**The Tatton-Brown-Rahman Syndrome: a clinical study of 55 individuals with *de novo* constitutive *DNMT3A* variants.**

**Katrina Tatton-Brown1,2,3, Anna Zachariou1, Chey Loveday1, Lise Aksglaede4, Diana Baralle5, Daniela Barge-Schaapveld6, Moira Blyth7, Mieke Bouma8, Jeroen Breckpot9, CAUSES study10, Tabib Dabir11, Valerie Cormier-Daire12, Marie-Ange Delrue13, Christine Fauth14, Richard Fisher15, Blanca Gener16, David Goudie17, Tessa Homfray2,3, Matthew Hunter18, Agnete Jorgensen19, Sarina Kant6, Cathy Kiraly-Borri20, David Koolen21, Ajith Kumar22, Anatalia Labilloy23, Carlo Marcelis21, Catherine Mercer5, Cyril Mignot24, Kathryn Miller25, Katherine Neas26, Ruth Newbury-Ecob27, Daniela Pilz28, Renata Posmyk29, Carlos Prada23, Keri Ramsey30, Linda Randolph31, Lisa Read32, Angelo Selicorni33, Debbie Shears34, Mohnish Suri35, I Karen Temple5, Peter Turnpenny36, Lionel Van Maldergem37, Vinod Varghese38, Irma Veenstra-Knol8, Naomi Yachelevich39, Laura Yates15, DDD study40, Nazneen Rahman1,41**

1Division of Genetics and Epidemiology, Institute of Cancer Research, London, UK

2South West Thames Regional Genetics Service, St George’s University Hospitals NHS Foundation Trust, London, UK

3St George’s University of London, London, UK

4Department of Clinical Genetics, Copenhagen University Hospital, Copenhagen, Denmark

5Human Genetics and Genomic Medicine, Faculty of Medicine, University of Southampton, Southampton, UK

6Department of Clinical Genetics, Leiden University Medical Centre, Leiden, the Netherlands.

7Department of Clinical Genetics, Chapel Allerton Hospital, Leeds, UK.

8Clinical genetics, University Medical Center Groningen, Groningen, The Netherlands

9Center for Human Genetics, University Hospitals and KU Leuven, Leuven, Belgium.

10Departments of Pediatrics and Medical Genetics, University of British Columbia, Vancouver, Canada

11Northern Ireland Regional Genetics Centre, Clinical Genetics Service, Belfast City Hospital, Belfast, UK

12INSERM UMR1163, IMAGINE Institute affiliate, Paris, France

13Département de Génétique Médicale, CHU Sainte Justine, Montréal, Canada

14Division of Human Genetics, Medical University Innsbruck, Innsbruck, Austria

15Teesside Genetics Unit, The James Cook University Hospital, Middlesbrough, United Kingdom

16Servicio de Genética, BioCruces Health Research Institute, Hospital Universitario Cruces, Bizkaia, Spain

17Department of Human Genetics, Ninewells Hospital and Medical School, Dundee, UK

18Faculty of Medicine, University of Newcastle, Newcastle, New South Wales, Australia.

19Division of Child and Adolescent Health, Department of Medical Genetics, University Hospital of North Norway, Tromsø, Norway

20Genetic Services of WA, Department of Health Level 3, SUBIACO WA 6008

21Department of Human Genetics and Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands

22North East Thames Regional Genetics Service and Department of Clinical Genetics, Great Ormond Street Hospital, London, UK

23Division of Human Genetics Cincinnati Children's Hospital Medical Center University of Cincinnati College of Medicine Cincinnati, Ohio.

24AP-HP, Département de Génétique and Centre de Référence Déficiences Intellectuelles de Causes Rares, Paris, France

25Albany Medical Center, New York, USA

26Genetic Health Service, Wellington, New Zealand

27University Hospitals Bristol NHS Trust/University of Bristol, Bristol, UK.

28West of Scotland Clinical Genetics Service, Queen Elizabeth University Hospital, Glasgow, UK

29Department of Clinical Genetics, Podlaskie Medical Center, Bialystok, Poland.

30Center for Rare Childhood Disorders, Translational Genomics Research Institute, Phoenix, Arizona, USA.

31Division of Medical Genetics, Children's Hospital Los Angeles, University of Southern California/ Keck School of Medicine, Los Angeles, CA, USA

32Genetics Dept, Children's Hospitals and Clinics of Minneapolis, USA

33Ambulatorio di Genetica Clinica Pediatrica, Clinica Pediatrica dell’Università di Milano Bicocca, La Fondazione Monza e Brianza il Bambino e La Sua Mamma (MBBM), Azienda Ospedaliera (AO), San Gerado, Monza, Italy

34Department of Clinical Genetics, Churchill Hospital, Oxford, UK

35Nottingham City Hospital, Nottingham NG5 1PB, UK

36Peninsula Clinical Genetics, University of Exeter Medical School, Royal Devon & Exeter NHS Foundation Trust, Exeter, United Kingdom

37Centre de Génétique Humaine and Integrative and Cognitive Neuroscience Research Unit EA481, Université de Franche-Comté, Besançon, France

38Institute of Medical Genetics, University Hospital of Wales, Cardiff, UK

39Clinical Genetics Services, New York University Hospitals Center, New York University, New York, New York, USA

40Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK

41Cancer Genetics Unit, Royal Marsden NHS Foundation Trust, London, UK

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**Contact**

Dr Katrina Tatton-Brown

St George’s University of London

Cranmer Terrace

London

SW17 0RE

Email [ktatton@sgul.ac.uk](mailto:ktatton@sgul.ac.uk)

Telephone 0208 725 0572

**Abstract**

**Tatton-Brown-Rahman syndrome (TBRS, OMIM 615879), also known as the DNMT3A-overgrowth syndrome, is an overgrowth intellectual disability (OGID) syndrome first described in 2014 with a report of 13 individuals with constitutive heterozygous *DNMT3A* variants. Here we have undertaken a detailed clinical study of 55 individuals with *de novo* *DNMT3A* variants; including the 13 previously reported individuals. An intellectual disability and overgrowth were reported in >80% of individuals with TBRS and were designated major clinical associations. Additional frequent clinical associations (reported in 20-80% individuals) included an evolving facial appearance with low-set, heavy, horizontal eyebrows and prominent upper central incisors; joint hypermobility (73%); obesity (weight ≥2SD, 67%); hypotonia (54%); behavioral/psychiatric issues (most frequently autistic spectrum disorder, 51%); kyphoscoliosis (33%) and afebrile seizures (22%). One individual was diagnosed with acute myeloid leukemia (AML) in teenage years. Based upon the results from this study, we present our current management for individuals with TBRS.**

**Introduction**

Tatton-Brown-Rahman syndrome (TBRS, OMIM 615879), also known as the DNMT3A-overgrowth syndrome, is an overgrowth intellectual disability (OGID) syndrome first described in 2014 with a report of 13 individuals with *de novo* heterozygous *DNMT3A* variants (24614070, 28475857). Subsequently, a further 22 individuals with TBRS have been reported (28449304, 27701732, 27317772, 28432085, 27991732, 26866722 and 28941052).

In this report we have undertaken a detailed clinical evaluation of 55 individuals with *de novo DNMT3A* variants; including the 13 individuals we first reported in 2014. We have expanded and clarified the TBRS phenotype, delineating major and frequent clinical associations, which has informed our management of individuals with this new OGID syndrome.

**Methods**

The study was approved by the London Multicentre Research Ethics Committee (MREC MREC/01/2/44) and consent was obtained from all participating individuals and/or parents. Photographs, with accompanying consent to publish, were requested from all and received from the families of 41 individuals. Detailed phenotype data were collected through a standardized clinical proforma and a *DNMT3A* specific clinical proforma.

The degree of intellectual disability was defined in relation to educational support as a child and living impairment as an adult: an individual with a mild intellectual disability typically had delayed milestones but would attend a mainstream school with some support and live independently, with support, as an adult; an individual with a moderate intellectual disability typically required high level support in a mainstream school or special educational needs schooling and an individual with a severe intellectual disability typically required special educational needs schooling, had limited speech and would not live independently as an adult.

55 individuals were included with a range of *de novo* heterozygous *DNMT3A* variants: missense variants (36 individuals with 30 different variants); stop gain variants (six individuals); frameshift variants (six individuals); whole gene deletions (four individuals including identical twins (COG1961 and COG2006)); in-frame deletions (two individuals) and a splice site variant (one individual, figure 1, table 1). Computational tools (Mutation Taster and SIFT) predicted all 30 missense variants to be deleterious and the splice site variant was predicted to disrupt normal splicing (supplementary table 1). Importantly, some of the variants are common in the general population due to age-related clonal hematopoiesis, limiting the utility of databases such as gnomAD in *DNMT3A* variant pathogenicity stratification (supplementary table 1, 25426838 and 25426837).

**Results**

All 55 individuals had an intellectual disability: 18% had a mild intellectual disability (10/55); 65% had a moderate intellectual disability (36/55) and 16% had a severe intellectual disability (9/55) (table 1, figure 2). Behavioral/psychiatric issues were reported in 51% (28/55) individuals and included combinations of autistic spectrum disorder (20 individuals); anxiety (three individuals); neurodevelopmental regression (four individuals two of whom regressed in teenage years); psychosis/schizophrenia (three individuals); aggressive outbursts (two individuals), and bipolar disorder (two individuals, table 1).

Postnatal overgrowth (defined as a height and/or head circumference at least two standard deviations above the mean ((≥2SD), 28475857, 23606607) was reported in 83% (44/53) individuals. Obesity, with a weight ≥2SD, was reported in 67% (34/51). The range of individual postnatal heights, head circumferences and weights are shown in table 1 and figure 3. The mean birth weight was 1.3SD with a range from -1.1 to 4.0 SD. We had limited data for birth head circumference and birth length but their mean was 2.3SD and 1.6SD respectively.

There were some shared, but subtle, facial characteristics often only becoming apparent in early adolescence (figure 4a and 4b). These included low-set, horizontal thick eyebrows; narrow palpebral fissures; coarse features and a round face. The two upper central incisors were also frequently enlarged and prominent.

Additional clinical features reported in greater than 20% (≥ 11) individuals included: joint hypermobility (73%, 36/49); hypotonia (54%, 28/52); kyphoscoliosis (33%, 18/55) and afebrile seizures (22%, 12/55) (table 1). In addition, short, widely spaced toes were frequently mentioned, but the overall frequency is unclear as we did not specifically ask about feet/toes on the clinical proforma (figure 4c).

Clinical features reported in at least two but fewer than 20% individuals included cryptorchidism (six individuals); ventriculomegaly (four individuals) and Chiari malformation (three individuals). In addition a range of cardiac anomalies (including atrial septal defect, mitral / tricuspid valve incompetence, patent ductus arteriosus, aortic root enlargement and atrio-ventricular re-entry tachycardia) were reported in nine individuals. However, of note, two individuals with cardiac anomalies (patent ductus arteriosus, COG1961 and COG2006) were identical twins with *DNMT3A* whole gene deletions encompassing >40 genes. The patent ductus arteriosus in these individuals may, therefore, be attributable to twinning, alternative genes in the deleted region or the combined effect of a number of deleted genes.

Acute myeloid leukaemia (AML), AML-FAB (French-American-British classification) type M4, was diagnosed in one individual at the age of 12 years (COG2004). This individual had a *de novo* heterozygous c.2204A>C p.(Tyr735Ser) *DNMT3A* variant, identified in DNA obtained seven years prior to the diagnosis of AML.

Full clinical details from the 55 individuals are provided in table 1.

**Discussion**

We have evaluated clinical data from 55 individuals with *de novo* constitutive *DNMT3A* variants to define the phenotype of TBRS. An intellectual disability (most frequently in the moderate range) and overgrowth (defined as height and/or head circumference) were reported in ≥ 80% of individuals and have been designated major clinical associations. Frequent clinical associations, reported in 20-80% of individuals with constitutive *DNMT3A* variants, included joint hypermobility, obesity, hypotonia, behavioral/psychiatric issues (most frequently autistic spectrum disorder), kyphoscoliosis and afebrile seizures. In addition, many individuals had a characteristic facial appearance although this may only be recognizable in adolescence.

TBRS overlaps clinically with other OGID syndromes including Sotos syndrome (OMIM 117550), Weaver syndrome (OMIM 277590), Malan syndrome (OMIM 614753) and the OGID syndrome due to *CHD8* gene variants (28475857). However, TBRS is more frequently associated with increased weight than the other OGID syndromes and may be distinguishable through recognition of the associated facial features, and absence of the facial gestalt of other OGID syndromes.

Somatic *DNMT3A* variants are known to drive the development of adult acute myeloid leukaemia (AML) and myelodysplastic syndrome and over half of the *DNMT3A* somatic variants target a single residue, the p.Arg882 residue (21067377, 21399634, 23640996, 22234528). AML, diagnosed in childhood, has now been identified in two individuals with (likely) constitutive *DNMT3A* variants from a total of 77 (1/55 individuals in the current study and 1/22 previously reported individuals, 28432085). One of these individuals had a *de novo* c.2644CT p.(Arg882Cys) *DNMT3A* variant and developed AML at 15 years of age (28432085). The variant was present in genomic DNA extracted from the patient’s remission blood sample and skin fibroblasts. The second individual had a c.2204A>C p.(Tyr735Ser) *DNMT3A* variant identified in DNA obtained at 5 years of age and developed AML at the age of 12 years. Whilst these data indicate that AML may be a rare association of TBRS, currently the numbers of individuals reported with TBRS and AML are too few to either accurately quantify the risk of AML in TBRS or determine whether this risk is influenced by the underlying *DNMT3A* genotype. Further studies are required to address this.

The majority of individuals with TBRS are healthy and do not require intensive clinical follow up. However, our practice is to inform families and pediatricians of the possible TBRS complications of behavioral/psychiatric issues, kyphoscoliosis and afebrile seizures to introduce a low threshold for their investigation and/or management. In addition, we undertake a baseline echocardiogram at initial diagnosis to investigate cardiac anomalies detectable on ultrasound scan and frequently refer patients to physiotherapy to evaluate the degree of hypotonia and/or joint hypermobility and to determine whether targeted exercises may be beneficial. Finally, in the absence of evidence-based surveillance protocols for hematological malignancies, we advise clinical vigilance for symptoms possibly related to a hematological malignancy such as easy bruising, recurrent bleeding from gums or nosebleeds, persistent tiredness and recurrent infections.

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URLs

Online Mendelian Inheritance in man (OMIM), www.omim.org

Genome Aggregation Database, http://gnomad.broadinstitute.org

**Figures Legends**

Figure 1 DNMT3A and the positions and types of variants with protein truncating variants shown below the protein (black and red lollipops) and missense variants and inframe deletions (yellow and blue lollipops) shown above the protein. Whole gene deletions and the splice site variant are not shown on this figure. The three DNMT3A domains are shaded in grey: the proline-tryptophan-tryptophan-proline (PWWP) domain, the ATRX-Dnmt3-Dnmt3L (ADD) domain and the Methyltransferase (MTase) domain.

Figure 2 Graph showing the range of intellectual disability in TBRS.

Figure 3 Growth profile in individuals with TBRS a) height, b) head circumference and c) weight. The red line represents the mean.

Figure 4 a) The facial appearance of children and adults with TBRS; b) the evolving facial appearance in four individuals with TBRS and c) the characteristic short, widely spaced toes seen in TBRS.

**Table 1 Table of all individuals with TBRS and their associated phenotypes including growth and cognitive profiles**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case number** | **Variant type** | **Nucleotide change** | **Protein change** | **Inherit-ance** | **BW/**  **SD** | **BHC/**  **SD** | **BL/**  **SD** | **Age/**  **yrs** | **Ht/**  **SD** | **HC/**  **SD** | **Wt/**  **SD** | **ID** | **Behavioral**  **issues** | **Joint hyper-**  **mobility** | **Hypo-tonia** | **Kypho-scoliosis** | **Afebrile seizures** | **Other clinical issues** |
| COG1849 | frameshift | c.26\_27delinsT |  | de novo | 1.0 | nk | nk | 10.0 | 5.1 | nk | nk | mod | ASD | no | yes | no | yes | Multiple fungal and viral infections, precocious puberty, leg length discrepancy |
| COG1919 | missense | c.541C>T | p.(Arg181Cys) | de novo | nk | nk | nk | 11.3 | 3.1 | 1.6 | 2.8 | mod | no | no | no | no | no | Pre-auricular skin tags, 5th toe nail hypoplasia |
| COG2017 | frameshift | c.759dupC |  | de novo | -0.4 | nk | nk | 7.7 | 3.9 | 2.2 | 3.3 | mod | no | yes | yes | no | no | CAL macules, soft skin |
| COG0274 | in-frame deletion | c.889\_891delTGG |  | de novo | 3.3 | nk | 1.7 | 18.0 | 3.0 | 2.7 | nk | mod | no | nk | yes | no | yes |  |
| COG1843 | missense | c.892G>T | p.(Gly298Trp) | de novo | 1.6 | nk | 4.4 | 12.1 | 4.1 | 2.2 | 3.9 | mod | ASD, anxiety | yes | yes | no | no | Arachnoid cyst, hypospadias |
| COG2008 | missense | c.892G>A | p.(Gly298Arg) | de novo | 2.1 | 2.8 | nk | 18.0 | 0.2 | 0.7 | 2.9 | mod | Anxiety | yes | no | yes | no | Myopia (-3D) |
| COG2019 | missense | c.901C>T | p.(Arg301Trp) | de novo | nk | nk | nk | 9.3 | 2.1 | 2.1 | 1.3 | mild | no | yes | no | no | no |  |
| COG1963 | stop gain | c.918G>A | p.(Trp306X) | de novo | 1.5 | 1.2 | nk | 6.2 | 2.7 | 4.0 | 1.9 | sev | ASD, regression | nk | yes | no | yes | Seizures |
| COG1770 | missense | c.929T>A | p.(Ile310Asn) | de novo | 2.2 | 2.8 | 2.7 | 10.3 | 3.8 | 3.3 | 3.3 | sev | ASD, compulsive eating | yes | yes | yes | yes | Ventriculomegaly and Chiari malformation, multiple renal cysts, multiple urinary tract infections, constipation, lumbar haemangioma |
| COG1670 | frameshift | c.934\_937dupTCTT |  | de novo | 3.6 | nk | nk | 20.5 | 3.2 | 2.8 | 2.8 | sev | Temper tantrums, aggressive, Psychosis (paranoid hallucinations) | no | no | no | no |  |
| COG1962 | stop gain | c.941G>A | p.(Trp314X) | de novo | 0.7 | nk | nk | 5.0 | 2.1 | 0.5 | 2.2 | mod | no | no | no | no | no |  |
| COG1974 | frameshift | c.1015delC |  | de novo | 1.4 | 1.6 | 0.4 | 10.0 | 2.0 | 1.4 | 2.1 | mod | no | no | no | no | no |  |
| COG1998 | missense | c.1154C>T | p.(Pro385Leu) | de novo | -0.7 | 2.3 | 1.4 | 5.2 | 3.1 | 0.8 | 2.1 | mod | ASD | yes | yes | yes | no |  |
| COG1916 | stop gain | c.1296C>G | p.(Tyr432X) | de novo | 2.9 | 4.4 | 3.6 | 21.0 | 3.9 | 0.6 | 3.2 | mod | ASD | yes | no | yes | no | AVRNT, mitral regurgitation, pectus carinatum, amblyopia, photophobia |
| COG2007 | stop gain | c.1320G>A | p.(Trp440X) | de novo | 1.8 | nk | nk | 10.5 | 3.2 | 2.8 | 1.3 | mod | no | yes | no | no | no | Cryptorchidism |
| COG1925 | missense | c.1523T>C | p.(Leu508Pro) | de novo | 2.8 | 6.5 | 3.8 | 6.3 | 4.0 | 3.7 | 4.4 | mild | ASD | yes | yes | yes | no | Cryptorchidism |
| COG0141 | missense | c.1594G>A | p.(Gly532Ser) | de novo | 2.2 | nk | nk | 25.0 | 2.3 | 2.9 | 4.5 | mod | ASD | no | no | no | no |  |
| COG1995 | missense | c.1594G>A | p.(Gly532Ser) | de novo | 3.9 | nk | nk | 22.0 | 2.9 | 3.6 | 3.0 | mild | ASD | yes | no | no | no |  |
| COG0422 | missense | c.1643T>A | p.(Met548Lys) | de novo | 1.3 | 1.6 | nk | 15.3 | 1.4 | 3.4/12.8 yrs | 3.4 | sev | Aggression | yes | yes | no | no | Atrial septal defect |
| COG2009 | missense | c.1643T>C | p.(Met548Thr) | de novo | 1.7 | nk | nk | 15.3 | 1.7 | 3.4 | 1.9 | sev | ASD | yes | yes | no | yes | Umbilical hernia, early puberty, cryptorchidism |
| COG1288 | missense | c.1645T>C | p.(Cys549Arg) | de novo | 1.1 | 1.6 | 2.6 | 17.9 | 1.6 | 3.6 | 2.6 | mod | no | yes | yes | yes | no | Atrial septal defect, sagittal craniosynostosis |
| COG2010 | missense | c.1684T>C | p.(Cys562Arg) | de novo | nk | nk | nk | 9.5 | 1.7 | -0.3/5.1yrs | 1.0/5.1yrs | mod | no | yes | no | no | no | Mild tonsillar ectopia |
| COG2003 | missense | c.1743G>C | p.(Trp581Cys) | de novo | -1.0 | nk | nk | 20.3 | 1.1 | 1.1 | 1.2 | sev | no | yes | yes | no | yes | Cryptorchidism, lipoma, hirsutism |
| COG2013 | missense | c.1743G>T | p.(Trp581Cys) | de novo | 0.7 | nk | 2.3 | 2.5 | 2.5 | 2.7 | 1.4 | mod | no | yes | yes | no | yes | Chiari malformation and ventriculomegaly, umbilical hernia |
| COG2002 | missense | c.1748G>A | p.(Cys583Tyr) | de novo | 2.5 | nk | 1.1 | 15.4 | 1.7 | 1.6 | 1.2 | sev | regression | yes | yes | yes | yes | Seizures (tonic-clonic) |
| COG0510 | stop gain | c.1803G>A | p.(Trp601X) | de novo | 2.9 | nk | 1.5 | 18.8 | 2.1 | 0.6 | 4.1 | sev | obsessive | yes | no | no | no | Endochrondroma |
| COG1972 | splice site | c.1851+3G>C |  | de novo | 1.3 | nk | nk | 6.6 | 4.0 | -1.2 | 3.1 | mod | no | nk | no | yes | no | Strabismus, myopia, thyroid cyst |
| COG0553 | missense | c.1943T>C | p.(Leu648Pro) | de novo | -0.4 | nk | nk | 19.0 | 2.5 | 3.1 | 4.3 | mild | ASD | no | no | no | no |  |
| COG2021 | frameshift | c.2056delG |  | de novo | 0.8 | 1.8 | 0.8 | 10.0 | 0.6 | 2.0 | 0.7 | mild | no | nk | no | no | yes | Seizures |
| COG1942 | missense | c.2094G>C | p.(Trp698Cys) | de novo | 0.4 | nk | nk | 21.0 | 3.7 | 2.5 | 1.4/18.9yrs | mod | ASD, severe psychosis and bipolar disorder | yes | yes | yes | no | Menorrhagia, severe constipation |
| COG1688 | missense | c.2099C>T | p.(Pro700Leu) | de novo | 1.2 | nk | 0.4 | 15.4 | 2.6 |  | 3.3 | mod | ASD | yes | yes | yes | no |  |
| COG0316 | missense | c.2141C>G | p.(Ser714Cys) | de novo | 1.2 | nk | nk | 4.4 | 3.0 | 1.4 | 2.9 | sev | no | yes | yes | yes | no | Bilateral hydroureteronephrosis and left ureteral ectasia, platelet disorder, thick skull vault and sclerosis of sutures |
| COG2004 | missense | c.2204A>C | p.(Tyr735Ser) | de novo | 1.6 | nk | nk | 20.0 | 2.5 | 2.8 | 2.5 | mild | no | no | no | no | no | AML-FAB type M4 diagnosed age 12 years |
| COG0447 | missense | c.2207G>A | p.(Arg736His) | de novo | 1.0 | nk | 0.6 | 8.5 | 3.0 | 2.0 | 2.5 | mild | no | yes | no | no | no |  |
| COG1695 | missense | c.2245C>T | p.(Arg749Cys) | de novo | 0.8 | 0.6 | 2.0 | 15.5 | 2.8 | 3.8 | 1.4 | mod | no | yes | no | yes | no | Vesico-ureteric reflux, hypodontia |
| COG2005 | missense | c.2245C>T | p.(Arg749Cys) | de novo | -1.0 | nk | 0.4 | 23.0 | 0.5 |  | 2.7 | mod | ASD, psychosis and schizophrenia | yes | no | no | no |  |
| COG0108 | missense | c.2246G>A | p.(Arg749His) | de novo | 0.3 | nk | nk | 20.8 | 1.2 | 1.3 | 4.4 | mod | no | yes | yes | no | no |  |
| COG1632 | in-frame deletion | c.2255\_2257delTCT |  | de novo | 1.8 | 2.2 | 2.5 |  | nk | nk | nk | mod | no | nk | no | no | no | Tight achilles tendons |
| COG1512 | frameshift | c.2297dupA |  | de novo | 4.0 | 3.5 | nk | 13.3 | 3.8 | 1.5 | 1.9 | mod | no | yes | no | no | no |  |
| COG2011 | missense | c.2309C>T | p.(Ser770Leu) | de novo | 0.9 | nk | nk | 16.3 | 2.6 | -0.1 | 0.4 | mod | Bipolar disorder | yes | yes | yes | no | Aortic root enlargement and mitral valve regurgitation, hyperthyroidism |
| COG1971 | missense | c.2312G>A | p.(Arg771Gln) | de novo | 1.2 | nk | nk | 3.1 | 3.4 | 3.4/2.6yrs | 3.1 | mod | ASD | nk | yes | no | no | Keratosis pilaris |
| COG1964 | missense | c.2401A>G | p.(Met801Val) | de novo | 3.0 | 2.8 | 2.6 | 8.8 | 2.1 | -0.2 | 2.0 | mod | regression | yes | nk | yes | yes |  |
| COG1771 | missense | c.2512A>G | p.(Asn838Asp) | de novo | 0.8 | nk | 1.5 |  | nk | nk | nk | mild | no | yes | nk | yes | yes | Testicular atrophy |
| COG1923 | missense | c.2644C>T | p.(Arg882Cys) | de novo | 3.0 | 4.4 | nk | 5.8 | -0.2 | 2.5 | 1.1 | mod | no | yes | yes | no | no | Hydrocephalus secondary to neonatal intraventricular bleed, swallowing difficulties |
| COG1945 | missense | c.2644C>T | p.(Arg882Cys) | de novo | 0.8 | 0.5 | 0.6 | 2.0 | 2.7 | 0.3 | 2.9 | mod | no | no | yes | no | no | Cryptorchidism, capillary malformation, strabismus, bilateral inguinal herniae, ventriculomegaly |
| COG1999 | missense | c.2644C>T | p.(Arg882Cys) | de novo | 0.9 | nk |  | 2.0 | 0.9 | 2.1 | 2.2 | mod | no | yes | yes | no | no | Ventriculomegaly, obstructive and central sleep apnoea, cryptorchidism |
| COG2012 | missense | c.2645G>A | p.(Arg882His) | de novo | 0.3 | 2.2 | 1.2 | 1.5 | -0.2 | -0.8 | -1.4 | mod | no | yes | yes | yes | no | Atrial septal defect, bifid sternum, umbilical hernia |
| COG1760 | stop gain | c.2675C>A | p.(Ser892X) | de novo | 0.9 | 1.2 | 0.4 | 12.9 | 4.2 | 3.0 | 3.4 | mild | no | no | no | no | no | Pes planus |
| COG0109 | missense | c.2705T>C | p.(Phe902Ser) | de novo | 1.7 | nk | 2.0 | 21.5 | 1.5 | 1.4 | 1.7 | mod | ASD | yes | no | yes | no | Mitral and tricuspid regurgitation, polycystic ovarian syndrome, myopia |
| COG1677 | missense | c.2711C>T | p.(Pro904Leu) | de novo | 0.7 | nk |  | 7.3 | 3.9 | -0.4 | 3.9 | mod | ASD | yes | yes | no | no | Gowers manoeuvre on standing |
| COG1887 | missense | c.2711C>T | p.(Pro904Leu) | de novo | 1.8 | nk | 0.0 | 9.5 | -0.3 | 0.3 | -1.1 | mod | Anxiety and ADHD | yes | yes | yes | no | Mitral regurgitation, Chiari malformation |
| COG1813 | gene del |  |  | de novo | 1.0 | 1.6 | 1.5 | 23.0 | 3.0 | 3.2 | 4.0 | mod | no | yes | no | no | no | Double teeth, recurrent infections, polycystic ovaries syndrome |
| COG1961 | gene del |  |  | de novo | -0.1 | nk | nk | 5.8 | 2.7 | 1.9 | 2.8 | mod | ASD | no | yes | no | no | Patent ductus arteriosus, hirsutism |
| COG2006 | gene del |  |  | de novo | -1.1 | nk | nk | 5.8 | 2.3 | 1.6 | 2.1 | mod | ASD | no | yes | no | no | Patent ductus arteriosus, hirsutism |
| COG2014 | gene del |  |  | de novo | 0.3 | 0.8 | 0.2 | 3.0 | 2.2 | 0.7/2.0yrs | 2.8 | mild | ASD, regression | no | no | no | yes | Recurrent ear infections, subclinical seizures |

Abbreviations: nk, not known; ID, intellectual disability; CAL, café au lait; SD, standard deviation; gene del, whole gene deletion; BW, birth weight; BHC, birth head circumference; BL, birth length; Ht, height; Wt, weight; HC, head circumference; mod, moderate; sev, severe; ASD, autistic spectrum disorder; br MRI, brain magnetic resonance imaging; AML, acute myeloid leukemia; FAB, Franco-American-British; ADHD, attention deficit hyperactivity disorder; AVRNT, atrio-ventricular nodal re-entry tachycardia,

**Figure 1**



**Figure 2**

**Figure 3**

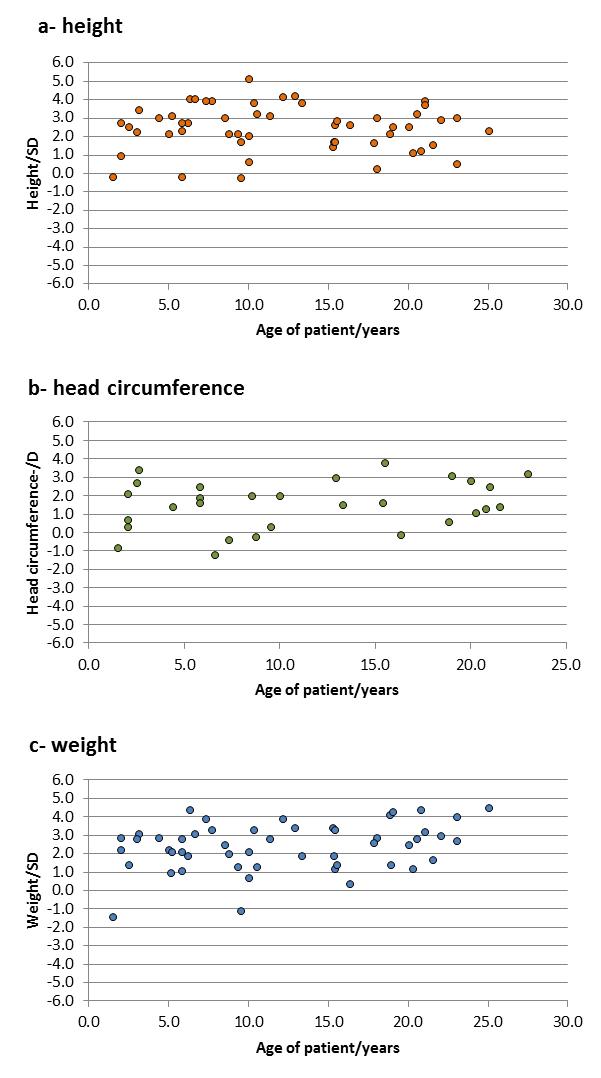


Figure 4

**Supplemental note**

The Childhood Overgrowth Collaboration

The following individuals coordinated recruitment and collection of the families and samples. M-C. Addor, M. Akgul, L. Aksglaede, M. Ahmed, D. Amor, K. Anderson, R. Anderson, S. Andries, H. Archer, R. Armstrong, P. Ashton-Prolla, M. Bahceci, M. Balasubramanian, D. Baralle, D. Barge, A. Barnicoat, M. Barrow, J. Barwell, G. Baujat, G. Baynam, P. Beales, K. Becker, E. Beckh-Arnold, A. Ben-Yehuda, J. Berg, B. Bernhard, S. Bhal, M. Bhat, J. Birch, L. Bird, M. Bitner-Glindzicz, E. Blair, J. Bliek, M. Blyth, A. Bottani, M. Bouma, M. Boxill, F. L. Bradley, A. Brady, Breatnach, G. Brice, B. Buehler, A. Burke, J. Burn, J. Campbell, N. Canham, B. Castle, K. Chandler, R. Chandrasena, E. Chang, C. Christenden, C. Chu, D. Cilliers, A. Clarke, J. Clayton-Smith, C. Clericuzio, V. Clowes, T. Cole, A. Colley, A. Collins, F. Connell, J. Cook, I. Cordeiro, E. Crocker, Y. Crow, V. Culic, T. Cushing, T. Dabir, A. Dalton, S. Danda, R. Davidson, S. Davies, R. Day, D. Dearnaley, M-A. Delrue, M. De Roy, V. de Soberanis, M. de Ville, N. Dennis, C. Deshpande, B. Desouza, L. Devlin, A A. Dieckmann, -M. Differ, R. Dinwiddie, A. Dixit, A. Dobbie, J. Dominguez, A. Donaldson, D. Donnai, D. Donnelly, H. Dorkins, M. Doz, J. Dupont, D. Eastwood, M. Edwards, I. Ellis, F. Elmslie, L. Escobar, R. Evans, F. Faravelli, C. Fauth, H. Firth, R. Fisher, T. Fiskerstrand, D. Fitzpatrick, A. Flanagan, F. Flinter, P. Foley, A. Foster, N. Foulds, W. Foulkes, J. Franklin, A. Fryer, H. Fryssira, A. Gallagher, S. Garcia, C. Gardiner, M. Gardner, C. Garrett, B. Gener, M. Gerrard, R. Gibbons, Y. Gillerot, H. Goel, D. Goudie, K. Gowrishankar, C. Graham, A. Green, N. Gregersen, J. Hale, M. Hamilton, J. Harper, R. Harrison, V. Harrison, A. Henderson, P. Henman, R. Hennekam, E. Hobson, S. Hodgson, M. Holder, S. Holder, T. Homfray, D. Horovitz, H. Hughes, Z. Huma, M. Hunter, J. Hurst, W-L. Hwu, A. Irvine, M. Irving, L. Izatt, M-L. Jacquemont, S. Jagadeesh, L. Jenkins, U. Jensen, C. Jessen, D. Johnson, J. Johnson, E. Jones, L. Jones, A. Jorgensen, D. Josifova, S. Joss, Dr. Kanabar, P. Kannu, K. Keppler-Noreuil, B. Kerr, H. Kingston, J. Kingston, U. Kini, E. Kinning, A. Krause, V. Krishnamurthy, A. Kumar, D. Kumar, A. Medeira, V. Meiner, C. Mercer, K. Milstein, Y. Miyoshi, E. Moran, K. Lachlan, W. Lam, P. Lapunzina, M. Lees, N. Leonard, G. Levitt, I. Lewis, J. Liebelt, A. Livesey, C. Longman, T. Lopponen, Dr Lozano, A. Lucassen, P. Lunt, S-A Lynch, S. Lyonnet, J. MacDonnell, A. Magee, E. Maher, S. Maitz, A. Male, S. Mansour, C. Marcelis, E. McCann, V. McConnell, T. McDevitt, M. McEntagart, J. McGaughran, G. McGillivray, R. McGowan, S. McKee, C. McKeown, C. Meany, S. Mehta, K. Metcalfe, Z. Miedzybrodzka, S. Mohammed, G. Monaghan, T. Montgomery, A. Morgan, B. Morland, P. Morrison , J. Morton, R. Mudgal, A. Munaza, V. Murday, S. Nampoothiri, K. Nathanson, K. Neas, A. Nemeth, G. Neri, R. Newbury-Ecob, C. Nur Semerci, C. Ockeloen, C. Oley, C. Owen, K. Ozono, Panarello, S-M. Park, M. Parker, C. Patel, M. Patton, S. Payne, M. Pearson, J. Piard, D. Pilz, M. Pinkney, B. Plecko, M. Pocha, G. Poke, R. Posmyk, C. Pottinger, K. Prescott, S. Price, K. PritchardJones, A. Proctor, V. Puthi, O. Quarrell, A. Raas-Rothchild, E. Rahikkala, W. Raith, J. Rankin, L. Raymond, G. Rea, L. Read, W. Reardon, E. Reid, H.Rees, N. Revencu, O. Rittinger, M. Robards, A. Roposch, E. Rosser, D. Rourke, D. Ruddy, A. Saggar, N. Saleh, V. Saletti, J. Sampson, R. Sandford, H. Santos, A. Sarkar, R. Scott, I. Scurr, C. Searle, A. Selicorni, R. Semple, S. Sharif, A. Shaw, C. Shaw-Smith, D. Shears, J. Shelagh, N. Shur, L. Side, M. Simon, F. Skovby, G. Smith, S. Smithson, M. Splitt, M. Stevens, A. Stewart, F. Stewart, H. Stewart, K. Stopps, C. Stumpel, K. Stuurman, D. Subramanian, M. Suri, A. Swain, E. Sweeney, K. Szakszon, Y. Sznajer, G. Tanateles, A. Taylor, C. Taylor, M. Teixeira, I.K. Temple, E. Thomas, E. Thompson, F. Thonney, M. Tischowitz, J. Tolmie, S. Tomkins, S. Turkmen, A. Turner, P. Turnpenny, M. Van-Haelst, L. Van Maldergem, P. Vasudevan, I. Veenstra-Knol, C. Verellen, I.C. Verma, J. Vigneron, E. Wakeling, L. Wainwright L. Walker, D. Weaver, P. Wheeler, K. White, S. White, M. Whiteford, D. Williams, L. Wilson, R. Winter, G. Woods, M. Wright, N. Yachelevich, A. Yeung, A. Zankl

**Supplementary table 1**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Nucleotide change** | **Protein change** | **GnomAD allele count** | **Mutation Taster** | **SIFT** |
| c.541C>T | p.(Arg181Cys) | 0 | Disease causing | Damaging |
| c.892G>A | p.(Gly298Arg) | 0 | Disease causing | Damaging |
| c.892G>T | p.(Gly298Trp) | 0 | Disease causing | Damaging |
| c.901C>T | p.(Arg301Trp) | 0 | Disease causing | Damaging |
| c.929T>A | p.(Ile310Asn) | 0 | Disease causing | Damaging |
| c.1154C>T | p.(Pro385Leu) | 7 | Disease causing | Damaging |
| c.1523T>C | p.(Leu508Pro) | 0 | Disease causing | Damaging |
| c.1594G>A | p.(Gly532Ser) | 0 | Disease causing | Damaging |
| c.1643T>A | p.(Met548Lys) | 0 | Disease causing | Damaging |
| c.1643T>C | p.(Met548Thr) | 0 | Disease causing | Damaging |
| c.1645T>C | p.(Cys549Arg) | 0 | Disease causing | Damaging |
| c.1684T>C | p.(Cys562Arg) | 0 | Disease causing | Damaging |
| c.1743G>C | p.(Trp581Cys) | 2 | Disease causing | Damaging |
| c.1748G>A | p.(Cys583Tyr) | 2 | Disease causing | Damaging |
| c.1943T>C | p.(Leu648Pro) | 0 | Disease causing | Damaging |
| c.2094G>C | p.(Trp698Cys) | 0 | Disease causing | Damaging |
| c.2099C>T | p.(Pro700Leu) | 1 | Disease causing | Damaging |
| c.2141C>G | p.(Ser714Cys) | 2 | Disease causing | Damaging |
| c.2204A>C | p.(Tyr735Ser) | 3 | Disease causing | Damaging |
| c.2207G>A | p.(Arg736His) | 11 | Disease causing | Damaging |
| c.2245C>T | p.(Arg749Cys) | 7 | Disease causing | Damaging |
| c.2246G>A | p.(Arg749His) | 5 | Disease causing | Damaging |
| c.2309C>T | p.(Ser770Leu) | 6 | Disease causing | Damaging |
| c.2312G>A | p.(Arg771Gln) | 1 | Disease causing | Damaging |
| c.2401A>G | p.(Met801Val) | 4 | Disease causing | Damaging |
| c.2512A>G | p.(Asn838Asp) | 3 | Disease causing | Damaging |
| c.2644C>T | p.(Arg882Cys) | 35 | Disease causing | Damaging |
| c.2645G>A | p.(Arg882His) | 62 | Disease causing | Damaging |
| c.2705T>C | p.(Phe902Ser) | 1 | Disease causing | Damaging |
| c.2711C>T | p.(Pro904Leu) | 9 | Disease causing | Damaging |