Cytogenetic and Genome Research

Novel Insights from Clinical Practice

Cytogenet Genome Res 2020;160:185–192
DOI: 10.1159/000507409

Received: December 16, 2019
Accepted: March 10, 2020
Published online: April 22,2020

Directly Transmitted 12.3-Mb Deletion with a Consistent Phenotype in the Variable 11q21q22.3 Region

Beth Kirk[a] Mira Kharbanda[b] Mark S. Bateman[a] David Hunt[b, c] Emma-Jane Taylor[a] Amanda L. Collins[b] David J. Bunyan[a, c] Morag N. Collinson[a] Louisa M. Russell[a] Sarah Bowell[a, d] John C.K. Barber[c]

[a]Wessex Regional Genetics Laboratory, Salisbury NHS Foundation Trust, Salisbury, UK; [b]Wessex Clinical Genetics Service, Southampton University Hospitals NHS Foundation Trust, Princess Anne Hospital, Southampton, UK; [c]Human Development and Health, Faculty of Medicine, Southampton General Hospital, University of Southampton, Southampton, UK; [d]Laboratory Genetics Service, Liverpool Women's NHS Foundation Trust, Liverpool, UK

Established Facts

- Medial 11q contains 2 pairs of G-dark bands of which a phenotype is emerging for the proximal pair (11q14.1 and q14.3) but not yet for the distal pair (11q22.1 and q22.3) due to variable deletion sizes and phenotypes.
- At least 4 large deletions of 11q22 have been directly transmitted from parents to children, of which 2 had few or no apparent phenotypic consequences.

Novel Insights

- A mother and daughter had the same directly transmitted 12.3-Mb interstitial deletion of 11q21q22.3 and common features of initial feeding difficulties and failure to thrive, speech delay, learning difficulties, and mild dysmorphism.
- This family and the features in 17 overlapping deletions may provide the basis for a phenotype for this variable region.
- *CNTN5*, *YAP1*, and *GRI4* are the most likely candidate genes.
- Non-penetrance of haploinsufficient genes and dosage compensation among related genes may account for variable phenotypes that can extend into the normal range.

Keywords
Candidate genes · Phenotype · Transmitted deletion · 11q

Abstract
A phenotype is emerging for the proximal pair of G-dark bands in 11q (11q14.1 and q14.3) but not yet for the distal pair (11q22.1 and q22.3). A mother and daughter with the same directly transmitted 12.3-Mb interstitial deletion of 11q21q22.3 (GRCh37: 93,551,765–105,817,723) both had initial feeding difficulties and failure to thrive, speech delay, learning difficulties, and mild dysmorphism. Among 17 patients with overlapping deletions, developmental or speech delay, dysmorphism, hypotonia, intellectual disability or learning difficulties, short stature, and coloboma were each found in 2 or more. These results may provide the basis for a

karger@karger.com
www.karger.com/cgr

Dr. John C.K. Barber
Human Development and Health, Faculty of Medicine
Southampton General Hospital, University of Southampton
Tremona Road, Southampton SO16 6YD (UK)
john.barber@soton.ac.uk

consistent phenotype for this region. Among the 53 deleted and additional breakpoint genes, *CNTN5*, *YAP1*, and *GRI4* were the most likely candidates. Non-penetrance of haploinsufficient genes and dosage compensation among related genes may account for the normal cognition in the mother and variable phenotypes that can extend into the normal range.

Medial 11q contains 2 major pairs of proximal (11q14.1 and q14.3) and distal G-dark bands (11q22.1 and q22.3) that could not be reliably distinguished using G-banding in the past [Li et al., 2006]. Fluorescence in situ hybridisation (FISH) [Horelli-Kuitunen et al., 1999; Li et al., 2002], comparative genomic hybridization (CGH) [Goumy et al., 2008], and array CGH (aCGH) [Li et al., 2006; Sparkes et al., 2009; Kariminejad et al., 2010; Melis et al., 2010; Wincent et al., 2010; Nacinovich et al., 2014] have overcome this problem, and an emerging phenotype of mild to moderate developmental delay, ptosis, and dysmorphism has been described for interstitial deletions involving the proximal 11q14.1q14.3 block of medial 11q [Joyce et al., 1996; Melis et al., 2010; Wincent et al., 2010]. However, the heterogeneity of overlapping deletions and the variability of the associated phenotypes have prevented the delineation of a corresponding phenotype for interstitial deletions of the distal 11q22.1q22.3 block of medial 11q [Nacinovich et al., 2014; Tucker et al., 2016].

Directly transmitted deletions remain rare but provide the opportunity of finding common features in more than one family member [Barber, 2005; Bateman et al., 2018]. Here, we report a mother and daughter with a 12.3-Mb deletion of 11q21q22.3 who have similar phenotypes and features in common with those in 17 overlapping deletions. These may provide the basis for a consistent phenotype for this region.

Clinical Patient Reports

The index patient was originally referred during her first pregnancy at 8 weeks gestation for a family history of myotonic dystrophy. She had not inherited the expansion found in her father as her alleles (of 12 and 16 repeats) were within the normal range. This pregnancy ended in a spontaneous abortion at 18 weeks. Tissue karyotyping was normal with no evidence of a 22q11.2 deletion using FISH. Two years later, her second pregnancy had a raised nuchal measurement giving a combined risk of 1 in 50 but ended in a spontaneous miscarriage at 16 weeks gestation. Tissue karyotyping was normal female. Low-set ears, micrognathia, possible hypotelorism, incomplete closure of the foramen ovale, and a cystic hygroma were found at post-mortem, but cervical incompetence was suspected, and these features could be attributed to chronic amniotic fluid loss. The proband was re-referred 2 years later due to her mild dysmorphisms, short stature, 2 mid-trimester miscarriages, and an endocrine disorder. She was 32 years old, 145 cm tall (<0.4th centile; –3.09 SD), had slightly unusual ears, a thin upper lip, prominent forehead, mildly short metacarpals, and had been diagnosed with polycystic ovary syndrome and hypothyroidism (Fig. 1A). Apart from her short stature, she had normal mental and physical development with menarche at age 15 years. A maternal aunt was reported to be of similar height and also hypothyroid. As a child, the index patient had failure to thrive and poor food intake, speech delay (did not speak until 5 years old), mild learning difficulties (needed extra support at school), recurrent infections, hypermobility, and dyspraxia. She possibly has some autistic traits but has never been formally assessed.

Her only surviving daughter was referred for microarray analysis at the age of 5 years with speech and language delay, learning difficulties, and autistic traits. Growth parameters were height 101 cm (2nd–9th centiles; –1.51 SD), weight 16.65 kg (25th centile; –0.58 SD), and head circumference 49.3 cm (2nd centile; –1.92 SD). She has mild hypertelorism, a prominent forehead, a thin upper lip, and a high narrow palate (Fig. 1B). She has subsequently been diagnosed with autism spectrum disorder (ASD). She has relatively long fingers, and mild bilateral 2–3 toe syndactyly. Both mother and daughter are facially similar (Fig. 1A, B).

Material and Methods

G-banded chromosomes were prepared using standard methods. Oligonucleotide aCGH (oaCGH) was performed on the index patient with a targeted Oxford Gene Technologies (OGT, Oxford, UK) 60-mer oligonucleotide array customized by the International Standard Cytogenomic Array Consortium (ISCA) (http://www.ncbi.nlm.nih.gov/clinvar/) [Baldwin et al., 2008], printed in an 8x60K configuration and analysed with OGT CytoSure Interpret Software configured to genome assembly NCBI build 36/hg18. This and other published hg18 base pair coordinates were converted to GRCh37/hg19 using the University of Santa Clara California (UCSC) LiftOver tool. For the daughter, an OGT CytoSure™ Constitutional v3 oligonucleotide array was used and analysed using CytoSure Interpret version 4.9.40 software configured to genome assembly NCBI build GRCh37/hg19. The average backbone resolution of this array varies from 189 kb in high priority regions, to 375 kb in medium priority regions and 663 kb in low priority regions, depending on the significance of the region in relation to developmental delay. For multiplex ligation-dependent probe amplification analysis (MLPA), the standard protocol of MRC-Holland was used [Schouten et al., 2002] with an in-house probe pair targeting exon 21 of the *CNTN5* gene (5′ probe AACCCAGTGCTGCTCCCACAGATGTCAAGGCGACAAGTGTGTCTGTGTCAGAGATTCTTGTTGCA and 3′ probe TGGAAACACATTAAAGAGAGTCTAGGAAGACCACAGGGATTTGAG with the gene-specific parts of the probes underlined). MLPA PCR products were separated on an Applied Biosystems 3100 Sequencer (ABI, Santa Clara, CA, USA), analysed using ABI Genotyper version 2.0 and the results collated with an Excel spreadsheet [Bunyan et al., 2004]. Haploinsufficiency likelihood scores were taken from Dataset 2 of Huang et al. [2010]. Probability of loss-of-function intolerance (pLI) scores were taken from the Genome Aggregation Database (gnomAD v2.1; https://

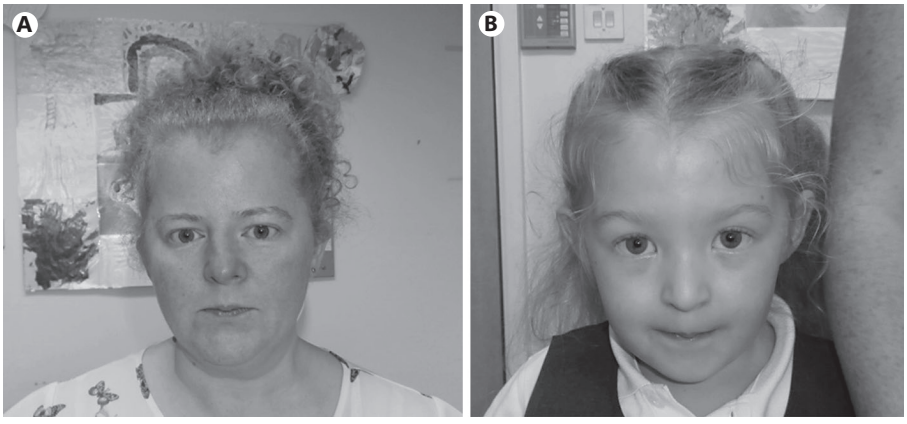

Fig. 1. Portrait views of the mother (**A**) and daughter (**B**). Note the similar facial appearance.

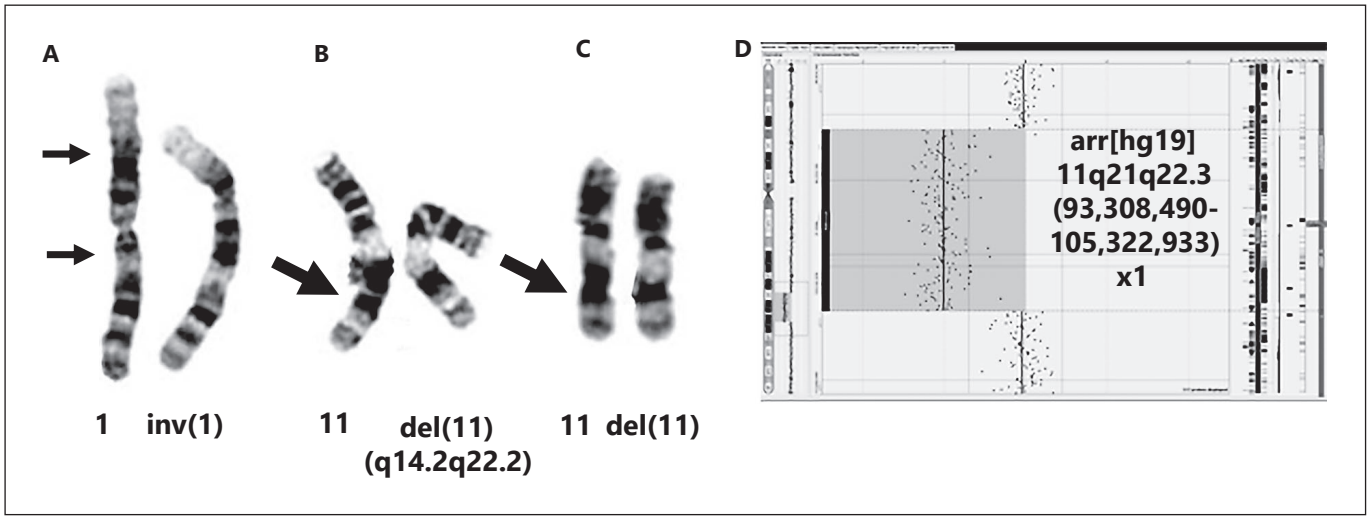

Fig. 2. Partial karyotypes (with regions of interest arrowed on the normal chromosomes) and oaCGH results. **A** G-banded chromosomes 1 of the mother showing the balanced 1p32q21.1 inversion. **B** Chromosomes 11 of the index patient showing the 11q14.2q22.2 deletion. **C** Chromosomes 11 of the daughter showing the 11q14.2q22.2 deletion. **D** The deletion in the mother reassigned to browser bands 11q21q22.3 by oaCGH with a vertical idiogram of chromosome 11 on the left and a magnified image of the minimum extent of the deleted region in the centre with the GRCH37/hg19 base pair coordinates.

gnomad.broadinstitute.org) [Lek et al., 2016]. This report makes use of data from the ClinVar database (http://www.ncbi.nlm.nih.gov/clinvar/) [Landrum et al., 2014], the Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER) (https://decipher.sanger.ac.uk/) [Firth et al., 2009], and Online Mendelian Inheritance in Man (OMIM, http://www.omim.org/).

Results

An apparently balanced pericentric inversion between bands 1p32 and 1q21.1 was found in the index patient (Fig. 2A) and an interstitial deletion of 11q14.2q22.2 in both the index patient (Fig. 2B) and her daughter (Fig. 2C). Using oaCGH, there was no evidence of imbalances at the inversion breakpoints in chromosome 1, and the deletion was reassigned to 11q21q22.3 (Fig. 2D). The deletion was 12.27 to 12.47 Mb in size and contained 53 protein-coding genes as well as 6 microRNAs. Six genes may have been deleted or partially deleted at the 143-kb centromeric and/or 63-kb telomeric breakpoint intervals (Fig. 3). The normal karyotype in the mother of the index patient and the normal dosage of the *CNTN5* gene in her father using MLPA (data not shown), implies that the deletion was de novo (Fig. 3).

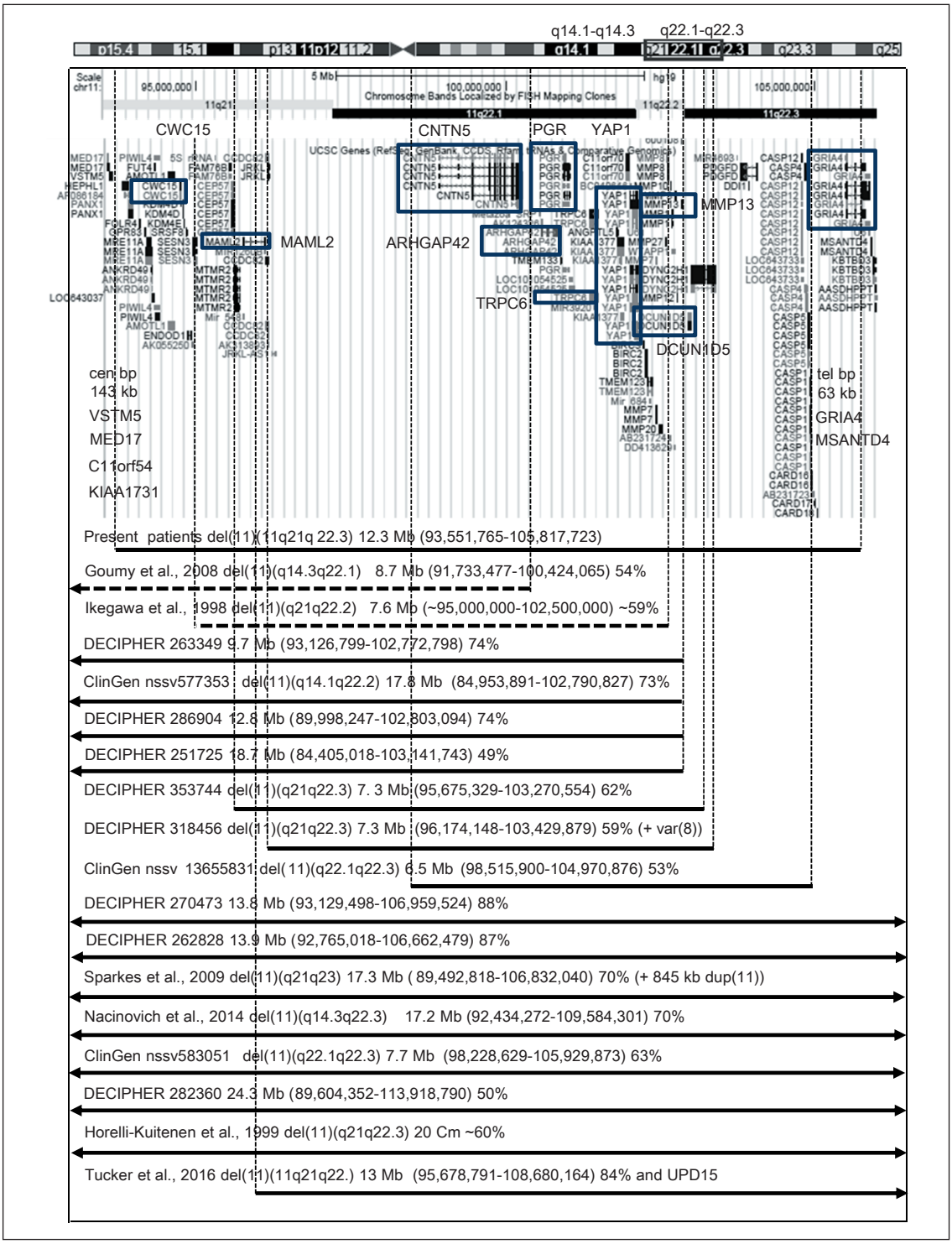

Fig. 3. The present and 17 overlapping deletions displayed beneath a screenshot of 11q from 93.5 to 106 Mb UCSC genome browser (GRCh37/hg19) (http://genome.ucsc.edu/) with the major pairs of proximal (11q14.1 and q14.3) and distal G-dark bands (11q22.1 and q22.3) labelled above. The deletions are represented by horizontal lines with dashed lines for those with no apparent phenotype and arrows for those that extend beyond the screenshot. The deleted intervals, size (Mb), minimum extent, and degree of overlap (%) are given for each deletion (>3 Mb) analysed with molecular cytogenetic techniques. Selected UCSC genes discussed in the text are in oblong boxes and labelled. The almost exactly overlapping deletion in DECIPHER patient 767 was excluded due to 2 large additional imbalances.

Table 1. Ascertainment and phenotypes associated with 17 overlapping deletions of 11q

Reference	Deletion	Minimum extent (hg19)	Size, Mb	Overlap, Mb (%)	Ascertainment	Phenotype
Present mother	11q21q22.3 de novo	93,668,842–105,817,723	12.3	12.3 (100)	Family history of muscular dystrophy	**Mild dysmorphism** (unusual ears); mildly short metacarpals; **short stature**; PCOS. As a child, failure to thrive, poor food intake, **speech delay**, **mild learning difficulties**, recurrent infections, hypermobility, and dyspraxia.
Present daughter	11q21q22.3 (transmitted)	93,551,765–105,817,723	12.3	12.3 (100)	Speech and language delay	**Mild dysmorphism**, **speech and language delay**, **learning difficulties,** and autism spectrum disorder
Goumy et al., 2008	11q14.3q22.1 (transmitted)	BAC FISH: 91,733,477–100,424,065	8.6	6.6 (54)	Raised serum at prenatal diagnosis	Mother: endometrial polyps, toe camptodactyly, hypermetropia, astigmatism and strabismus; all regarded as common in the population Grandfather: none
Ikegawa et al., 1998	11q21q22.2 (transmitted)	Cosmid FISH: LN215-4–CN2900 (~95–102.5)	7.3	7.3 (~59)	Short stature and knee deformities	Pseudoachondroplasia (due to a *COMP* mutation)
DECIPHER 263349	11q21q22.2 de novo	93,126,799–102,772,798	9.7	9.1 (74)	n/a	**Delayed speech and language development**, epicanthus; feeding difficulties in infancy; **intellectual disability**; joint laxity; muscular **hypotonia**
ClinGen nssv 577353	11q14.1q22.2	84,953,891–102,790,827	17.8	9 (73)	n/a	Facial **dysmorphism**; muscular **hypotonia**
DECIPHER 286904	11q14.3q22.2 de novo	89,998,247–102,803,094	12.8	9.1 (74)	n/a	**Dysmorphism**: cleft palate; downslanted palpebral fissures; ectropion of lower eyelids; blue sclerae; fine hair; hearing abnormality; hypoplasia of dental enamel; soft skin
DECIPHER 251725	11q14.1q22.3 de novo	84,405,018–103,141,743	18.7	6 (49)	n/a	**Dysmorphism**: midface retrusion
DECIPHER 353744	11q21q22.3 de novo	95,675,329–103,270,554	7.6	7.6 (62)	n/a	**Delayed speech and language development**; **mild global developmental delay**
DECIPHER 318456	11q21q22.3; var(8)(p23.1p23.1)	96,174,148–103,429,879	7.3	7.3 (59)	n/a	**Delayed gross motor development; mild expressive language delay; mild receptive language delay**
ClinGen nssv 13655831	11q22.1q22.3	98,515,900–104,970,876	6.5	6.5 (53)	n/a	**Developmental delay** and/or other significant developmental or morphological phenotypes
DECIPHER 270473	11q21q22.3; dup16p13.11; dup(11q23.3) (231 kb)	93,129,498–106,959,524	13.8	12.2 (88)	n/a	**Dysmorphism**: deeply set eyes; macrocephaly; **intellectual disability**; **short stature** and 16p13.11 microduplication syndrome
DECIPHER 262828	11q14.3q22.1 (transmitted)	92,765,018–106,662,479	13.9	12.1 (87)	n/a	Proband: **abnormality of the face** at age of less than 1 inherited from parent with a **similar phenotype**
Sparkes et al., 2009	11q21q22.3 (transmitted)	89,492,818–106,832,040	17.3	12.1 (70)	Multiple USS markers and anomalies in fetus at prenatal diagnosis	Fetus: left **talipes equinovarus**; right atrial and ventricular enlargement; global cerebellar hypoplasia and a small area of gray matter heterotopia in the deep white matter of the occipital lobe Mother: anisometropia with high myopia, posterior subcapsular cataract and congenital left superior oblique palsy; non-specific multifocal white matter changes and subtle superior cerebellar atrophy on MRI; no evidence of heterotopia
Nacinovich et al., 2014	11q14.3q22.3	92,434,272–109,584,301	17.2	12.1 (70)	**Hypotonia**; minor **dysmorphism** at birth	Speech and mild **developmental delay**; cognitive development in the lower normal range (WIPPSI); submucous cleft palate
ClinGen nssv 583051	11q22.1q22.3	98,228,629–105,929,873	7.7	7.6 (63)	n/a	**Developmental delay** and/or other significant developmental or morphological phenotypes
DECIPHER 282360	11q14.1q23.2	89,604,352–113,918,790	24.3	12.1 (50)	n/a	Iridoretinal **coloboma** [Williamson et al., 2014]
Horelli-Kuitunen et al., 1999	11q21q22.3	YAC FISH: 11H7-1H4	20 cM	12.1 (~61)	Choroid plexus cysts and mildly dilated renal pelvices on USS; minor anomalies; **short stature**	**Dysmorphism**; **hypotonia**; mild hydronephrosis; small cerebral cysts; enlarged lateral brain ventricles; thin corpus callosum and diminished quantity of parietal white matter; **speech delay**
Tucker et al., 2016	11q22.1q22.3; UPD15	95,678,791–108,680,164	13.0	10.1 (84)	Phenotype at age 1 year and 8 months	Global **developmental delay**; **short stature**; behavioural abnormalities; **hypotonia**; limb contractures; del(11q)**: dysmorphism**; **coloboma**; **clubfoot** UPD15: unsteadiness, delayed speech and walking; sleep disorder; seizures

cM, centimorgan; COMP, cartilage oligomeric matrix protein precursor; MRI, magnetic resonance imaging; n/a, not available; PCOS, polycystic ovary syndrome; USS, ultrasound screening; WIPPSI, Wechsler preschool and primary scale of intelligence. Common features are in bold.

Table 2. Genes of interest with autosomal dominant or recessive inheritance, relatively high haploinsufficiency or loss-of-function intolerance

HLS[a] band, %	Genes, *n*	Genes, %	Genome, %	Deleted genes with acronyms[b]	HLS[a] score	pLI[c] score	Congenital disease association[b]	OMIM[d]
0–10	1/44	2.3	10	Meiotic recombination 11 homolog A, *MRE11A* (AR)	0.2	0.0	Ataxia-telangiectasia-like phenotype (AR)	604391
10–20	3/44	6.8	10	Yes-associated protein 1, *YAP1* (AD)	10.9	**1**	Coloboma, +/- hearing impairment, cleft lip/palate, and/or mental retardation (AD)	120433
				Defective in cullinneddylation 1, domain 5, *DCUN1D5*	15.7	**0.99**	–	
				Centrosomal protein 57, *CEP57* (AR)	19.5	0.07	Mosaic variegated aneuploidy type 2 (AR)	614114
20–30	2/44	4.5	10	Matrix metalloproteinase 1, *MMP1* (AR)	20.9	0.0	Modifier of epidermolysis bullosa dystrophica (AR)	226600
				Matrix metalloproteinase 13, *MMP13* (AD)	29.3	0.0	Metaphyseal anadysplasia (AD and AR)	602111 250400
30–40	8/44	18.2	10	Baculoviral IAP repeat-containing protein, *BIRC3*	31.0	0.07	–	
				Sestrin 3, *SESN3*	32.0	0.68	–	
				CWC15, homolog	32.9	**0.98**	–	
				Angiomotin like 1, *AMOTL1*	33.8	0.0	–	
				Mastermind-like 2, *MAML2* (AR)	33.9	**1**	–	
				Hephaestin-like 1, *HEPHL1* (AR)	35.8	–	Abnormal hair, joint laxity, and developmental delay (AR)	261990
				Contactin 5, *CNTN5*	35.9	0.0	Autism spectrum disorder [van Daalen et al., 2011]	
				Caspase 4, *CASP4*	38.0	0.0	–	
40–100	30/44	68.2	60	30 genes including				
				Transient receptor potential cation channel, subfamily c, member 6, *TRPC6* (AD)	57.0		Focal segmental glomerulosclerosis type 2 (AD)	603965
				Progesterone receptor, *PGR* (AR)	64.4	0.05	Progesterone resistance (AR)	264080
				Rho GTPase activating protein 42, *ARHGAP42*	–	**1**	–	
Additional gene at breakpoint[e]				Glutamate receptor, ionotropic, AMPA 4, *GRI4*[e]	42.6	**0.99**	Neurodevelopmental disorder +/- seizures and gait abnormalities (AD)	617864

[a]HLS, haploinsufficiency likelihood scores [Huang, et al., 2010]. [b]AD, genes associated with autosomal dominant conditions; AR, genes associated with autosomal recessive conditions. [c]pLI, probability of loss-of-function intolerance scores from gnomAD v2.1 (https://gnomad.broadinstitute.org/) [Lek et al., 2016] with those >0.9 in bold. [d]OMIM, Online Mendelian Inheritance in Man numbers for the disease associations. [e]Gene at breakpoint deleted for at least the first 14 out of 17 exons.

The karyotype of the index patient was 46,XX,inv(1)(p32q21.1),del(11)(q14.2q22.2)dn.ish del(11)(RP11-878E11+,RP11-684B20–).rsa 11q22.1(CNTN5)×1.arr [hg18] 11q21q22.3(93191472×2,93308490_105322933×1, 105386297×2) and that of her daughter 46,XX.arr[GRCh37] 11q21q22.3(93408848×2,93551765_105817723×1, 105881087×2)mat.

Discussion

Most regions of the human genome have been associated with phenotypes, but the variability of deletion size and features has made this difficult for 11q22.1q22.3. The present 12.3-Mb interstitial deletion of medial 11q was found in this 32-year-old patient when she was re-ascertained because of her mild dysmorphisms and 2 mid-trimester miscarriages. She also had normal mental development, short stature, polycystic ovary syndrome (PCOS), and hypothyroidism. Both miscarriages were chromosomally normal, and the physical abnormalities in the second were attributed to cervical incompetence. Despite the deletion being de novo in the mother and transmitted to the daughter, both had the consistent features of initial feeding difficulties and failure to thrive, speech delay, learning difficulties, and mild dysmorphism, while the daughter was diagnosed with ASD.

Phenotypic information was available for 17 overlapping deletions (Fig. 3; Table 1) that had been analysed with molecular cytogenetic or molecular techniques and were larger than the 3 Mb cut-off point used by the Database of Genomic Variants (http://dgv.tcag.ca/dgv/app/home). Four of these 17 deletions were directly transmitted [DECIPHER 262828] of which 2 were apparently benign [Ikegawa et al., 1998; Goumy et al., 2008] and one had a cognitively normal mother [Sparkes et al., 2009]. Among the other 15 with a phenotype, 2 or more patients had developmental or speech delay (9), dysmorphism that was inconsistent and could be mild (6), hypotonia (5), short stature (4), intellectual disability or learning difficulties (2), and coloboma (2) (Table 1, bold type). Short stature has been found in patients with larger [Horelli-Kuitunen et al., 1999; Li et al., 2006] and similar deletions of 11q [Tucker et al., 2016; DECIPHER patient 270473] but was attributed to concomitant deletion of 11q14.1q14.2 [Kariminejad et al., 2010] or pseudochondroplasia [Ikegawa et al., 1998] in others.

Low gene density, a high degree of gene family relatedness, and a lack of highly dosage-sensitive genes have been associated with previous large directly transmitted imbalances with few or mild consequences [Li et al., 2002; Barber, 2005; Daniel et al., 2007; Bateman et al., 2018]. The present deletion contained 53 protein-coding genes, of which none overlapped with segmental duplications. Gene density was approximately half the genome average of 9 (4.4 genes per Mb) but higher than the 2.51 genes per Mb found among other transmitted unbalanced chromosome abnormalities with few if any phenotypic consequences [Daniel et al., 2007]. The incidence of 46/53 (87%) genes belonging to a common family or group was higher than the genome average of 67% [Braschi et al., 2019].

Of the 44/53 genes with haploinsufficiency likelihood scores, only 6/44 were in the 3 upper bands of haploinsufficiency likelihood and 30/44 were in the lower 6 bands of which 3 were autosomal dominant (*YAP1*, *MMP13*, and *TRPC6*) (Table 2). Of these, *YAP1* has been associated with mental retardation (OMIM 120433) but also with coloboma, hearing impairment, and cleft lip/palate (DECIPHER 282360) [Tucker et al., 2016]. Although not excluded by fundoscopy, the absence of coloboma in this family and in 15/17 overlapping deletions might be due to incomplete penetrance related to the use of alternative transcripts [Williamson et al., 2014] as recently found for loss-of-function mutations in *YAP1* and other genes [Ropers and Wienker, 2015]. Of the 6 recessive genes, *HEPHL1* has been associated with developmental delay and deletion of *PGR* with PCOS [Meyer et al., 2000], but PCOS is also a multifactorial condition that has been linked with multiple biochemical pathways and 240 other genes [Joseph et al., 2016].

Loss-of-function intolerant genes are not necessarily dosage sensitive, but 48/53 genes had pLI scores of which 33 were zero, 10 above zero, and 6 >0.9 (*YAP1*, *MAML2*, *CWC15*, *DCUN1D5*, *ARHGAP42*, with the addition of *GRI4* at the distal breakpoint) (Table 2). This 63-kb breakpoint interval deletes all or most of 5′*GRI4* from exons 1 to 14 leaving a 3′ partial copy that is unlikely to be functional. De novo heterozygous mutations in this gene have been associated with mild to severe developmental delay with intellectual disability and poor or absent speech with or without seizures and gait abnormalities [Martin et al., 2017]. Of the other deleted genes, loss of *CNTN5* cosegregated in a family with ASD [van Daalen et al., 2011] but was diagnosed only in the daughter of the present family, consistent with the idea that *CNTN5* may be regarded as a risk factor rather than a direct cause [van Daalen et al., 2011].

Alternative causes of the features found in this family have not been excluded by, for instance, whole-genome sequencing [Lindstrand et al., 2019] or epigenetic analysis [Barbosa et al., 2018]. However, the relatively consistent phenotypes in the present family together with the common features among patients with overlapping deletions may provide the basis for a characteristic phenotype for this region with *YAP1*, *CNTN5*, and *GRI4* as possible candidate genes for some of the observed features. Non-penetrance of haploinsufficient genes and dosage compensation among related genes may account for variable phenotypes in this region that can extend into the normal range.

Acknowledgements

We thank the family for their collaboration and Dr. Janet Kelsall for her help with the assessment of autism. This study makes use of data generated by the DECIPHER community. A full list of centres who contributed to the generation of the data is available from http://decipher.sanger.ac.uk and via email from decipher@sanger.ac.uk. Funding for DECIPHER was provided by the Wellcome Trust.

Statement of Ethics

Written informed consent for publication was obtained from the family, and all tests were carried out in accordance with relevant guidelines and regulations.

Disclosure Statement

The authors declare that they have no conflicts of interest.

Author Contributions

B.K., M.S.B., E.-J.T., M.N.C., L.M.R., and S.B. carried out the molecular cytogenetic analyses and/or provided the results, with E.J.T. providing additional gene density data and L.M.R. and M.N.C. interpreting the results. D.J.B. designed and carried out the molecular genetic analysis. M.K., D.H., and A.L.C. acquired, provided, and wrote up the clinical data. J.C.K.B. co-ordinated and wrote the remaining sections of the paper.

References

- Baldwin EL, Lee JY, Blake DM, Bunke BP, Alexander CR, et al: Enhanced detection of clinically relevant genomic imbalances using a targeted plus whole genome oligonucleotide microarray. Genet Med 10:415–429 (2008).
- Barber JC: Directly transmitted unbalanced chromosome abnormalities and euchromatic variants. J Med Genet 42:609–629 (2005).
- Barbosa M, Joshi RS, Garg P, Martin-Trujillo A, Patel N, et al: Identification of rare de novo epigenetic variations in congenital disorders. Nat Commun 9:2064 (2018).
- Bateman MS, Collinson MN, Bunyan DJ, Collins AL, Duncan P, et al: Incomplete penetrance, variable expressivity, or dosage insensitivity in four families with directly transmitted unbalanced chromosome abnormalities. Am J Med Genet A 176:319–329 (2018).
- Braschi B, Denny P, Gray K, Jones T, Seal R, et al: Genenames.org: the HGNC and VGNC resources in 2019. Nucleic Acids Res 47:D786–D792 (2019).
- Bunyan DJ, Eccles DM, Sillibourne J, Wilkins E, Thomas NS, et al: Dosage analysis of cancer predisposition genes by multiplex ligation-dependent probe amplification. Br J Cancer 91:1155–1159 (2004).
- Daniel A, Darmanian A, Peters G, Goodwin L, Hort JR: An innocuous duplication of 11.2 Mb at 13q21 is gene poor: sub-bands of gene paucity and pervasive CNV characterize the chromosome anomalies. Am J Med Genet Part A 143A:2452–2459 (2007).
- Firth HV, Richards SM, Bevan AP, Clayton S, Corpas M, et al: DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources. Am J Hum Genet 84:524–533 (2009).
- Goumy C, Gouas L, Tchirkov A, Roucaute T, Giollant M, et al: Familial deletion 11q14.3-q22.1 without apparent phenotypic consequences: a haplosufficient 8.5 Mb region. Am J Med Genet A 146A:2668–2672 (2008).
- Horelli-Kuitunen N, Gahmberg N, Eeva M, Palotie A, Jarvela I: Interstitial deletion of bands 11q21-22.3 in a three year-old girl defined using fluorescence in situ hybridization on metaphase chromosomes. Am J Med Genet 86:416–419 (1999).
- Huang N, Lee I, Marcotte EM, Hurles ME: Characterising and predicting haploinsufficiency in the human genome. PLoS Genet 6:e1001154 (2010).
- Ikegawa S, Ohashi H, Hosoda F, Fukushima Y, Ohki M, Nakamura Y: Pseudoachondroplasia with de novo deletion [del(11)(q21q22.2)]. Am J Med Genet 77:356–359 (1998).
- Joseph S, Barai RS, Bhujbalrao R, Idicula-Thomas S: PCOSKB: A KnowledgeBase on genes, diseases, ontology terms and biochemical pathways associated with polycystic ovary syndrome. Nucleic Acids Res 44:D1032–D1035 (2016).
- Joyce CA, Zorich B, Pike SJ, Barber JC, Dennis NR: Williams-Beuren syndrome: phenotypic variability and deletions of chromosomes 7, 11, and 22 in a series of 52 patients. J Med Genet 33:986–992 (1996).
- Kariminejad A, Kariminejad R, Tzschach A, Najafi H, Ahmed A, et al: 11q14.1-11q22.1 deletion in a 1-year-old male with minor dysmorphic features. Am J Med Genet A 152A:2651–2655 (2010).
- Landrum MJ, Lee JM, Riley GR, Jang W, Rubinstein WS, et al: ClinVar: public archive of relationships among sequence variation and human phenotype. Nucleic Acids Res 42:D980–985 (2014).
- Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks, et al: Analysis of protein-coding genetic variation in 60,706 humans. Nature 536: 285–291 (2016).
- Li L, Moore P, Ngo C, Petrovic V, White SM et al: Identification of a haplosufficient 3.6-Mb region in human chromosome 11q14.3-q21. Cytogenet Genome Res 97:158–162 (2002).
- Li P, Zhang HZ, Huff S, Nimmakayalu M, Qumsiyeh M, et al: Karyotype-phenotype insights from 11q14.1-q23.2 interstitial deletions: *FZD4* haploinsufficieny and exudative vitreoretinopathy in a patient with a complex chromosome rearrangement. Am J Med Genet Part A 140:2721–2729 (2006).
- Lindstrand A, Eisfeldt J, Pettersson M, Carvalho CMB, Kvarnung M, et al: From cytogenetics to cytogenomics: whole-genome sequencing as a first-line test comprehensively captures the diverse spectrum of disease-causing genetic variation underlying intellectual disability. Genome Med 11:68 (2019).
- Martin S, Chamberlin A, Shinde DN, Hempel M, Strom TM, et al: De novo variants in *GRIA4* lead to intellectual disability with or without seizures and gait abnormalities. Am J Hum Genet 101:1013–1020 (2017).
- Melis D, Genesio R, Cozzolino M, Del Giudice E, Mormile A, et al: An emerging phenotype of proximal 11q deletions. Eur J Med Genet 53: 340–343 (2010).
- Meyer MF, Gerresheim F, Pfeiffer A, Epplen JT, Schatz H: Association of polycystic ovary syndrome with an interstitial deletion of the long arm of chromosome 11. Exp Clin Endocrinol Diabetes 108:519–523 (2000).
- Nacinovich R, Villa N, Redaelli S, Broggi F, Bomba M, et al: Interstitial 11q deletion: genomic characterization and neuropsychiatric follow up from early infancy to adolescence and literature review. BMC Res Notes 7:248 (2014).
- Ropers HH, Wienker T: Penetrance of pathogenic mutations in haploinsufficient genes for intellectual disability and related disorders. Eur J Med Genet 58:715–718 (2015).
- Schouten JP, McElgunn CJ, Waaijer R, Zwijnenburg D, Diepvens F, Pals G: Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. Nucleic Acids Res 30:e57 (2002).
- Sparkes RL, Shetty S, Chernos JE, Mefford HC, Micheil Innes A: Interstitial deletion of 11q in a mother and fetus: implications of directly transmitted chromosomal imbalances for prenatal genetic counseling. Prenat Diagn 29: 283–286 (2009).
- Tucker T, Steinraths M, Oh T, Nelson TN, Van Allen MI, et al: Incidental finding of paternal UPD15 in a child with a deletion of 11q21-q22.3, presenting with developmental delay, coloboma and characteristic dysmorphic features. Clin Dysmorphol 25:77–81 (2016).
- van Daalen E, Kemner C, Verbeek NE, van der Zwaag B, Dijkhuizen T, et al: Social responsiveness scale-aided analysis of the clinical impact of copy number variations in autism. Neurogenetics 12:315–323 (2011).
- Williamson KA, Rainger J, Floyd JA, Ansari M, Meynert A, et al: Heterozygous loss-of-function mutations in *YAP1* cause both isolated and syndromic optic fissure closure defects. Am J Hum Genet 94:295–302 (2014).
- Wincent J, Schoumans J, Anderlid BM: De novo deletion of chromosome 11q13.4-q14.3 in a boy with microcephaly, ptosis and developmental delay. Eur J Med Genet 53:50–53 (2010).