Novel deletions of 14q11.2 associated with developmental delay, cognitive impairment and similar minor anomalies in three children

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Methods and results: We identified de novo submicroscopic chromosome 14q11.2 deletions in two children with idiopathic developmental delay and cognitive impairment. Vancouver patient 5566 has a ~200 kb deletion and Vancouver patient 8326 has a ~1.6 Mb deletion. The Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER) revealed a third patient with idiopathic developmental delay and cognitive impairment, DECIPHER patient 126, who has a ~1.1 Mb deletion of 14q11.2. The deletion of patient 5566 overlaps that of patient 126 and both of these deletions lie entirely within that of patient 8326. All three children have similar dysmorphic features, including widely-spaced eyes, short nose with flat nasal bridge, long philtrum, prominent Cupid's bow of the upper lip, full lower lip and similar auricular anomalies.

Conclusion: The minimal common deletion region on chromosome 14q11.2 is only ~35 kb (from 20.897 to 20.932, University of California at Santa Cruz (UCSC) Genome Browser; build hg18, March 2006) and includes only two genes, *SUPT16H* and *CHD8*, which are good candidate genes for the phenotypes. The non-recurrent breakpoints of these patients, the presence of normal copy number variants in the region and the local genomic structure support the notion that this region has reduced stability.

The incidence of mental retardation (MR) is about 3% globally.¹ Chromosomal abnormalities are the most frequently diagnosed cause of MR,² and recent studies show that submicroscopic deletions or duplications cause MR at least as frequently as cytogenetically detectable chromosomal abnormalities.^{3–5}

We performed array genome hybridisation (AGH) on 100 children with idiopathic developmental delay and cognitive impairment and both their clinically normal parents using Affymetrix Genechip® Mapping 100K Assays.⁴ We detected and independently validated apparently pathogenic de novo submicroscopic copy number variants (CNVs) in 10 children. These patients were recorded in DECIPHER (Database of Chromosomal Imbalance and Phenotype in Human using Ensembl Resources (<http://www.decipher.sanger.ac.uk>), a database of clinical and genomic findings on individuals with submicroscopic chromosomal imbalance. In this paper, we discuss genotype–phenotype correlations for three patients with mild developmental delay and cognitive impairment and minor physical abnormalities, who have similar submicroscopic deletions of chromosome 14q11.2, two from our centre and one patient from the UK that we located through DECIPHER. They share similar features of minor dysmorphism, which also resemble those reported for some children with MR and cytogenetically visible deletions of proximal chromosome 14q. The deletions reported in these three patients overlap at a common genomic region of around 35 kb, which we believe is critical as this genomic segment contains portions of two genes that are strong candidates for involvement in the phenotypes.

METHODS AND RESULTS

These studies were approved by appropriate ethics boards in Canada and the UK.

Vancouver patient 5566

Patient 5566, a girl, was the second child born after an uncomplicated 38 week gestation to healthy non-related parents of English–Canadian descent. Their first child is a healthy boy. The family history is unremarkable except for cutaneous syndactyly of both second and third toes in the maternal grandfather and maternal great-aunts.

The infant's birth weight was 3900 g (91st percentile), birth length, 54 cm (98th percentile) and birth head circumference, 38 cm (99.6th percentile). She had prominent strawberry naevi over her left eyelid, philtrum and occiput at birth. The occipital naevus has persisted, whereas the others have faded. She had hypotonia as an infant that resolved as she grew older.

On evaluation at 28 months of age, her height was 89 cm (75th percentile), weight 12 kg (25th percentile) and head circumference 51.5 cm (97th percentile). She had mildly dysmorphic facies (figure 1A) with short palpebral fissures (5th percentile). Her eyebrows were rounded with a triangular medial aspect and distal tapering. She had normally positioned ears with unusual auricles in which the helical root swept into a horizontal bar of cartilage dividing the concha into a lower and an upper portion, limited superiorly by a horizontal inferior crux of the antihelix (figure 1A). The posterior portion of the helix and antihelix were fused bilaterally. She had a short nose with small nasal tip and flat nasal bridge, long philtrum and small mouth with prominent Cupid's bow of the upper lip. She also had micrognathia. Her heels were prominent and her feet

Abbreviations: AGH, array genome hybridisation; CNV, copy number variants; DECIPHER, Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources; DEI, duplication enrichment index; FACT, FACT, facilitates chromatin transcription; FISH, fluorescence in situ hybridisation; LCR, low copy repeat; MR, mental retardation; SNP, single nucleotide polymorphism; UCSC, University of California at Santa Cruz

Figure 1 (A–C) Our three patients: Vancouver patients 5566 and 8326 and DECIPHER patient 126 (parental/guardian informed consent was obtained for publication of these photographs). (A) Patient 5566: face and ear. Deletion 20 896 740 to 20 998 178, size 101 kb. (B) Patient 8326: face and ear. Deletion 19 584 863 to 22 207 935, size ~1.62 Mb. (C) Patient 126: face and ear. Deletion 19 853 310 to 20 931 827, size ~1.08 Mb. (D) Previously published patient A of Zanolli *et al.*⁶ Reprinted with permission of Wiley-Liss, Inc. a subsidiary of John Wiley & Sons, Inc. Zanolli R, Mostardini R, Pucci L, Sorrentino L, Biagioli M, Perotti R, Guarna M, Hadjililianou T, Zerega G, Pierluigi M, Franco B, D'Ambrosio A, Morgese G. Corpus callosum agenesis, multiple cysts, skin defects and subtle ocular abnormalities with a de novo mutation [45,XX,der(5),t(5;14)(pter;q11.2)]. *Am J Med Genet* 2001;102:29–35.

were flat with cutaneous syndactyly of the second and third toes. Formal developmental assessment at 4.5 years of age found her gross motor skills in the 2–3-year range and fine motor skills in the 3–4-year range.

Cytogenetic analysis at >550 band resolution showed a normal female karyotype. AGH (GeneChip Mapping 100K Assay; Affymetrix, Santa Clara, California, USA) on patient 5566 and both her parents showed a de novo deletion of around 200 kb of chromosome 14q11.2.⁴ The presence and de novo status of the CNV were confirmed by fluorescence in situ hybridisation (FISH).⁴ Owing to the small size of the lesion, we reanalysed the child and both parents by AGH using the Affymetrix 500K assay and found the deletion to be only 101 kb, with breakpoints at 20 896 740 bp and 20 998 178 bp based on the locations of the most proximal and distal deleted SNPs respectively (UCSC build hg18, March 2006) (figure 2). The chromosome with the deletion is probably maternal, based on presence of one informative paternal single nucleotide polymorphism (SNP) in the interval.

Vancouver patient 8326

Patient 8326, a boy, was the first child of healthy unrelated parents of Japanese descent. He was born at 37 weeks' gestation after an uncomplicated pregnancy and normal vaginal delivery. The family history is non-contributory.

At birth, weight was 2730 g (~50th percentile), length 51 cm (75th percentile) and head circumference 32 cm (10th percentile). The neonatal course was complicated by respiratory distress, and a ventricular septal defect and large patent ductus arteriosus were diagnosed by echocardiogram. The ductus was ligated at 10 days of age and the septal defect closed spontaneously by 6 months. There were no subsequent cardiac problems.

The patient has a history of hypotonia, acquiring good head control only at 6 months. Walking was achieved at 2 years. He also showed delays in fine motor and language skills. A Gesell

developmental test at 26 months of age estimated his gross and fine motor skills at the 13-month level, adaptive skills at the 11–13-month level and language skills at the 15-month level. Ophthalmological and auditory evaluations were both normal. On physical examination at 44 months, his height was 97.7 cm (25th percentile), weight 13.8 kg (10th percentile) and head circumference, 49 cm (25th percentile). He had mildly dysmorphic facies (figure 1B) with a broad forehead, epicanthic folds, very short palpebral fissures (2 SD below the mean) and rounded eyebrows with a triangular medial aspect and distal tapering. The nose was small with a very flat broad nasal bridge and small nasal tip. The ears were normally placed with malformed auricles that were remarkably similar to those of patient 5566 (figure 1b). He also had a small mouth, a very narrow high-arched palate, a long philtrum and a prominent Cupid's bow. He had a bridged palmar crease on the right hand and a single palmar crease on the left hand. He had significant pronation of the left foot, mild syndactyly of the second and third toes and clinodactyly of both fourth toes.

Cytogenetic analysis at >550-band resolution showed a normal male karyotype. AGH on the child and both his parents (GeneChip Mapping 100K Assay; Affymetrix) showed a de novo deletion of ~1.6 Mb at chromosome 14q11.2, with proximal and distal breakpoints at 19 584 863 bp and 21 207 935 bp (UCSC build hg18, March 2006), respectively.⁴ The presence and de novo status of this deletion were confirmed by FISH.⁴ SNP genotype data determined the deletion-bearing chromosome to be paternal.

DECIPHER patient 126

DECIPHER patient 126, a girl, was the first child of healthy unrelated parents of English descent with no relevant family history. She was born at 40 weeks' gestation by emergency caesarean section for fetal distress, weighing 3657 g (50–75th percentile). She did not require resuscitation but was admitted to the neonatal unit with respiratory problems and required

Figure 2 SNP genotyping data on patient 5566 and both her parents by AGH using Affymetrix 500K (top panel) and 100K (bottom panel) Genechip assays. (A) Child vs father comparison; (B) child vs mother comparison; (C) child vs father comparison; (D) child vs mother comparison. All graphs show "zoomed-in" views of chromosome 14q11.2 (19–23 Mb), generated using proprietary and locally developed software.

nasogastric feeding for the first few days of life. At 6–8 weeks of age, she still had marked head lag and was generally hypotonic. Her first year of life was characterised by lack of social interaction. She had a brief febrile convulsion at 10 months and sat at 11 months of age.

On review at 14 months, she did not make eye contact and demonstrated hand regard and bruxism. She walked at 26 months. At 29 months, her developmental level was assessed at the 12–17-month range, with speech and language skills and spontaneous play both at approximately the 10-month level. A moderate left alternate convergent squint and hypermetropia were noted. She had rather deep-set eyes, a prominent philtrum and prominent antihelix of both ears (figure 1C).

On review at 58 months, she had some single words, and showed an increased desire to communicate and some imitative play. On physical examination, height was 102 cm (9th percentile), weight 15.9 kg (9th–25th percentile) and head circumference 50.7 cm (9th–25th percentile).

Cytogenetic analysis at >550-band resolution and cranial MRI scan were normal. A multiplex ligation dependent probe amplification-based telomere assay showed deletion of one of the 'control' regions on chromosome 14q11. FISH analysis demonstrated a de novo deletion of the region defined by clones RP11-203M5 and RP11-524O1 on chromosome 14q11.2, identifying a ~1.079 Mb minimal deletion from 19 853 310 to 20 932 827 bp (UCSC build hg18, March 2006). The deletion is flanked by the clones RP11-597A11 (19.2 Mb) and RP11-124D2 (22.8 Mb), both of which are present in two copies. Studies of her parents confirmed that the deletion was de novo. The parental origin of the deletion-bearing chromosome was not determined.

DISCUSSION

The three patients described present similar degrees of developmental delay and cognitive impairment and a similar

mild dysmorphic appearance, despite having different ethnic origins. All three have widely-spaced eyes, a broad flat nasal bridge and short nose, a long philtrum, prominent Cupid's bow of the upper lip, full lower lip, similar eyebrows and an usual abnormality of helical root formation of the ear. Hypotonia in infancy was also reported for all three children.

Previously reported patients with chromosome 14q11.2 deletion

We found published reports on 10 patients with deletions of cytogenetic band 14q11.2.^{6–13} FISH mapping was performed for five of these patients,⁷ but none was found to have a deletion involving the region deleted in our three patients. No molecular characterisation is available for four other published patients, precluding molecular genotype–phenotype correlations. However, some phenotypic features found in our patients were also noted among these patients, including psychomotor delay,¹³ hypotonia,^{11–13} alternating esotropia,¹³ micrognathia¹¹ and other facial dysmorphisms.^{9–11} Two unpublished patients with cytogenetic deletions of 14q11.2 were found in the online Chromosome Abnormality Database (<http://www.ukcad.org.uk>, accessed October 2006). The unavailability of molecular breakpoint mapping for these patients excluded them from molecular genotype–phenotype correlations.

The only previously reported patient with a deletion shown molecularly to overlap the region involved in our patients is that described by Zanolli *et al.*⁶ In this patient, a der(5)t(5;14)(5qter→5pter::14q11.2→14qter) chromosome replaced both a normal chromosome 5 and a chromosome 14, deleting the entire short arm and the centromere of chromosome 14 (chromosome 5 bore a very small deletion distal to the subtelomeric region, involving a region composed of repetitive sequence). This was a de novo rearrangement involving the paternal chromosomes. The distal breakpoint on chromosome 14 was mapped by FISH between D14S72 (20.4 Mb, deleted) and D14S64 (23.6 Mb, retained).⁶ Therefore, the deletion in this

Table 1 Other genes within 500K of our minimal critical deletion region (20.4–21.5 Mb on chromosome 14)

Gene name	Genomic co-ordinates (UCSC genome browser, build hg18, March 2006)	Function
NDRG2*	Chr14:20554763–20563775	Member of the N-myc downregulated gene family. Role in neurite outgrowth ²⁵
SALL2*	Chr14:21059074–21075177	Transcription regulator ²⁶
METT11D1	Chr14:20527805–20535032	Methyl transferase activity related
KIAA0737	Chr14:21015175–21037157	Epidermal Langerhans cell protein
METTL3	Chr14:21036129–21049291	Methyl transferase activity related
FLJ10357	Chr14:20608367–20627875	Hypothetical protein
HNRPC	Chr14:20748939–20807424	Heterogeneous nuclear ribonucleoprotein C

*Best candidates of these based on function.

patient overlaps those in our patient 8326 and DECIPHER patient 126 up to 20.4 Mb distally and may also overlap our minimal critical deleted region. The patient described by Zanolli *et al.* was a 2-year-old girl whose facial appearance is quite similar to that of our patients (figure 1D). She had delayed psychomotor development and hypotonia, which are common to all our patients. She also had an alternating squint, a palmar crease on both hands, and skin pigmentation abnormalities, each of which was found in at least one of our patients.

Candidate genes

The minimal region of overlap for our three patients lies between the proximal breakpoint of patient 5566 and the distal breakpoint of patient 126, a region of 35 kb between 20 896 740 bp and 20 931 827 bp on chromosome 14. Portions of only two RefSeq¹⁴ genes are included in this region: *SUPT16H* (20 889 478–20 922 265, minus strand) and *CHD8* (20 923 470–20 975 242, minus strand) (figure 2). Both *CHD8* and *SUPT16H* show high expression levels in normal human adult and fetal brain ([http://symatlas.gnf.org/SymAtlas, V.1.2.4](http://symatlas.gnf.org/SymAtlas,V.1.2.4)).

SUPT16H (EntrezGene ID 11198) encodes the larger subunit of the conserved facilitates chromatin transcription (FACT) complex.¹⁵ The gene lies almost entirely within our minimal critical region and the deleted segment includes all known transcription start sites (<http://www.ncbi.nlm.nih.gov/IEB/Research/Acembly/av.cgi?db=35g&c=Gene&l=SUPT16H>). Therefore, the deletion probably produces a null mutation of *SUPT16H*. The FACT complex is an essential facilitator of transcription in yeast.¹⁵ It has also been directly implicated in maintenance of chromatin structure in yeast^{16,17} and is known to associate with CHD1, a chromatin remodelling factor in yeast and higher organisms.¹⁸ A role in histone methylation has also been suggested because FACT interacts with the PAF complex,^{19,20} which is known to regulate transcription-related histone modification in yeast.²¹ In addition, FACT may be involved in DNA replication and DNA repair.¹⁸

The possibility that haploinsufficiency of *SUPT16H* may be the cause of the congenital anomalies and developmental delay and cognitive impairment in our patients is supported by the fact that mutations in other genes that encode transcription factors or chromatin remodelling complexes are recognised causes of MR.²²

CHD8 (EntrezGene ID 57680) encodes at least seven different transcripts, of which only three form complete protein products. Approximately 10 kb of the gene's 3' end, which includes the 3' ends of all of the complete transcripts, is found in our minimal critical deletion region, therefore the deletions in all of our patients would be expected to result in altered and possibly

non-functional protein products (<http://www.ncbi.nlm.nih.gov/IEB/Research/Acembly/av.cgi?db=human&l=CHD8>).

The CHD8 protein directly interacts with the chromatin insulator-binding protein CTCF and is involved in epigenetic regulation of transcription.²³ Ishihara *et al* showed that RNA interference-mediated knockdown of *CHD8* in HeLa cells alters CpG methylation and histone acetylation around CTCF-binding sites.²³ They concluded that CTCF–CHD8 has a role in insulation and epigenetic regulation at active insulator sites,²³ suggesting the importance of adequate *CHD8* function in development. The potential pathogenicity of *CHD8* haploinsufficiency is also suggested by analogy to the known pathogenicity of *CHD7* loss-of-function mutations, which are causative of CHARGE syndrome.²⁴ *CHD7* is a member of the conserved chromodomain helicase DNA-binding protein family to which CHD8 belongs.

To examine possible position effects and regional genomic effects, we expanded our candidate gene search to include regions ~500 kb proximal and distal to our minimal critical region. This region contains 13 additional RefSeq genes, of which six belong to the highly redundant olfactory receptor and RNase gene families, undermining the possibility that a heterozygous deletion of any of these genes would contribute to pathogenicity. The remaining seven genes are listed in table 1.

Low copy repeat sequences in the region

We scanned the genomic sequence of chromosome 14 from 19.0 to 21.50 Mb (covering sequence ~500 kb upstream and downstream of our largest deletion) for known low copy repeat (LCR) sequences (duplications of >1 kb of non-repeat masked sequence with over 90% similarity). There were no LCR pairs flanking any of our deletion breakpoints. However, there were a total of nine LCR pairs located within this region (figure 3). The duplication enrichment index (DEI), defined as the ratio of the observed percentage of duplications in a region to the percentage in the whole genome, is a measure of how enriched a specific region of the genome is for repeat elements.²⁷ We calculated a DEI of 4.0 for the region between 19.0 and 21.5 Mb on chromosome 14 (supplementary table 1, available online at <http://jmg.bmj.com/supplemental>), indicating moderate LCR enrichment for this region.

The lack of recurrent breakpoints and the absence of LCR pairs that flank any of the de novo deletions in our patients argue against non-allelic homologous recombination as the mutation mechanism. However, the relative abundance of LCR pairs within the genomic region is consistent with a suggested stimulatory effect on deletion formation by other mechanisms,²⁸ such as non-homologous end joining²⁸ and replication fork shifting.²⁹ Sequence information for the deletion breakpoints and surrounding genomic segments of our patients is required to assess these possibilities.

Figure 3 The genomic region of chromosome 14 that contains the deleted region of our three patients (red horizontal lines; those ending in short vertical bars represent most probable deletion regions detected by SNP genotyping), genes in the critical region as well as candidate genes within 500 kb (only those in table 1) of our minimal critical deletion region, benign copy number variants and segmental duplications according to the UCSC genome browser (build hg18). On the benign copy number variant track, the brown bars represent common loss variants, blue bars common loss/gain variants and green bar, common gain variants (supplementary table 2, available online at <http://jmg.bmj.com/supplemental>). Our minimal critical deletion region is highlighted by the vertical pink bar, and deletes almost all of *SUPT16H* and disrupts the coding transcripts of *CHD8*. The genomic coordinates are given by the ruler at the top of the figure.

Common deletion polymorphisms in the region

We searched the Toronto Database of Genomic Variants (<http://projects.tcag.ca/variation/>) for reported benign CNVs within the region encompassed by the three de novo CNVs reported here. In total, two loss, two loss/gain and four gain polymorphisms mapped to this region (accessed 17 March 2007; supplementary table 2 (available online at <http://jmg.bmj.com/supplemental>); figure 3). Of these, only gain variant 0174 partially overlaps *CHD8*, while none of the other variants overlap either *SUPT16H* or *CHD8*. We also searched the Human Structural Variation Database (<http://humanparalogy.gs.washington.edu/structural-variation/>) and found a somatic variant mapping to our deletion region (supplementary table 2; available online at <http://jmg.bmj.com/supplemental>), providing further evidence of the region's genomic instability (figure 3).

CONCLUSION

We found a characteristic pattern of developmental delay and cognitive impairment and minor congenital anomalies associated with submicroscopic deletions of a minimal critical region of only 35 kb on chromosome 14q11.2. The only two RefSeq genes included in this minimal deletion, *SUPT16H* and *CHD8*, are both good candidate MR genes. Further studies are needed to determine whether this pattern of similar minor dysmorphism constitutes a novel MR syndrome. Using AGH and a subsequent genotype–phenotype correlation approach, we have been able to identify a similar pattern of dysmorphism associated with developmental delay and cognitive impairment and candidate genes for the phenotype.

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The supplementary tables are available on the JMG website at <http://jmg.bmj.com/supplemental>

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