles
  - Height substantially below the sex-adjusted mid-parental target range

Dauber et al, 2026

- IVF pregnancy
- Birth W <3rd, L 3rd centile and OFC 75th centile
- 13 months W 50th, L 10-25th and OFC 90th centile
- 1.5 cm discrepancy in leg length
- Feeding difficulties (multiple meals and nasogastric feeding)
- Walked unaided by 15 months



Douzgou S, pers obs

Russell Silver syndrome

- LBW
- OFC in normal range
- Pseudohydrocephalus
- asymmetry
- triangular face
- downturned mouth
- blue sclerae
- clinodactyly 5th finger
- Fasting hypoglycemia 24%-29%
- Excessive sweating w/ or w/o hypoglycemia has been reported in up to 67% of affected persons.



The Dian Donnai Dysmorphology archive

Russell Silver syndrome

Table 1.

Molecular Genetic Testing Used in Silver-Russell Syndrome

Method	Pathogenic Variants/Alterations Detected		Proportion of SRS Alterations Detected [1]
Methylation analysis [2]	Chr 11	Loss of methylation at *H19/IGF2* (paternal) [3]	~35%-67% [4]
		Somatic mosaicism for upd(11)mat [5, 6]	Rare
		Duplication of 11p15.5 (maternal)	Unknown [7, 8]
	Chr 7	upd(7)mat [9]	~7%-10% [10]
		Deletions, duplications, mosaic trisomy 7	Rare [11]
Chromosomal microarray analysis (SNP based)	Chr 11	Duplication of 11p15.5 (maternal)	Unknown [7, 8]
		Somatic mosaicism for upd(11)mat [5, 6]	Rare [12]
	Chr 7	Deletions, duplications of 7p, mosaic trisomy 7	Rare [11, 13, 14]
		upd(7)mat	Maternal isodisomy 7 only [15]
STR marker analysis	Chr 11	Somatic mosaicism for upd(11)mat [5, 6]	Rare
	Chr 7	upd(7)mat [9], maternal mosaic trisomy 7	~7%-10% [10]
Karyotype	Inversion or translocation of 11p15.5		Rare [5, 6]
Sequence analysis [16] / gene-targeted deletion/ duplication analysis [17]	*CDKN1C* (maternal transmission)		Rare [18]
	IGF2 (paternal transmission)		Rare [19]
	PLAG1		Rare [20]
	HMGA2		Rare [21]
Unknown			30%-40% [22]

Gene Reviews

Reduced IGF2-mediated growth signalling: the principal mechanism of 11p15-related SRS

Wakeling et al, 2026

- Hypotonia
- Developmental delay
- Poor weight gain
- Irritability
- Tremors
- Sweating



Douzgou S, pers obs

Allan-Herndon-Dudley syndrome (AHDS)

SLC16A2 (NM_006517.3) c.662G>A, p.(Gly221Glu)

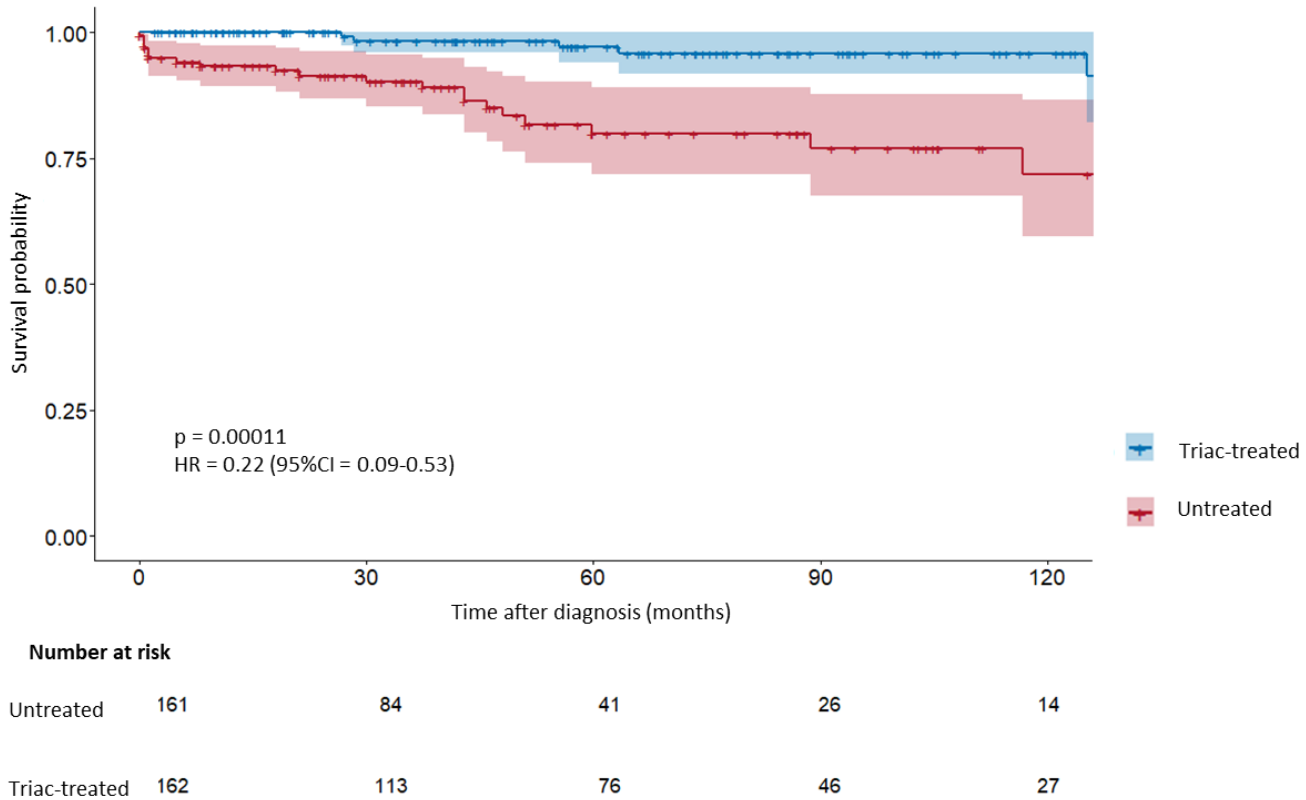
- hypotonia and feeding difficulties in infancy,
- developmental delay/intellectual disability (mild to severe)
- dystonia, choreoathetosis, paroxysmal movement disorder, hypokinesia
- seizures, often drug-resistant
- dysthyroidism (may manifest as poor weight gain, reduced muscle mass and variable cold intolerance, sweating, elevated heart rate, and irritability)
- ***pathognomonic thyroid function test results***

S-TSH	2.38	mIU/L	0,70 - 5,97
S-Fritt T4	**11.9**	pmol/L	12,3 - 22,8
S-Thyroxin (T4)	100	nmol/L	76 - 189
S-Fritt T3	**11.0**	pmol/L	3,7 - 8,5
S-Trijodthy. (T3)	**5.7**	nmol/L	1,4 - 3,8
S-Thyr.bind.glob	25.4	mg/L	14,0 - 31,0



Douzgou S, pers obs

T3 analogue triiodothyroacetic acid (Triac) treatment



Affected residue	Pathogenic variant	Residual capacity	LoF category
Met75	M75R		Moderate
Met75	M75T		Mild
Val178	V178E		Severe
Gly221	G221E		Mild
Ala222	A222V		Mild
Gly226	G226C		Mild
Val235	V235L		Severe
Gly243	G243V		Moderate
Gly258	G258D		Severe
Leu270	L270_L278del		Severe
Tyr275	Y275S		Severe
Leu278	L278P		Mild
Gly280	G280D		Severe
Gly303	G303D		Severe
Asn306	N306K		Severe
Gly307	G307V		Severe
Ser310	S310P		Severe
Leu340	L340R		Severe
Pro412	P412L		Mild
Leu496	L496R		Severe
Leu526	L526P		Severe
Gly536	G536W		Mild
Pro538	P538T		Mild
Ala540	A540P		Mild

Floor van der Most *et al, The Lancet Diabetes & Endocrinology, submitted*

Severe neonatal feeding difficulties



Generalised small growth



Douzgou S, pers obs

KMT2A – related Wiedemann-Steiner syndrome

c.3648dupA, p. (Glu1217ArgfsTer5)

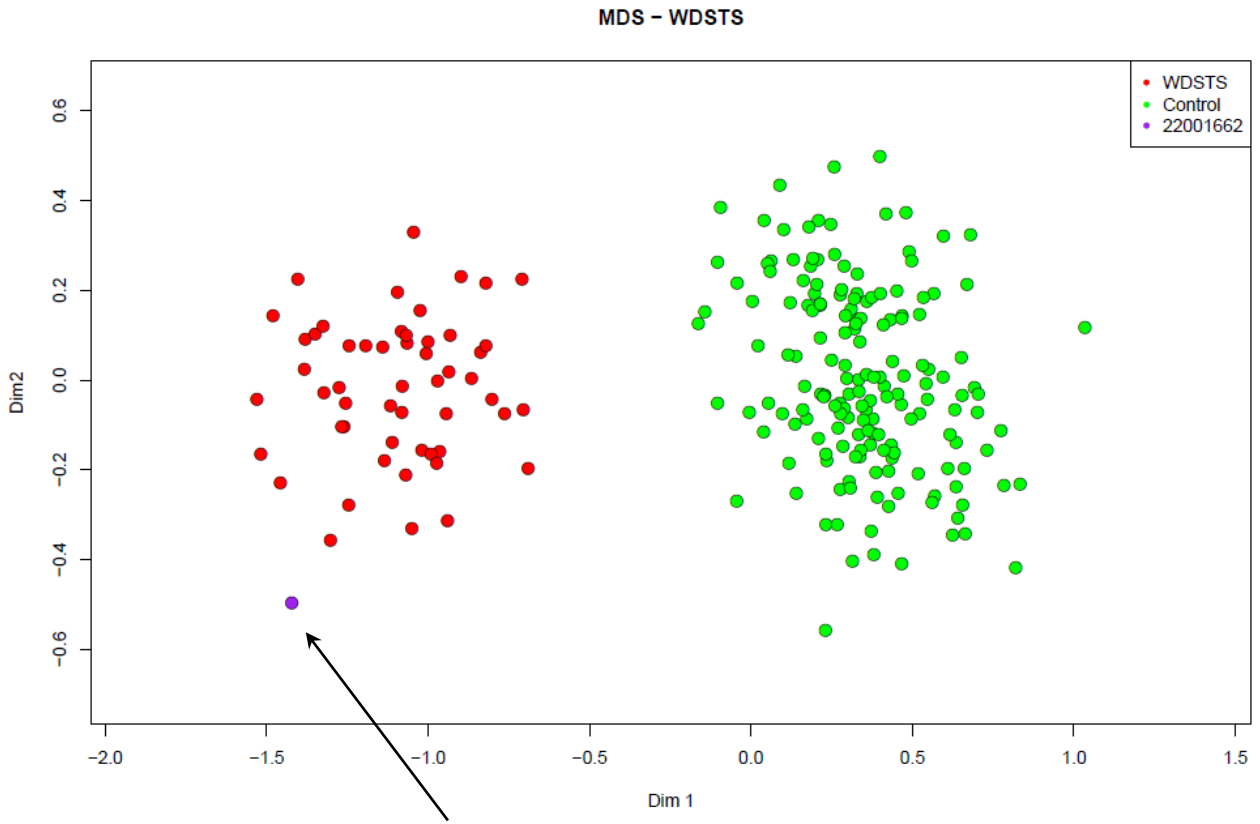


c.3460C>T, p.(Arg1154Trp)



Douzgou S, pers obs

Wiedemann-Steiner Syndrome



KMT2A (NM_001197104.1) c.3648dupA p. (Glu1217ArgfsTer5)

- Growth hormone deficiency might be part of the phenotypic spectrum of Wiedemann–Steiner Syndrome (WSS).
- Investigation of pituitary function should be undertaken in children with WSS and short stature. A pituitary MR scan should be considered if there is biochemical evidence of growth hormone deficiency (GHD).
- Recombinant human growth hormone treatment should be considered for treatment of GHD.

Stoyle et al., 2018

- 29 y, very small incl OFC, -6SD
- Obsessive ideation/psychotic episode
- Moderate intellectual disability;
- She was independent for most of the in-house tasks of her everyday routine, but could not prepare her own food.
- She could read quite well but only write a few sentences.
- She had a rich vocabulary, could name all the doctors that were treating her.
- She could not use means of transportation independently.
- She was of a happy disposition and was smiling and laughing frequently, but not inappropriately.



Douzgou S, pers obs

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- Born at term after a normal pregnancy, with v low birth W 1,900 g
- 5 years below-normal growth rate for both height and weight (<3rd centile), OFC <<3rd centile

- Lost to follow-up

Douzgou S, pers obs

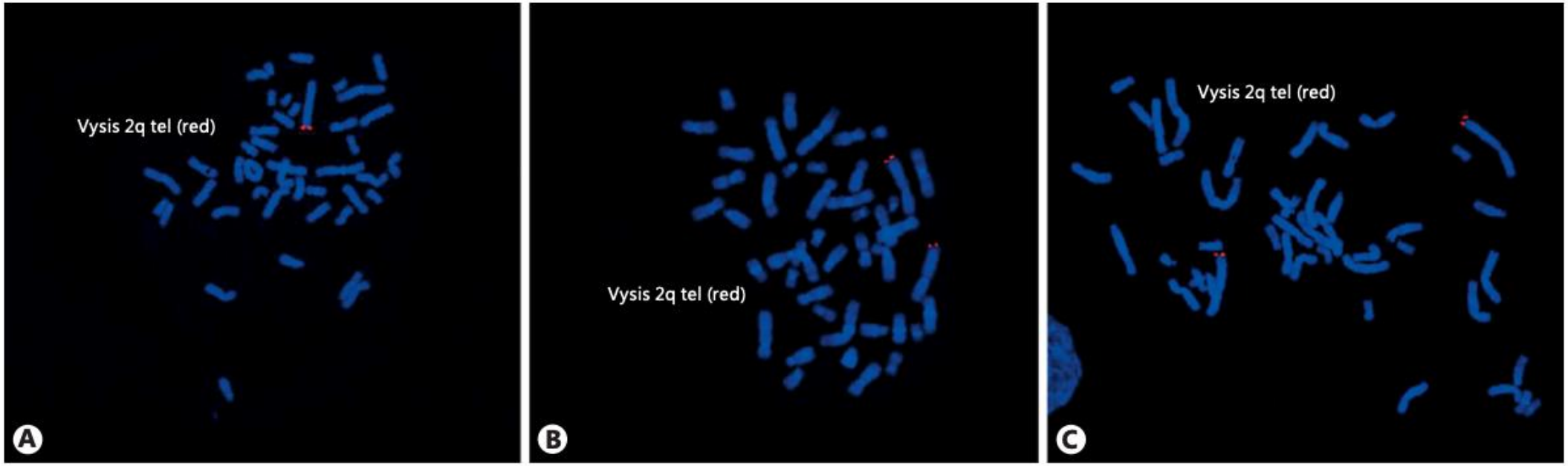


Fig. 2. FISH analysis with subtelomeric 2q probe (XX, Vysis) shows a signal on the long arm of the normal chromosome, but not on the ring chromosome 2, confirming the deletion of the index patient (**A**). The father (**B**) and the mother (**C**) have 2 FISH signals at the telomeres of chromosome 2q.

Sarri et al., 2015

The hypothesis of the 'ring chromosome syndrome'

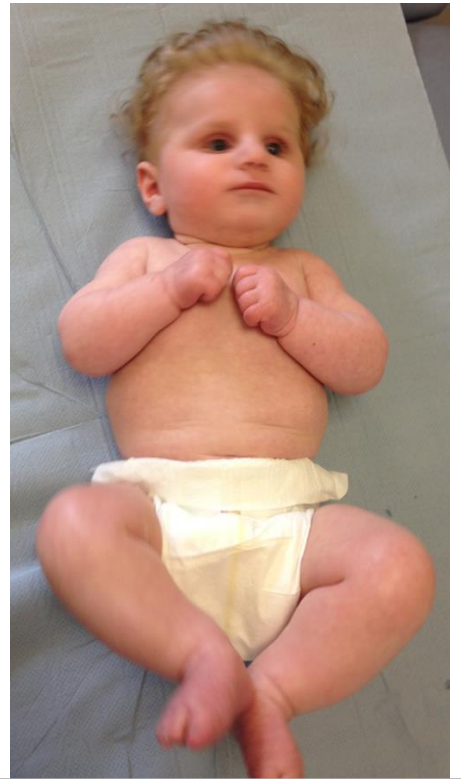
- growth failure
- few or minor malformations
- mild to moderate intellectual disability

'After conception, when the cells in the embryo that will become the baby are dividing and multiplying, the ring may not divide readily, and this will leave some cells with one ring, others with no ring, and yet others with two rings, entangled rings or double sized rings. This process, known as dynamic mosaicism, is particularly common with rings of the long chromosomes such as chromosome 2. The cells containing odd numbers of rings or no ring at all may die off and this constant loss of cells during growth is probably what causes the slowed growth rate in children with a ring chromosome disorder.'

Unique

- Girl, first child of healthy, non consanguineous parents referred at 5 months with
- Bilateral, congenital lamellar cataracts
- Progressive, significant microcephaly (-6 standard deviations)
- Failure to thrive
- Global developmental delay





Douzgou S, pers obs

COFS/Cockayne syndrome

Feature	CS Type I	CS Type II	CS Type III	COFS Syndrome
Typical age of onset	Early childhood (age <2 years)	At birth (severe)	Late childhood (age >2 years)	During fetal life
Growth failure	Prenatal growth normal; onset of growth failure age <2 years	Onset at birth	Late childhood (age >2 years)	Onset during fetal life
Photosensitivity	Clinically variable	Clinically variable	Clinically variable	Clinically variable
Vision issues	Cataracts, pigmentary retinopathy, optic atrophy	Congenital cataracts , pigmentary retinopathy, optic atrophy	Cataracts, pigmentary retinopathy, optic atrophy	Congenital cataracts, pigmentary retinopathy, optic atrophy
Hearing issues	Progressive neurosensorial hearing loss	Progressive neurosensorial hearing loss	Progressive neurosensorial hearing loss	Progressive neurosensorial hearing loss
Neurologic abnormalities	Developmental delay, intellectual disability, cerebellar ataxia, spasticity, peripheral neuropathy	Severe developmental delay, severe intellectual disability, cerebellar ataxia, spasticity, peripheral neuropathy	Intellectual disability, dementia, cerebellar ataxia, spasticity, peripheral neuropathy	Arthrogryposis, severe developmental delay, cerebellar ataxia, spasticity, peripheral neuropathy
Skin cancer predisposition	None	None	None	None
Progression	Progresses throughout childhood	Almost no psychomotor development	Progresses throughout childhood & adulthood	Almost no psychomotor development
Prognosis	Death during 1st or 2nd decade (mean age 16 years)	Death usually in 1st decade but prolonged survival possible in a few cases	Long-term survival into adulthood	Death usually in 1st decade but prolonged survival possible in a few cases
Typical facial appearance ("cachectic dwarfism" w/sunken eyes)	Present in early life	Present in early life	May appear progressively in late stages	Distinct morphologic features w/prominent nasal root & prominent metopic suture; no clear cachectic appearance in most cases

Gene Reviews

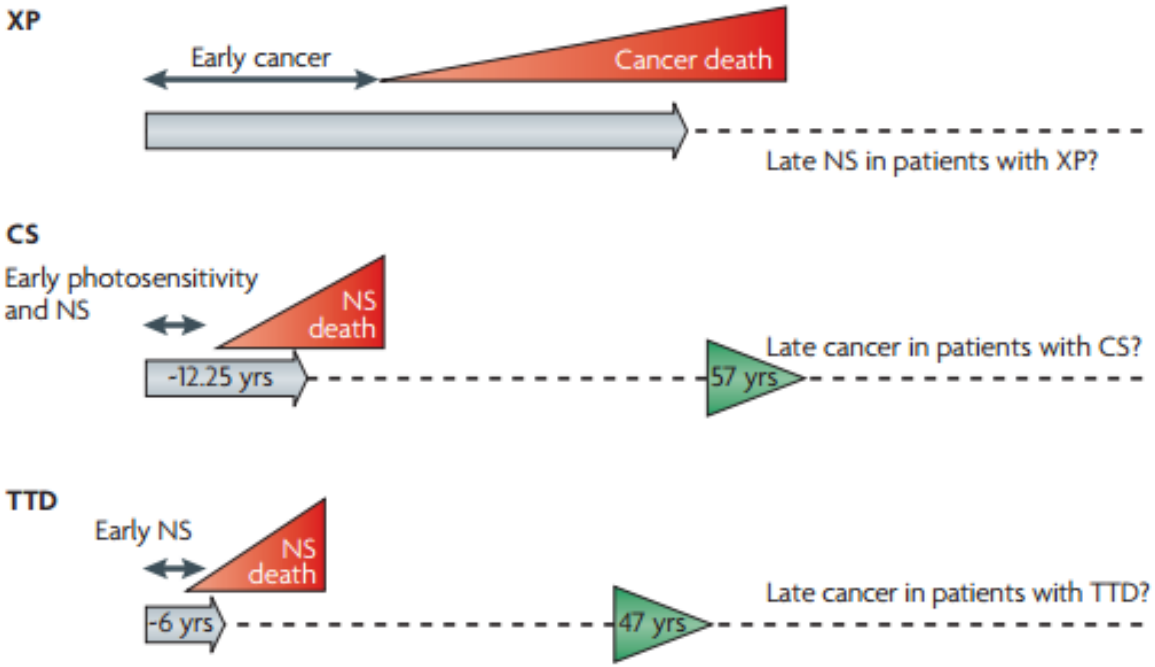


Facial appearances of the girl described at 4 months (left) months and 3 years (right). Note marked microcephaly (middle panel) when compared with 2-months-old younger sibling.

ERCC6 ACMG 4 c.2167C>T and c.2599-26A>G

Thornbinson et al., 2022

Disorders of nucleotide excision repair



TTD results from mutations in one of several different DNA repair genes (XPB, XPD or TTDA) and TTDN1, a gene of unknown function. Although XPB and XPD mutations are also seen in xeroderma pigmentosum, a disease with a 1000-fold increase in skin cancer, TTD and CS patients have not been reported to have an increase in cancer.

Cleaver JE et al., Nat Rev Genet. 2009

- BW 3.8 kg (75th centile)
- 4 months W <0.4th centile
- A community dietician was involved in an attempt to increase calorific intake, but the body weight remained stubbornly below the 0.4th centile.
- 13 months of age, the child was admitted to the local hospital for further investigations and ***safeguarding*** review.
- As an inpatient he was entirely well, with a healthy appetite and a series of blood tests that were unremarkable
- 18 months, W 6.560 kg (< 0.4th centile), OFC 45 cm (0.4th centile) and Ht 76 cm (2nd centile).
- ***Normal endocrinology*** and opthalmology review



Douzgou S, pers obs

Congenital lipodystrophy syndromes

Syndromes	Typical facial phenotype	Distribution of lipodystrophy	Cardiological features	Ear/ocular features	MSK features	Neurocognitive features	Endocrine abnormalities	Molecular abnormality
SHORT syndrome	Triangular facies, deep-set eyes, micrognathia and narrow nasal tip with thin alae	Partial	Uncommon	Rieger's anomaly	Small stature joint hyperextensibility	Normal	Insulin resistance	Heterozygous *PIK3R1* variants
MAD type A	Mandibular and clavicular hypoplasia. Prominent eyes, pinched nose and small mouth.	Partial	Nil	Nil	Nil	Normal	Insulin resistance and hypermetabolism	Biallelic *LMNA* variants. Commonly R527H.
MAD type B		Generalized	Early onset atherosclerosis	Nil	Myopathy and progeroid appearance	Normal	Insulin resistance and hypertriglyceridemia	Biallelic *ZMPSTE24* variants
MDPL syndrome	Mandibular hypoplasia, beaked nose, prominent eyes and small mouth	Generalized	Nil	Sensorineural deafness	Stiff joints and scleroderma-like skin	Normal	Insulin resistance	Heterozygous in-frame *POLD1* deletion (ser605)
Werner syndrome	Prematurely aged facies and beaked nose	Partial	Early onset arteriosclerosis	Cataracts	Small stature slender limbs	Normal	Insulin resistance	Biallelic *RECQL2* variants
ALDD syndrome	Thin facial appearance and violaceous eyelid swelling	Panniculitis induced partial lipodystrophy	Cardiomyopathy reported in few cases	Nil	Long clubbed fingers. Joint contractures.	Mild intellectual disability in few cases	Impaired glucose tolerance	Biallelic *PSMB8* variants
Congenital generalized lipodystrophy (types 1–4)	Triangular facies and pseudoproptosis. Appearance secondary to adipose paucity	Generalized	Cardiomyopathy in type 1 and 2	Nil	Myopathy in type 4. Bony lesions in type 1.	Intellectual disability seen in 50% of type 4	Insulin resistance and hypertriglyceridemia	Biallelic variants affecting *AGPAT2*, *BSCL2*, *CAV1* or *PTRF*
Familial partial lipodystrophy (types 1–7)	Increased fat stores in face produce cushingoid appearance	Partial: loss of fat from upper and lower extremities	Dilated cardiomyopathy seen in type 2	Nil	Cushingoid appearance	Normal	Insulin resistance	Type 2 (most common): heterozygous *LMNA* variants

ALDD, autoinflammation, lipodystrophy, and dermatosis syndrome; MAD type A, mandibuloacral dysplasia with type A lipodystrophy; MAD type B, mandibuloacral dysplasia with type B lipodystrophy; MDPL, mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome; SHORT, short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly and teething delay.

McDermott et al., 2018

Diencephalic syndrome

Head CT scan: a hypothalamic mass, characterized histopathologically as a pilocytic astrocytoma, WHO grade 1.

- A rare cause of faltering growth in childhood characterized by severe emaciation despite adequate calorific intake.

- mass effect of the space occupying lesion (nystagmus, locomotor hyper- activity, hyperemesis and visual field defects)

Overgrowth

Generalised

A relatively proportionate increase in stature (length or height) and/or head circumference at least 2 SDs above the mean compared to the age-related peer group.

When generalized overgrowth is accompanied by intellectual disability, the resulting disorders have been designated as “overgrowth with intellectual disability (OGID) syndromes ”

Regional

Increased growth of a discrete area of the body when compared to an equivalent body part

1. Progressive (grows disproportionately faster than the remainder of the body)
2. Non-progressive (remains concordant with the growth of the child)

Cohen, Neri, & Weksverg, 2002; Tatton-Brown, 2017; Neri, Boucutto, & Stevenson, 2019, Burkatdt D et al., 2019

- First child of healthy, non consanguineous parents
- Macrocephaly
- Tall stature
- Scoliosis
- Pectus
- ID: moderate



Courtesy of Daniela T Pilz

- First child of healthy, non consanguineous parents
- Macrocephaly
- Tall stature
- Scoliosis
- Pectus
- ID: moderate



Sotos syndrome

ID: mild – severe; moderate

Hypotonia

Pectus

Scoliosis

Seizures

Strabismus

Hearing impairment

Congenital Heart Defect

Cardiomyopathy

Renal anomalies

***NSD1* point mutation**

Histone methyltransferase (writer)

Courtesy of Daniela T Pilz

- Mother always tallest in the class
- Atrial Septal Defect
- Childhood epilepsy
- Sensorineural hearing loss
- Mild Learning Difficulties



Courtesy of Daniela T Pilz

Sotos syndrome – craniofacial signs

- Macrocephaly, dolichocephaly/scaphocephaly
- Craniostenosis (sagittal)
- High prominent forehead
- Frontotemporal hair sparsity
- Long (thin) face
- (usually) Downslanting palpebral fissure
- Prominent chin



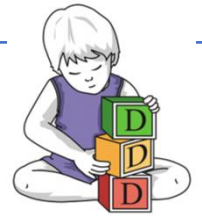
Courtesy of Daniela T Pilz

- Moderate-to-severe, global developmental delay
- Macrocephaly
- MRI: mild ventriculomegaly, large extra axial spaces, no structural brain anomalies
- Sleep Disorder
- Constipation



Douzgou S, pers obs

CHD8 protein truncating variant



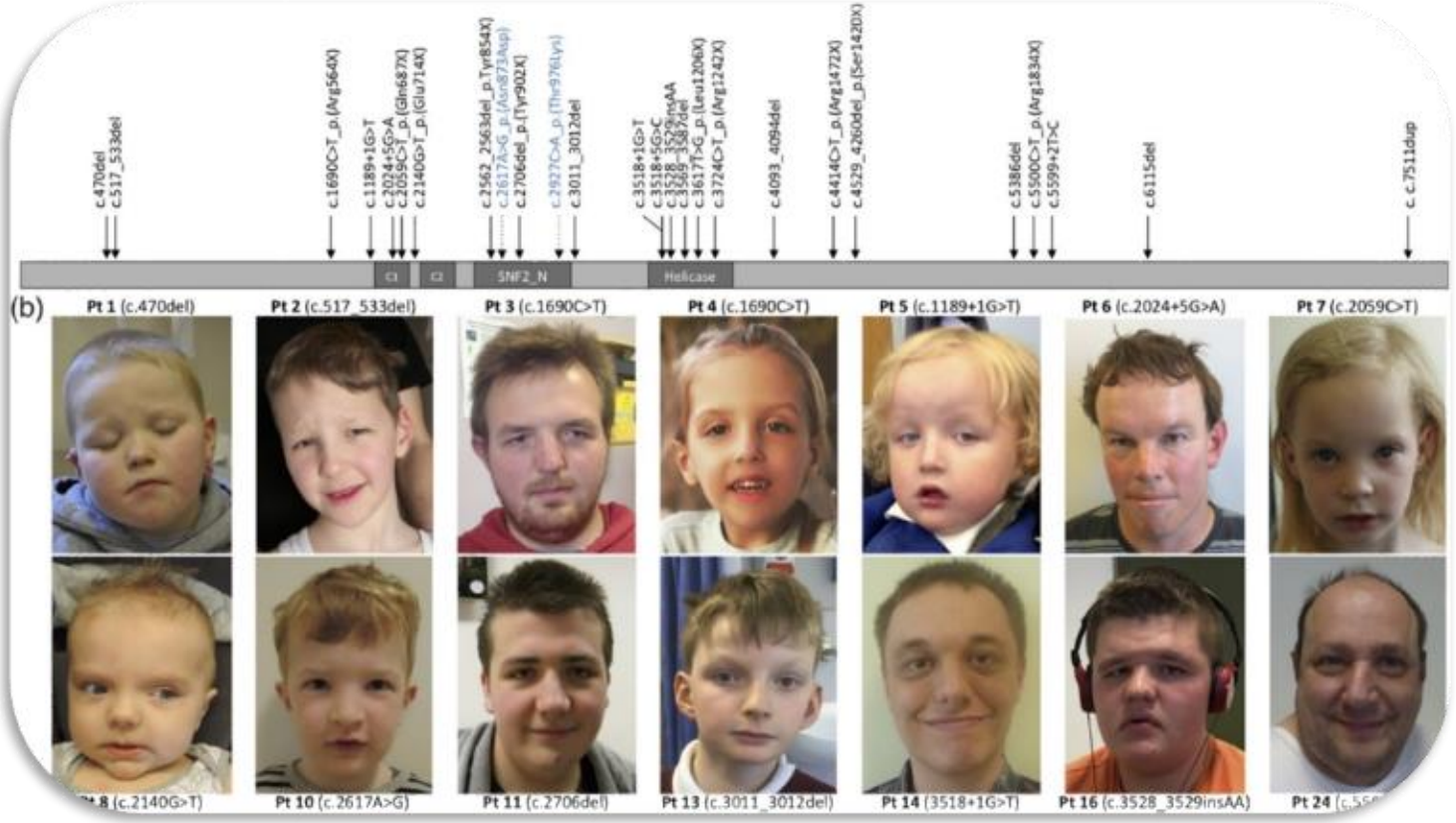
- Moderate-to-severe, global developmental delay
- Macrocephaly
- MRI: mild ventriculomegaly, large extra axial spaces, no structural brain anomalies
- Sleep Disorder
- Constipation



- Chromodomain Helicase DNA-binding Protein (reader)

Truncating *CHD8* variants cause an overgrowth and intellectual disability syndrome

- Macrocephaly
- Tall stature
- ID
- ASD
- ADHD
- Sleep problems
- Seizures
- Hypotonia
- Overgrowth
- Gastrointestinal difficulties
- Characteristic gestalt

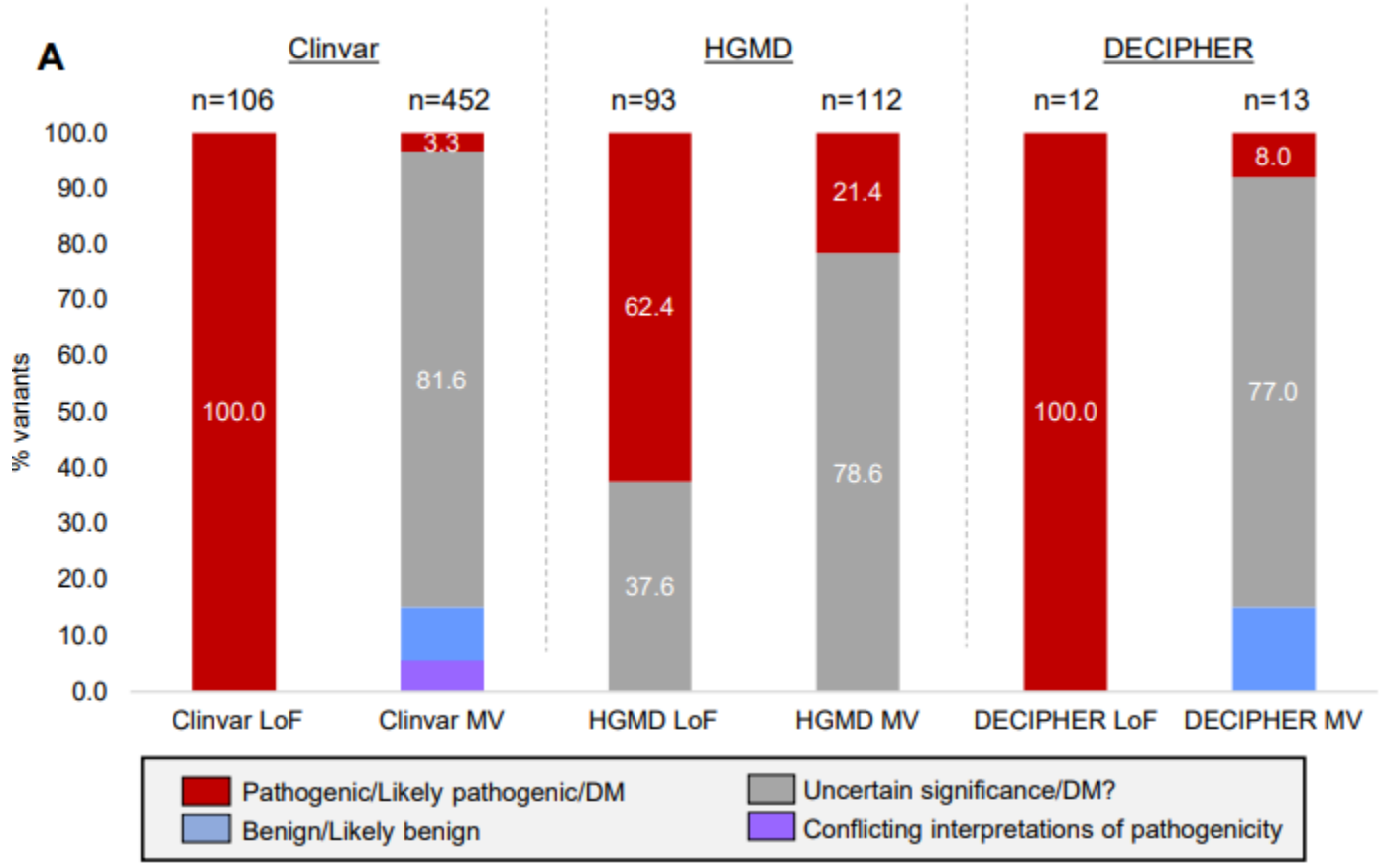


- ***CHD8* variants are found in about 0.5% of individuals with autistic spectrum disorder**

Douzgou et al, Clin Genet, 2019

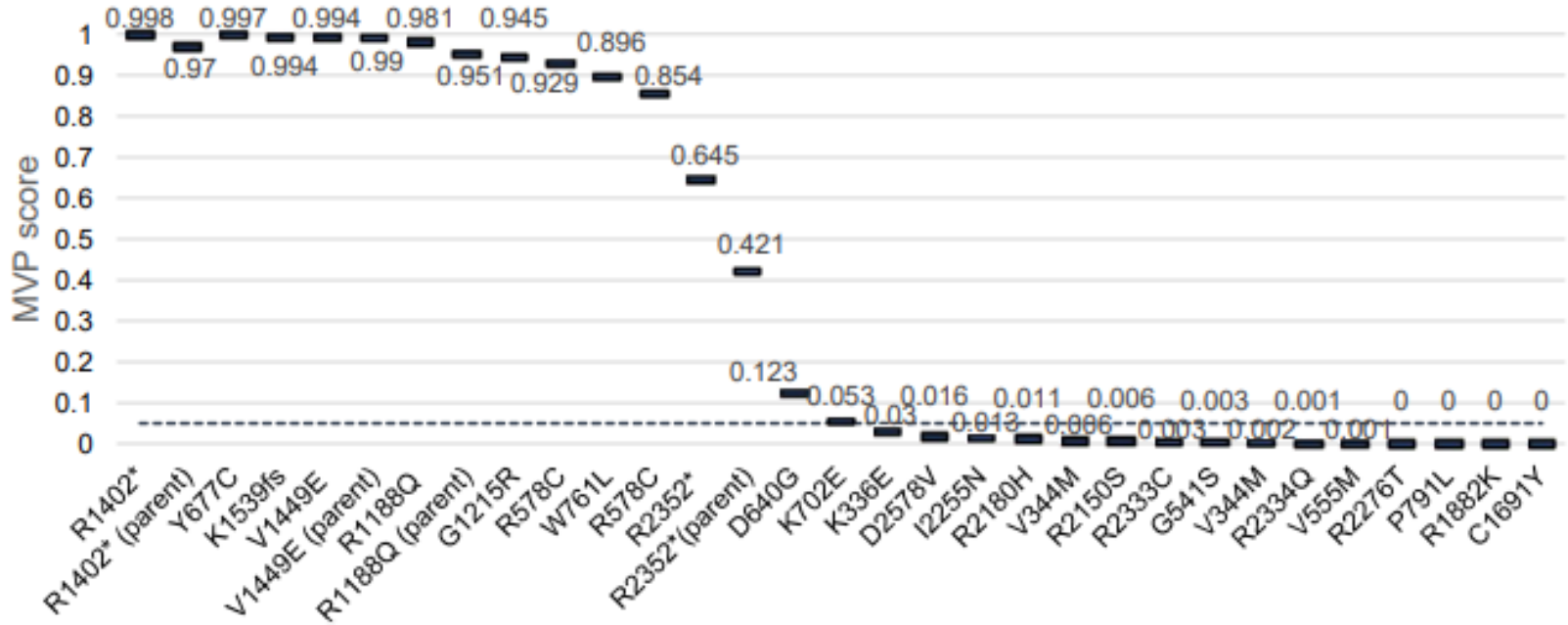
Ostrowski et al., 2019

… ascertaining the significance of CHD8 MVs is challenging

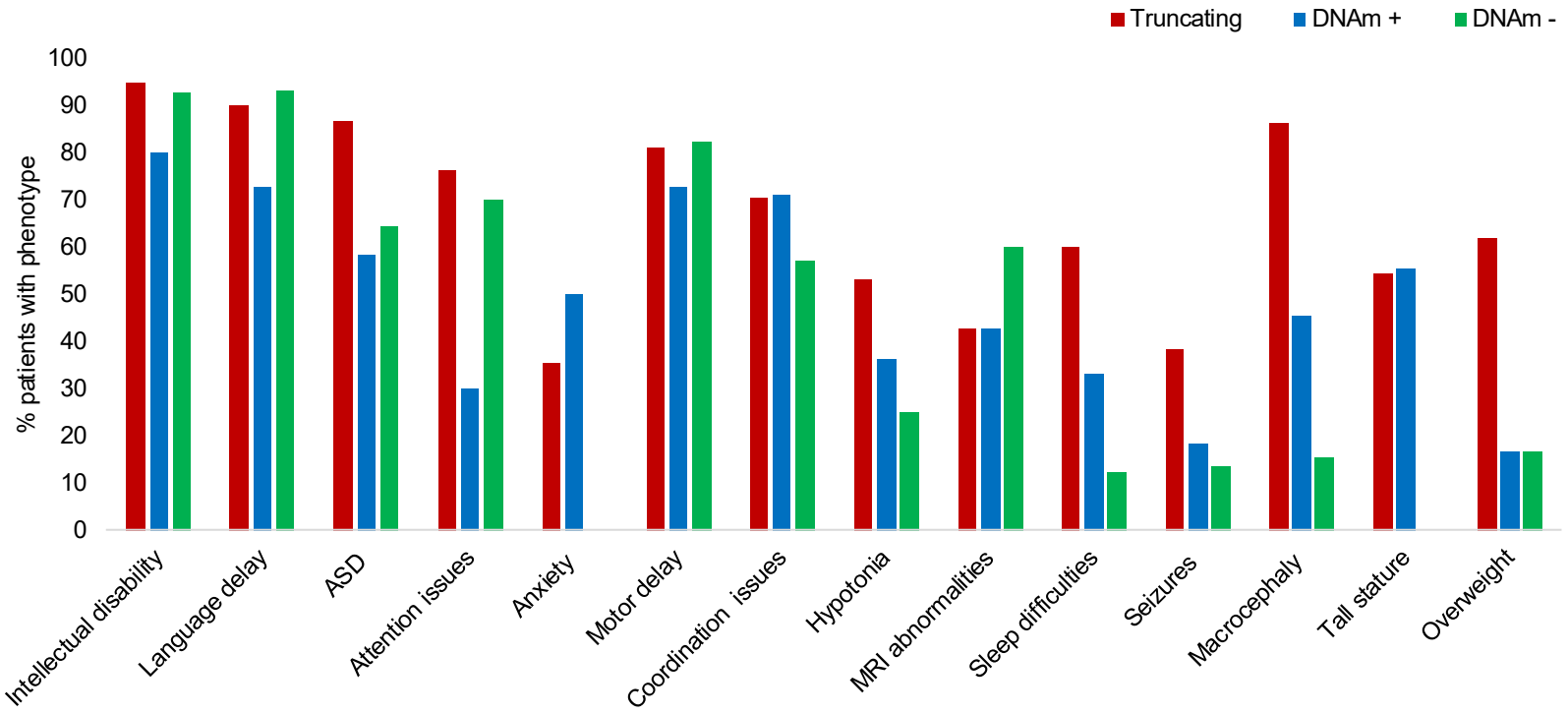


Godfrey et al., EJHG, 2026

… pathogenic CHD8 MVs result in episignature that overlaps with LoF variants



Godfrey et al., EJHG, 2026



Disease causing LoF variants



DNAm +ve (disease-causing) MVs



DNAm –ve MVs



Godfrey et al., EJHG, 2026

- FH non contributory, 2 healthy sisters
- Congenital, non progressive macrocephaly and hydrocephalus
- Absences well controlled with Sodium Valproate
- General cognitive functioning significantly below the normal range; did not speak intelligibly before 3 years of age
- ADHD, obsessive thoughts, phobias, tics
- Tremors



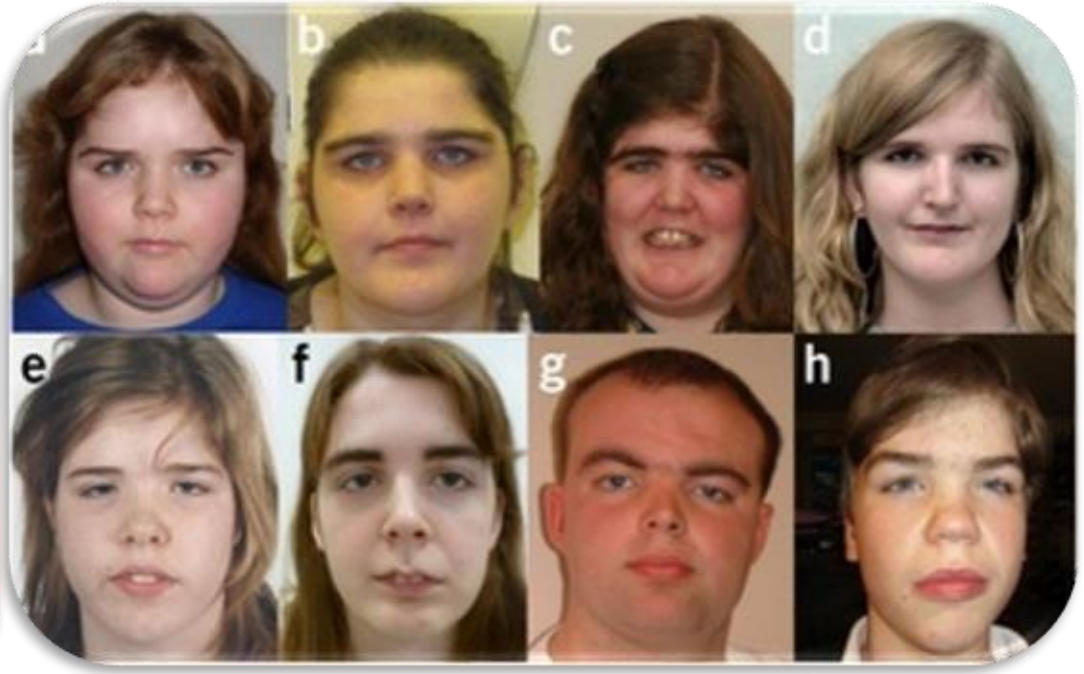


Douzgou S, pers obs

Tatton-Brown-Rahman Syndrome

- Tall stature
- Macrocephaly
- Distinct facial features
- ID – mild to moderate





- DNA methyltransferase (writer)

Tatton-Brown et al, 2018



***DNMT3A* Overgrowth Syndrome is associated with the development of hematopoietic malignancies in children and young adults**

Margaret A. Ferris[1], Amanda M. Smith[2], Sharon E. Heath[2], Eric J. Duncavage[3], Matthew Oberley[4], David Freyer[5], Robert Wynn[6], Sofia Douzgou[7], John M. Maris[8], Anne F. Reilly[8], Melinda D. Wu[9], Florence Choo[9], Roel B. Fiets[10], Saskia Koene[11], David H. Spencer[2], Christopher A. Miller[2], Marwan Shinawi[1], Timothy J. Ley[2#]



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CCR Pediatric Oncology Series

Recommendations for Surveillance for Children with Leukemia-Predisposing Conditions

Christopher C. Porter, Todd E. Druley, Ayelet Erez, Roland P. Kuiper, Kenan Onel, Joshua D. Schiffman, Kami Wolfe Schneider, Sarah R. Scollon, Hamish S. Scott, Louise C. Strong, Michael F. Walsh, and Kim E. Nichols

DOI: 10.1158/1078-0432.CCR-17-0428 Published June 2017

- 8/202 (4%) affected individuals known worldwide (similar to the incidence of leukemia in patients with Li Fraumeni syndrome)
- Myeloid and lymphoid malignancies
- Mean age at diagnosis 9.6 years
- R882 Most common mutation site

- 18 years old
- Large throughout life, incl OFC (>97p)
- Ht 210 cm (midparent 190 cm)
- Truncal obesity
- Learning challenges at school
- Twice operated for knee epiphysiolysis
- Normal trio exome analysis

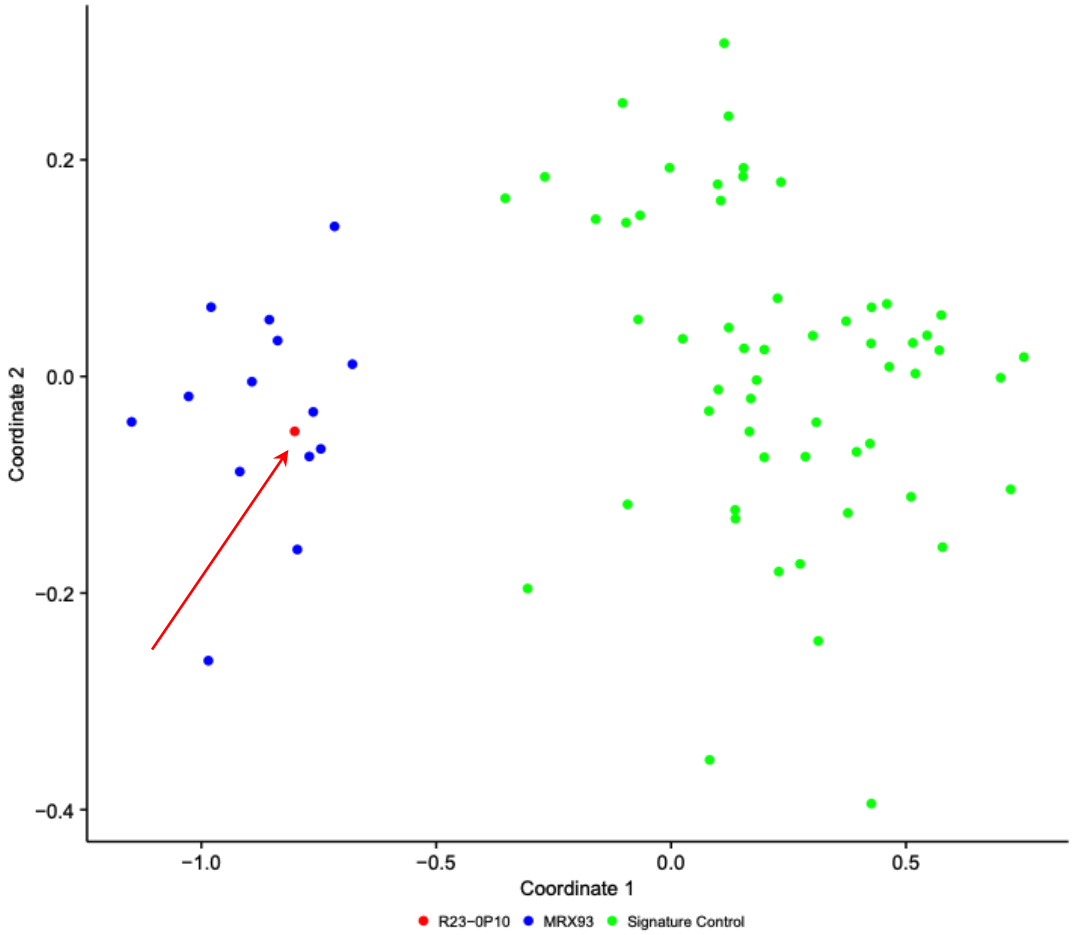


Douzgou Houge S, pers obs

Phenotype-first use of genomic technologies

OGID is enriched for chromatin / epigenetic disorders

(e.g. *NSD1, EZH2, DNMT3A, CHD8, NFIX-related syndromes*).



Null variants and deletions in *BRWD3* cause an X-linked syndrome of mild–moderate intellectual disability, macrocephaly, and obesity

Mizuguchi T et al. Clin Epigenetics 2025.

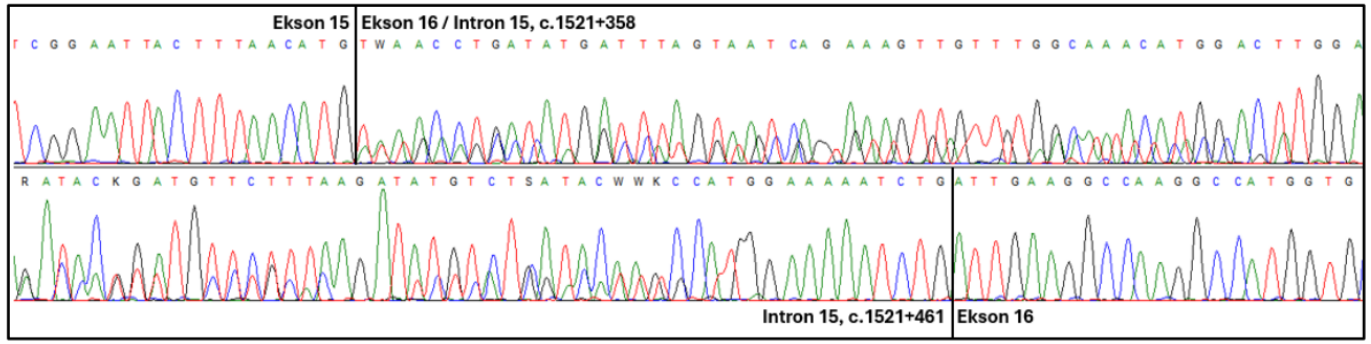
DNMT3A/TBRS methylation signature report: EJHG 2023.

Ostrowski, Philip J et al. AJMG. Part C, (2019).

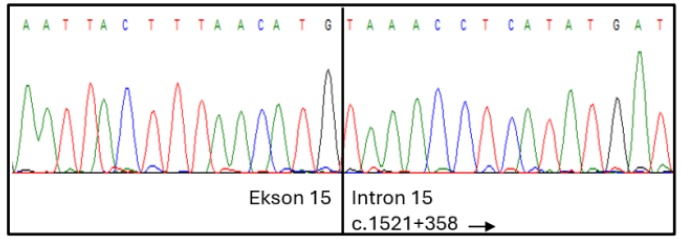
Phenotype-first use of genomic technologies

Long Revio PacBio sequencing: NM_153252.5(BRWD3):c.1521+356G>A

Oppsett cBRWD3 Ex15F/Ex16R, Primer Ex15F:



Oppsett cBRWD3 Ex15F/Intron15R, Primer Ex15F:



Konklusjon:
Begge PCR-oppsettene viser samme resultat.
NM_153252.5(BRWD3):c.1521+356G>A fører til bruk av nytt akseptorsete i intron 15 og bruk av konstitutivt donorsete 104 bp nedstrøms for dette igjen. Gel og sekvens antyder > 50% grad feilspleising.
Konsekvens RNA-nivå: r.1521_1522ins104 (c.1521+358_c.1521+461)
Konsekvens Proteinnivå: p.Ile508Stop

Bart van der Sanden
Christian Gilissen
Hilde Rusaas
Bjorn Ivar Haukanes

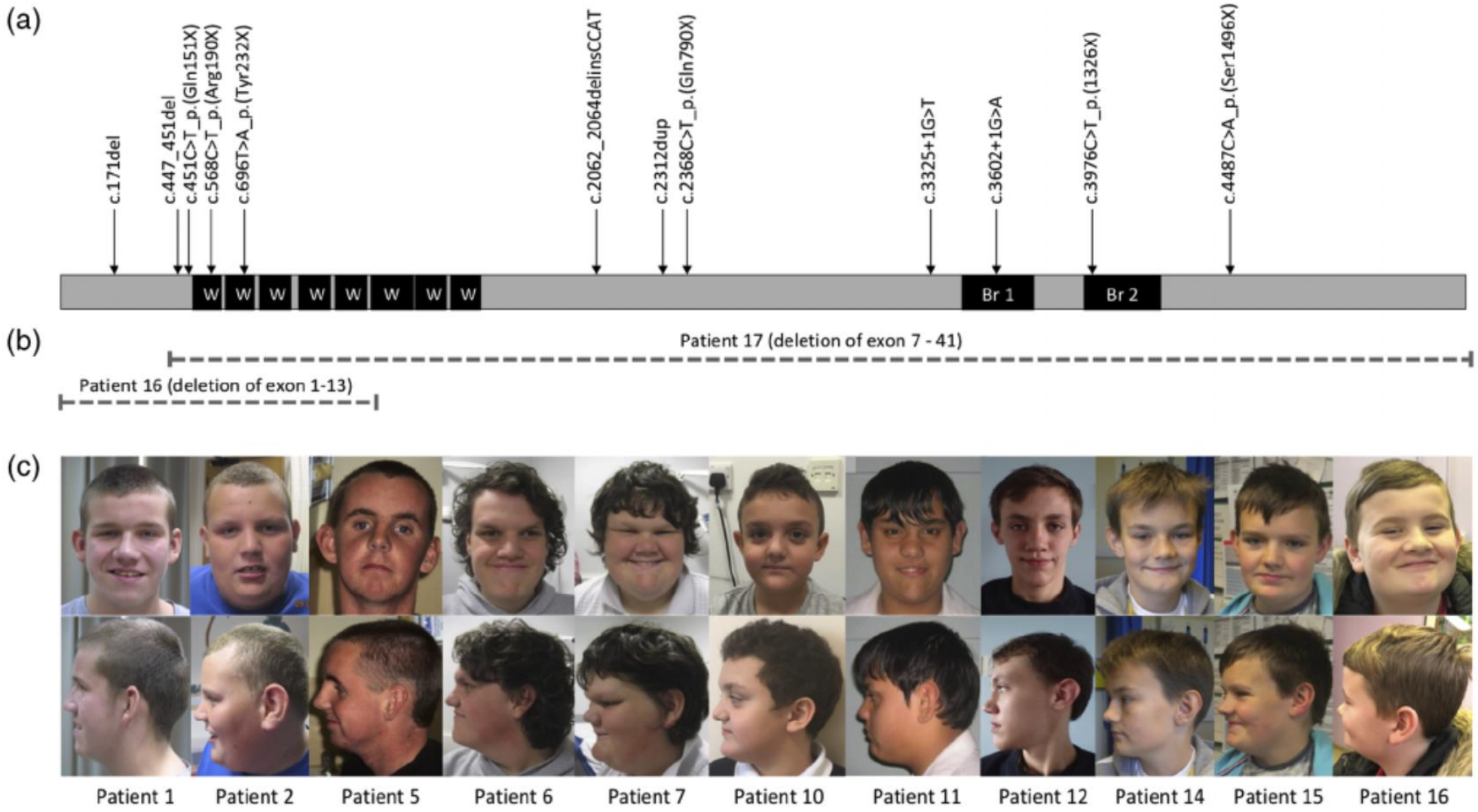


FIGURE 1 (a) BRWD3 protein domains and location of the 12 sequence variants. W, WD40 domains. Br, bromodomains. (b) Location of the two partial gene deletions. (c) Patient photographs showing common facial features including tall chin with associated horizontal skin crease, prognathism, broad forehead, and prominent supraorbital ridge. Note Patient 11 was included in the original publication describing the *BRWD3* phenotype (Field et al., 2007)

Ostrowski et al., 2019

Null variants and deletions in BRWD3 cause an X-linked syndrome of mild–moderate intellectual disability, macrocephaly, and obesity

- 100% intellectual disability: moderate (65%) or mild (35%)
- 75% behavioral issues including aggressive behavior, attention deficit/hyperactivity and/or autistic spectrum disorders.
- Mean head circumference +2.8 SD (2.8 standard deviations above the
- Mean)
- Mean BMI +2.0 SD (in the context of a mean height of +1.3 SD)
- Predominant macrocephaly/obesity phenotype

- The protein has been shown to associate with transcriptionally-active chromatin, and may mediate its effects through histone H3.3

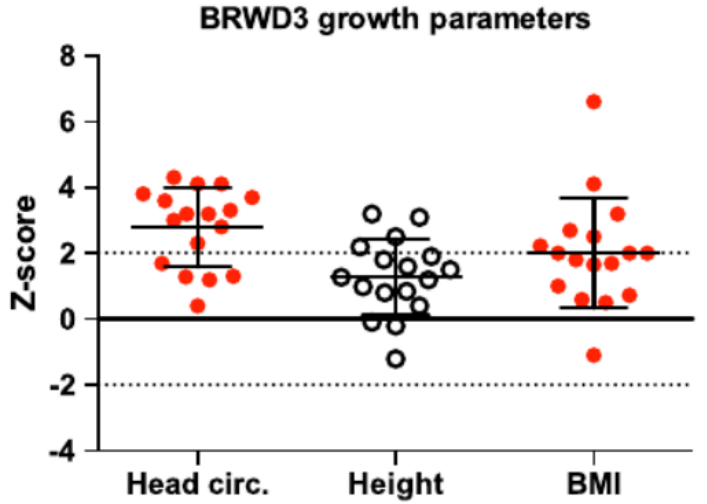


FIGURE 2 Standardized growth parameters (Z-scores) in *BRWD3* patients (n = 17). Bars represent mean ± *SD*. Solid horizontal line indicates the population average for age/gender (Z-score = 0 *SD*); dashed horizontal lines indicate Z-score cut-offs of ±2 *SD*. Solid red points indicate parameters with a mean Z-score of ≥ +2 *SD* (head circumference, body mass index); circles indicate parameters with a mean Z-score of < +2 *SD* (height)

D'Costa, Reifegerste, Sierra, & Moses, 2006

Ostrowski et al., 2019

Chen et al., 2015



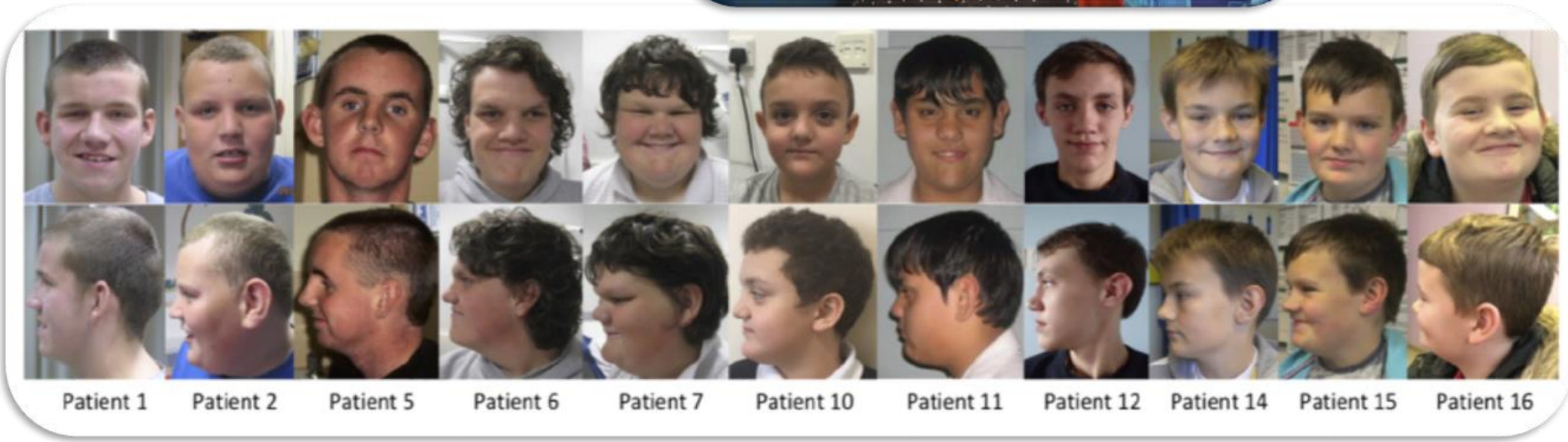




- Delayed learning
- Speech delay
- Truncal obesity
- Immature behaviour
- Sensorineural hearing loss
- Barret’s oesophagus
- Eosinophilia (resolved)
- Foetal fingers pads
- Brachydactyly
- 8y : W 33.75, H 132.8, OFC 55.9
- NB: his mother has sensorineural hearing loss without learning disabilities

Douzgou Houge S, pers obs





Ostrowski et al., 2019











- Neonatal hypotonia
- BW 4510 g, Tall stature (97,5 c) and normal HC (75 c)
- ASD secundum
- Bifid uvula
- ADHD / temper tantrums / good social skills

Courtesy of Gunnar D Houge



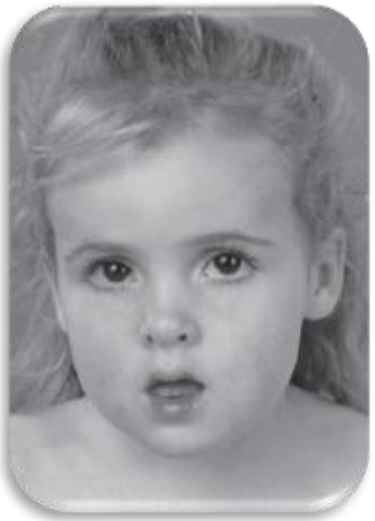
Simpson-Golabi-Behmel syndrome: *GPC3* R254X

Overgrowth syndromes tumourigenesis risk

- Simpson-Golabi-Behmel: **11%** (Wilms tumour, hepatoblastoma, gonadoblastoma, adrenal neuroblastoma)
- Beckwith-Wiedemann Syndrome: **7%**
  - High: ICR1 hypermethylation; pUPD 11p15
  - Intermediate: CDKNIC mutations
  - Low: ICR2 hypomethylation
- Weaver syndrome: **<5%** (lymphoma, ALL, neuroblastoma)
- TRBS, *DNMT3A*: **~4%** (hematologic malignancies and CNS tumours)
- Sotos syndrome: **~3%** (sacrococcygeal teratoma, neuroblastoma, presacral ganglioma, acute lymphoblastic leukemia (ALL) and small cell lung cancer)

- Perlman syndrome: high risk of Wilms tumour (for those who survive the neonatal period)

Tatton-Brown & Rahman, 2013; Luscan et al. JMG 2014; Milani et al 2014; Villani et al., 2017









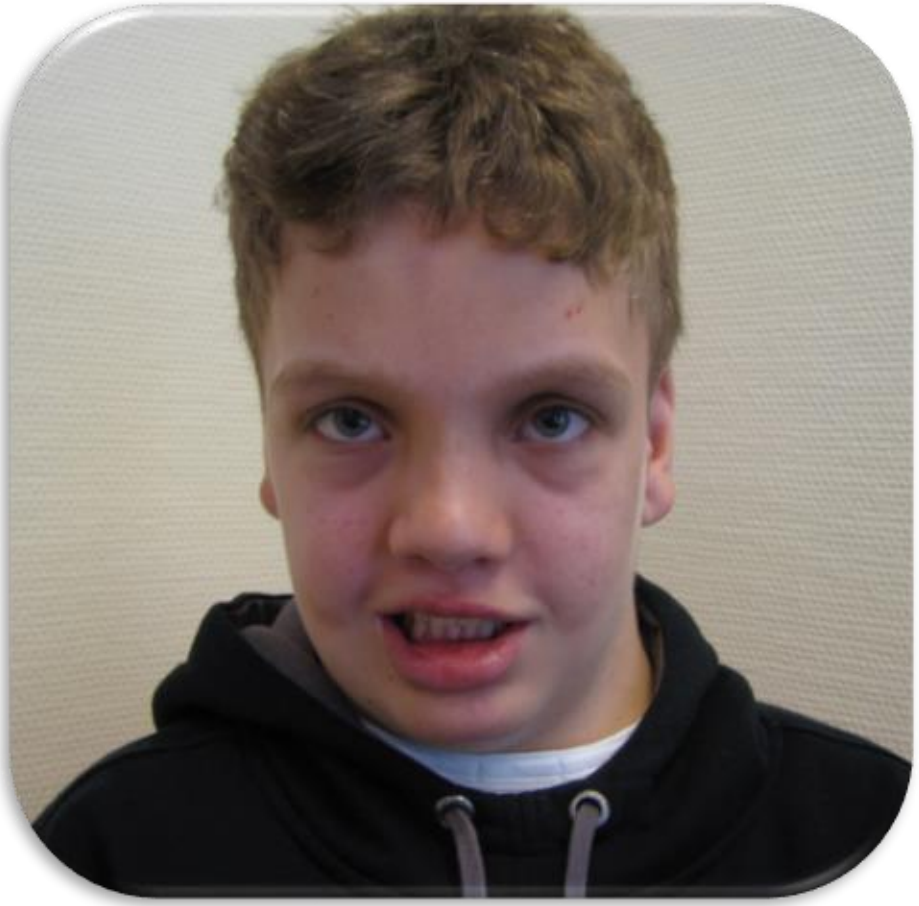





NFIX *DNMT3A* *EZH2* *NSD1* *BWS* *GPC3*



47,XXX







Trisomy 8 mosaicism (Warkany syndrome)

- 5-year-old girl
- Ht 5cm >97.5p, HC 90 p, W >>97 p
- Absences, Focal tonic clonic seizures treated with Levetiracetam; EEG: Frequent bilateral epileptiform activity without clinical correlate
- Walked by 1 year, clumsy
- Severe language and social delay
- Happy, smiles frequently



From Le Fevre et al 2017

Courtesy of Inger L Mero

mosaic Angelman Syndrome

- Partial hypomethylation at the SNRPN locus
- Developmental delay in nearly all, whereas the core features of AS in less than 40%
- Language and ability to manage activities of daily living markedly improved over that expected in AS
- mAS patients have a high incidence of behavioural challenges

Clinical Feature	Le Fevre et al., 2017 Present/total (%)	Carson and Duis, 2019 Present/total (%)
Word number	>10, 12/26 (46)	>20, 13/22 (59)
Age of onset walking (years)	1.5 (range 1–3)	1.7 (range 1–3)
Walked by age 5	24/24 (100)	22/22 (100)
Ataxia	11/25 (44)	6/21 (29)
Seizures	8/28 (29)	1/22 (5)
Microcephaly	3/26 (12)	5/22 (23)
Abnormal EEG	7/11 (64)	7/16 (44)
Hypopigmentation	2/11 (18)	5/22 (23)
Obesity	8/25 (32)	14/22 (64)
Hyperphagia	11/20 (55)	18/22 (82) (food seeking)
Feeding problem	7/24 (29) (Neonatal)	2/22 (9)
Behavioral problems	4/5 (80)	21/22 (95) anxiety 13/22 (59) hyperactivity
Sleeping Difficulties	5/6 (83)	16/22 (73)
Facial dysmorphic features	3/9 (33)	7/22 (32)

Manchester Rare Conditions Centre

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Thank you !

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