

## Discovery of a previously unrecognized microdeletion syndrome of 16p11.2–p12.2

Blake C Ballif<sup>1</sup>, Sara A Hornor<sup>2</sup>, Elizabeth Jenkins<sup>3</sup>, Suneeta Madan-Khetarpal<sup>3</sup>, Urvashi Surti<sup>4,5</sup>, Kelly E Jackson<sup>6</sup>, Alexander Asamoah<sup>6</sup>, Pamela L Brock<sup>6</sup>, Gordon C Gowans<sup>6</sup>, Robert L Conway<sup>7</sup>, John M Graham, Jr<sup>7</sup>, Livija Medne<sup>8</sup>, Elaine H Zackai<sup>8</sup>, Tamim H Shaikh<sup>8</sup>, Joel Geoghegan<sup>9</sup>, Rebecca R Selzer<sup>9</sup>, Peggy S Eis<sup>9</sup>, Bassem A Bejjani<sup>1,2,10</sup> & Lisa G Shaffer<sup>1,2</sup>

**We have identified a recurrent *de novo* pericentromeric deletion in 16p11.2–p12.2 in four individuals with developmental disabilities by microarray-based comparative genomic hybridization analysis. The identification of common clinical features in these four individuals along with the characterization of complex segmental duplications flanking the deletion regions suggests that nonallelic homologous recombination mediated these rearrangements and that deletions in 16p11.2–p12.2 constitute a previously undescribed syndrome.**

Pericentromeric regions of the genome are structurally complex regions adjacent to the centromeres that are enriched for repetitive sequence elements and segmental duplications<sup>1</sup>. This abundance of segmental duplications seems to have made the pericentromeric regions susceptible to deletion or rearrangement<sup>2</sup>. We screened 8,789 consecutive patients with developmental disabilities whose clinical specimens were submitted to our laboratory for analysis with the SignatureChip targeted microarray<sup>3</sup> (**Supplementary Methods** online), which includes a minimum of three to six overlapping BAC clones at the most proximal end of the pericentromeric region for each chromosome arm (excluding the short arms of the acrocentric chromosomes). Four individuals had recurrent deletions in 16p11.2–p12.2 (subjects 1, 2, 3 and 4) (**Fig. 1**). Parental analyses in three of the four subjects (1, 3 and 4) demonstrated that these are *de novo* chromosome abnormalities. Parents were unavailable for testing for subject 2. To clarify the sizes of the deletions further, we analyzed all four subjects with a high-density BAC-based microarray spanning ~5 Mb of the most proximal unique sequence adjacent to the centromere for all 43 unique pericentromeric regions of the human genome<sup>4</sup> (**Fig. 1a**). Because all four of these abnormalities

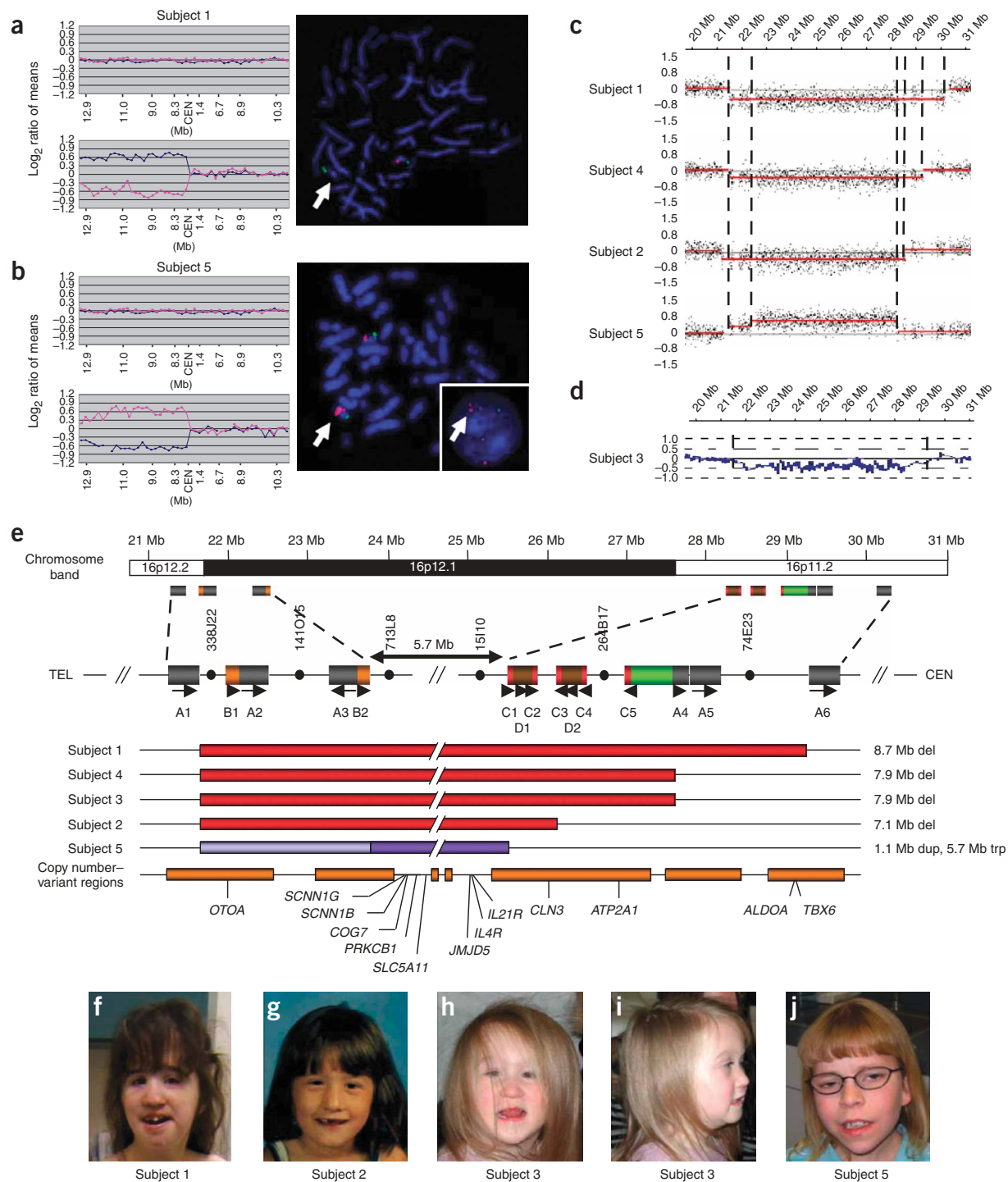
extended beyond the ~5-Mb coverage of this pericentromeric array, we characterized the full extent of each abnormality using NimbleGen whole-genome oligonucleotide arrays (for subjects 1, 2 and 4) and/or Affymetrix 250K SNP arrays (for subjects 3 and 4) (**Fig. 1c,d**). FISH analysis using BAC clones that map to the various breakpoint regions confirmed the results of the whole-genome arrays (**Fig. 1a**). Notably, all four deletions in 16p11.2–p12.2 shared the same distal breakpoint, located ~21.4 Mb from the 16p telomere. However, the proximal breakpoints were ~28.5 Mb (subject 2), ~29.3 Mb (subjects 3 and 4) and ~30.1 Mb (subject 1) from the 16p telomere, resulting in overall deletion sizes of ~7.1 Mb, ~7.9 Mb and ~8.7 Mb, respectively. Computational analysis of the 16p11.2–p12.2 region using the University of California Santa Cruz (UCSC) genome browser (<http://genome.ucsc.edu>) and the Human Genome Segmental Duplication Database (<http://projects.tcag.ca/humandup/>) identified a complex arrangement of segmental duplications, some of which directly flanked the deletion breakpoints (**Fig. 1e** and **Supplementary Note** online).

Misalignment of segmental duplications in meiosis followed by nonallelic homologous recombination (NAHR) can generate microdeletions, microduplications and inversions of the intervening genomic sequence, depending on the orientation of the duplicated segments<sup>2,5–7</sup>. The locations of the breakpoints in these four subjects with respect to the location and orientation of the segmental duplications in the 16p11.2–p12.2 region suggest that NAHR mediated these rearrangements (**Fig. 1e**). Although the proximal breakpoint in subject 2 seems to be atypical, in that it does not seem to have a paired segmental duplication at the distal breakpoint, this is not without precedent. For example, some of the more rare rearrangements of 17p11.2 associated with Smith-Magenis syndrome do not have breakpoints that fall within the typical paired segmental duplications and may not be associated with known genomic architectural features<sup>8</sup>.

The clinical features of the four subjects with microdeletions in 16p11.2–p12.2 include distinct facial features, including flat facies, downsloping palpebral fissures, low-set and malformed ears and eye anomalies (**Supplementary Table 1** online and **Fig. 1f–i**). Other commonly described features include orofacial clefting, heart defects, frequent ear infections with potential hearing loss, short stature, minor hand and foot anomalies, feeding difficulties, hypotonia and cognitive and developmental delays (**Supplementary Table 1**).

To our knowledge, only one other individual has been reported in the literature with a deletion in the 16p11.2 region. This individual, identified in ref. 9 using conventional CGH, was a 5-month-old male proband with distinct craniofacial features, including flat facies, microretrognathia, blepharophimosis, hypoplastic alae nasi and absent

<sup>1</sup>Signature Genomic Laboratories, Spokane, Washington 99202, USA. <sup>2</sup>Health Research and Education Center, Washington State University, Spokane, Washington 99210, USA. <sup>3</sup>Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA. <sup>4</sup>Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA. <sup>5</sup>Magee-Womens Hospital, Pittsburgh, Pennsylvania 15213, USA. <sup>6</sup>Weisskopf Child Evaluation Center, Louisville, Kentucky 40202, USA. <sup>7</sup>Cedars-Sinai Medical Center, Los Angeles, California 90048, USA. <sup>8</sup>The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104, USA. <sup>9</sup>NimbleGen Systems, Madison, Wisconsin 53711, USA. <sup>10</sup>Sacred Heart Medical Center, Spokane, Washington 99204, USA. Correspondence should be addressed to L.G.S. ([lshaffer@wsu.edu](mailto:lshaffer@wsu.edu)).



**Figure 1** Analysis of individuals with copy-number imbalances of 16p11.2–p12.2. **(a)** Pericentromeric array CGH profile and FISH confirmation (arrow) of a >4.99-Mb deletion in 16p11.2–p12.2 in subject 1. For the array CGH plots, clones are ordered on the x-axis according to physical mapping positions. The top plot shows a normal chromosome 16; the bottom plot shows the abnormal chromosome 16. **(b)** Pericentromeric array CGH profile and metaphase and interphase FISH confirmation (arrows) of a *de novo* triplication of ~4 Mb of 16p12.1–p12.1 and duplication of ~1 Mb of 16p12.1–p12.2 in subject 5. Microarray plots are arranged as in **a**. **(c)** NimbleGen whole-genome oligonucleotide array CGH profiles for subjects 1, 2, 4 and 5. **(d)** Affymetrix 250K SNP array profile for subject 3. **(e)** Schematic of the 16p11.2–p12.2 region with a summary of the abnormalities identified in five subjects. A simplified interpretation of the segmental duplications located in 16p11.2–p12.2 (see **Supplementary Note**) is shown with relative orientation of each duplication (arrows). The block of segmental duplications shown in green does not share identity with the 16p11.2–p12.2 region. Some of the RP11 BAC clones used for FISH confirmation of abnormalities are shown as black dots along the chromosome. Red bars indicate deleted regions for each subject. Light and dark purple bars for subject 5 indicate regions of duplication and triplication, respectively. Orange bars indicate regions of copy number variation based on the Database of Genomic Variants. The locations of select genes from >100 known genes in the region are shown. **(f)** Subject 1 at 13 years of age. Subject 1 has had multiple reconstructive surgeries for cleft lip and palate, multiple mandibular distraction, tracheostomy and cholesteatoma. **(g)** Subject 2 at 7 years of age. **(h,i)** Subject 3 at 3 years of age. **(j)** Subject 5 at 10 years of age.

nasal bridge, low-set and malformed ears and glossoptosis with hypoplastic palate. The proband was also described as having heart defects (tetralogy of Fallot with pulmonary atresia), eye abnormalities and other features that were similar to those described for the four subjects identified here (**Supplementary Table 1**). Although the precise breakpoints for the deletion in the individual described in ref. 9 were not determined, based on the brief clinical description, this individual probably contains a similar microdeletion in 16p11.2–p12.2.

Among the 8,789 patients screened in our laboratory, we also identified an individual with a complex *de novo* pericentromeric abnormality (subject 5) involving a duplication and triplication of the same region of 16p11.2–p12.2 that is deleted in the four microdeletion subjects. Because this abnormality extended beyond the ~5-Mb coverage of the pericentromeric microarray (**Fig. 1b**), we performed whole-genome oligonucleotide array CGH (NimbleGen) to refine the breakpoints further (**Fig. 1c**). The breakpoints in this subject also cluster at segmental duplications (**Fig. 1e**). By this analysis, the distal duplication was determined to be ~1.1 Mb in size, with the same distal breakpoint as all four individuals with 16p11.2–p12.2 microdeletions. The triplicated segment is ~5.7 Mb in size and is also flanked by segmental duplications. We confirmed these duplication and triplication breakpoints by FISH using BAC clones mapping within these regions of 16p11.2–p12.2 (**Fig. 1b** and **Supplementary Table 2** online). The clinical features of subject 5 are listed in **Supplementary Table 1**, and facial features are illustrated in **Figure 1j**.

Although we have not identified an exact reciprocal duplication product of one of the deletions in this region, two subjects with tandem duplications of 16p11.2–p12.2 have been reported and may constitute the reciprocal duplication product of this microdeletion syndrome<sup>10</sup>. Given the complex distribution of segmental duplications within 16p11.2–p12.2 (ref. 11), we anticipate that other deletions, duplications, triplications and inversions will be observed in this region of 16p11.2–p12.2. Indeed, the complex duplication and triplication observed here is most likely mediated by NAHR, and inversions in the distal region of 16p12.1 have already been reported in the Database of Genomic Variants (<http://projects.tcag.ca/variation/>).

Although **Supplementary Table 1** reports the major clinical findings in our subjects with 16p11.2–p12.2 imbalances, genotype-phenotype correlations are more difficult to establish for large microdeletions encompassing a substantial number of genes. Of the 104 RefSeq genes located within the largest deleted region of 16p11.2–p12.2, there are no obvious candidates for all of the features of these syndromes, nor are any known to be dosage sensitive. However, at least 13 genes (**Supplementary Table 3** online) are known to be associated with various genetic diseases in the autosomal recessive state or have functions potentially relevant to the clinical features of these patients (**Fig. 1e**).

The smallest region of overlap (SRO) for the four microdeletions in 16p11.2–p12.2 is ~7.1 Mb, equivalent in size to the deletion of subject 2. However, analysis of the Database of Genomic Variants suggests that structural and copy number variants (CNVs) exist within this region of 16p11.2–p12.2. These variants consist of inversions and copy number gains and losses identified in the apparently normal population. The locations of these CNVs relative to the SRO are shown in

**Figure 1e**. Assuming that regions of common copy number variation do not harbor dosage-sensitive genes<sup>6</sup>, they may be useful in refining the location of dosage-sensitive genes responsible for the phenotypic features of microdeletions in 16p11.2–p12.2. Of the 104 known RefSeq genes located within the 8.7-Mb region defined by the largest of the 16p11.2–p12.2 deletions identified in this study, only 33 are not located within regions of copy number variation. However, refinement of the SRO based on CNVs may be problematic, given the relatively recent discovery of the prevalence of CNVs and our immature understanding of them<sup>12–14</sup>.

We have established the identity of a previously unknown microdeletion syndrome of 16p11.2–p12.2 by analyzing individuals with mental retardation, developmental delay or dysmorphic features with array CGH. The screening of additional individuals using targeted BAC arrays and/or higher-resolution whole-genome oligonucleotide arrays is likely to uncover other new microdeletion and microduplication syndromes, thus adding to our growing knowledge of the cytogenetic basis of developmental disabilities.

For the subjects with 16p11.2–p12.2 abnormalities described here, we obtained informed consent to perform high-resolution molecular cytogenetic testing and to publish photographs, using a consent form approved by the Washington State University Institutional Review Board (for subjects 1, 2, 3 and 5) or by the Children's Hospital of Philadelphia Institutional Review Board (for subject 4).

Microarray data can be found at ArrayExpress under accession codes E-MEXP-1148 (Affymetrix platform) and E-TABM-286 (NimbleGen platform).

*Note: Supplementary information is available on the Nature Genetics website.*

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#### COMPETING INTERESTS STATEMENT

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at <http://www.nature.com/naturegenetics/>.

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## **Discovery of a novel microdeletion syndrome of 16p11.2p12.2**

Blake C. Ballif<sup>1</sup>, Sara A. Hornor<sup>2</sup>, Elizabeth Jenkins<sup>3</sup>, Suneeta Madan-Khetarpal<sup>3</sup>,  
Urvashi Surti<sup>4,5</sup>, Kelly E. Jackson<sup>6</sup>, Alexander Asamoah<sup>6</sup>, Pamela L. Brock<sup>6</sup>, Gordon C.  
Gowans<sup>6</sup>, Robert L. Conway<sup>7</sup>, John M. Graham, Jr.<sup>7</sup>, Livija Medne<sup>8</sup>, Elaine H. Zackai<sup>8</sup>,  
Tamim H. Shaikh<sup>8</sup>, Joel Geoghegan<sup>9</sup>, Rebecca R. Selzer<sup>9</sup>, Peggy S. Eis<sup>9</sup>, Bassem A.  
Bejjani<sup>1,2,10</sup>, Lisa G. Shaffer<sup>1,2</sup>

### **SUPPLEMENTARY METHODS**

#### *Patients and controls*

All 8,789 patients included in this study were originally referred by physicians for testing with the SignatureChip® targeted microarray at Signature Genomic Laboratories, LLC (Spokane, WA; [www.signaturegenomics.com](http://www.signaturegenomics.com)). The most common clinical presentations of the patients referred for testing were mental retardation, developmental delay, or multiple congenital anomalies. For the cases with 16p11.2p12.2 abnormalities described here, informed consent was obtained using a Washington State University IRB-approved consent form (cases 1, 2, 3 and 5) or Children's Hospital of Philadelphia IRB-approved consent form (case 4) to perform high-resolution molecular cytogenetic testing and to publish photographs.

#### *BAC Array CGH*

All patients were initially analyzed using the SignatureChip® targeted microarray which includes a minimum of 3-6 overlapping BAC clones at the most proximal end of the pericentromeric region for each chromosome arm (excluding the short arms of the acrocentric chromosomes)<sup>1</sup>. All five patients in whom the targeted microarray identified a

pericentromeric abnormality of 16p11.2p12.2 were selected for further characterization by a higher-density pericentromeric array which includes contigs of clones placed ~0.5 Mb apart that span ~5 Mb of the most proximal unique sequence adjacent to the centromere on all 43 unique pericentromeric regions<sup>2</sup> (Supplementary Table 1). Array CGH using the SignatureChip<sup>®</sup> and the pericentromeric array was performed as previously described<sup>1,2</sup>.

#### *Oligonucleotide Array CGH*

Four patients (1, 2, 4, and 5) in which the pericentromeric abnormalities of 16p11.2p12.2 extended beyond the ~ 5 Mb coverage of the pericentromeric array were analyzed using whole-genome tiling-path array CGH (NimbleGen Systems, Inc., Madison, WI) with a median probe spacing of 6 kb. Patient and reference DNAs were labeled and hybridized as previously described<sup>3</sup>.

#### *Affymetrix microarray experiments and data analysis*

Whole genome genotyping was performed using Affymetrix 250K SNP arrays (Affymetrix, Santa Clara, CA) for cases 3 and 4 to characterize the extent of the abnormalities. Copy number inferences were made using CNAG software based on the signal intensity of the probes and regions of homozygosity as previously described<sup>4</sup>.

#### *FISH*

Pericentromeric chromosome abnormalities were confirmed by FISH using BAC clones that mapped to the deleted, duplicated, or triplicated pericentromeric regions using previously published methodology<sup>5,6</sup> (Supplementary Table 1).

#### *Genomic sequence analysis*

Segmental duplications located within 16p11.2p12.2 were identified using the annotated May 2004 assembly of the human genome on the UCSC genome browser (<http://genome.ucsc.edu>) and the Human Genome Segmental Duplication Database (<http://projects.tcag.ca/humandup/>). Copy-number variations within 16p11.2p12.2 were identified using the Database of Genomic Variants (<http://projects.tcag.ca/variation/>). RefSeq genes within 16p11.2p12.2 were identified using the annotated May 2004 assembly of the UCSC genome browser and their functions were investigated using OMIM and PubMed (<http://www.ncbi.nlm.nih.gov/>).

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## Supplementary Note

The segmental duplications in the 16p11.2p12.2 region have been assigned the alphanumeric IDs of A1-A6, B1-B2, C1-C5, and D1-D2. Segmental duplications A1-A6 are 71 – 146 kb in size and share >98% sequence identity. Segmental duplication A1 is located at the distal breakpoint in all four deletion cases and is in the same orientation as A2, A4 and A5 (tandemly repeated), and A6. The proximal breakpoints in cases 4 and 3 are located just distal to the tandemly repeated segmental duplications A4 and A5, whereas the proximal breakpoint for case 1 is located just distal to A6. The B1-B2 segmental duplications are ~35 kb in size, are in the same orientation, and share >99% sequence identity. Segmental duplications C1-C5 are part of a more complex cluster that includes D1-D2. C1-C5 are 19-59 kb in size and share >99% sequence identity. The proximal breakpoint of case 2 is located just distal to C3. D1-D2 are ~133 kb in size, share >99% sequence identity, and encompass the flanking segmental duplications C1-C2 and C3-C4, respectively. The distal duplication breakpoint of case 5 is located at segmental duplication A1 as with all four 16p11.2p12.2 microdeletion cases. The proximal duplication breakpoint is the same as the distal triplication breakpoint and is located just proximally to segmental duplication B2. The triplicated segment of case 5 has a proximal breakpoint just distal to segmental duplication C1.

**Supplementary Table 1.** Clinical findings in patients with copy-number imbalances of 16p11.2p12.2.

<b>Imbalance</b>	<b>del(16)(p11.2p12.2)</b>				<b>trp(16)(p11.2p12.1) dup(16)(p12.1p12.2)</b>
<b>Case no.</b>	<b>1</b>	<b>4</b>	<b>3</b>	<b>2</b>	<b>5</b>
<b>Gender</b>	Female	Female	Female	Female	Female
<b>Age at diagnosis</b>	13 yr 8 mo	2 yr 9 mo	3 yr 1 mo	13 yr 9 mo	10 yr 11 mo
<b>Size of imbalance</b>	8.7 Mb deletion	7.8 Mb deletion	7.8 Mb deletion	7.1 Mb deletion	5.7 Mb triplication; 1.1 Mb duplication
<b>Previous cytogenetic testing</b>	Multiple normal karyotypes; normal subtelomere FISH, 22q11.2 FISH, SNRPN methylation, Rett, Noonan, and CHARGE syndrome testing	Normal karyotype; normal subtelomere FISH, 22q11.2 and 17p13.3 FISH, and SNRPN methylation testing	Normal karyotype; normal fragile X testing	Normal karyotype	Normal karyotype; normal 7q11.23 FISH and fragile X testing
<b>Craniofacial</b>	Head circumference 10 <sup>th</sup> percentile; long, narrow and flat facies; high forehead	Head circumference 8 <sup>th</sup> percentile; frontal bossing	Head circumference 25 <sup>th</sup> percentile; flat facies; frontal bossing	Head circumference 25 <sup>th</sup> percentile; flat facies	Head circumference (-1SD); round face with full cheeks
<b><i>Mouth &amp; Jaw</i></b>	Pierre Robin Sequence (cleft lip and palate, glossoptosis, micrognathia); mouth open with drooling		Prominent jaw; mouth open with drooling	Micrognathia	High-arched palate; some retrognathia; wide mouth; long philtrum; thin upper lip
<b><i>Eyes</i></b>	Downslanting palpebral fissures; bilateral epicanthal folds; deep-set eyes; absent tear ducts; strabismus	Downslanting palpebral fissures; mild epicanthal folds; deep-set eyes	Downslanting palpebral fissures; left epicanthal fold; hypotelorism	Short and downslanting palpebral fissures; relative hypotelorism (3 <sup>rd</sup> – 10 <sup>th</sup> percentile)	Narrow and slightly short palpebral fissures; relative hypertelorism (0 to +1SD); ptosis (right eye); strabismus (left eye); hyperopia
<b><i>Ears</i></b>	Low-set and malformed ears; frequent ear infections required PE tube placement; cholesteatoma; moderate hearing loss	Posteriorly rotated ears; prominent antihelix; frequent ear infections required PE tube placement	Posteriorly rotated ears; lacking lobes; frequent ear infections required PE tube placement	Frequent ear infections required PE tube placement	Low-set and posteriorly rotated ears; hyperacusis
<b><i>Nose</i></b>	Wide nasal bridge; anteverted nares; chronic sinusitis	Upturned nose	Short, prominent nose; slightly bulbous and bifid		Short nose with wide nasal bridge; round nasal tip; anteverted nares
<b>Cardiovascular</b>	Cyanosis; syncope episodes; bradycardia	Tricuspid regurgitation (Epstein's anomaly);	Normal echocardiogram		Persistent tachycardia

		pulmonary stenosis			
<b>Skeletal &amp; Muscular</b>	Height 3 <sup>rd</sup> percentile; weight 3 <sup>rd</sup> percentile; hypotonia; short fingers and hands; single palmar crease (right hand); proximally placed thumbs; camptodactyly; absent flexion creases; mild cutaneous syndactyly; unsteady gate	Height 25 <sup>th</sup> percentile; weight 3 <sup>rd</sup> percentile; hypotonia; arched dermatoglyphics; minimal syndactyly of toes (2,3 – left foot only)	Height 25 <sup>th</sup> – 50 <sup>th</sup> percentile; weight 50 <sup>th</sup> percentile; hypotonia; single palmar crease (right hand)	Height <3 <sup>rd</sup> percentile, weight 10 <sup>th</sup> – 25 <sup>th</sup> percentile; single palmar crease (left hand); camptodactyly; absent flexion creases	Height -3 to -4SD; weight -2SD; hypotonia; bridged palmar creases (left hand); short fifth fingers; prominent finger tip pads; bilateral hallux valgus, minimal 2,3 toe syndactyly
<b>Gastrointestinal &amp; Nutrition</b>	Feeding difficulties in infancy; GE reflux; uses G-tube	Feeding difficulties in infancy; GE reflux	Feeding difficulties in infancy; GE reflux	Feeding difficulties in infancy; GE reflux	Feeding difficulties in infancy
<b>Psychomotor &amp; Cognitive Delay</b>	Significant delay; speaks very few words; uses sign language of ~500 words; limited self-help skills	Significant delay; no speech; uses a limited number of signs; no self-help skills	Significant delay; starting to put two to three words together; uses some signs	Significant delay; mild to moderate mental retardation (IQ reportedly in 50's); can trace name and count to 12; has some self-help skills	Significant delay; IQ of 42 (WISC-IV assessment at age 9); 12 <sup>th</sup> percentile for reading, <1 <sup>st</sup> percentile for spelling and math (WRAT-3 assessment at age 9)
<b>Behavioral</b>		Irritability; head banging; hand flapping		Anxiety; energetic	Friendly and talkative; ADHD; anxiety and nervousness leading to nail biting and skin picking to the point of trauma
<b>Other</b>	Sleep apnea; staring spells; potential insensitivity to pain; chronic lung disease; significant hair growth on back and legs	Wide-based nipples; café-au-lait macule on chest		Sleep problems; potential insensitivity to pain; café-au-lait macules on chest, right arm, and right leg	Growth hormone deficiency

**Supplementary Table 2.** Genomic coordinates of BAC clones used in pericentromeric array CGH and FISH to delineate breakpoints in patients with abnormalities of 16p11.2p12.2.

<b>FISH Clone ID</b>	<b>Array CGH Clone ID</b>	<b>Accession No.</b>	<b>Genomic Coordinates <sup>1</sup></b>
RP11-338J22		AC092719	chr16:21,521,453-21,698,983
RP11-141O15	RP11-141O15	AC009034.10	chr16:22,055,031-22,221,449
	RP11-21M24	AC092338.4	chr16:22,201,600-22,344,731
	CTC-591M7	AC130466.2	chr16:22,674,919-22,781,917
	RP11-1137B22	AQ721894	chr16:22,705,489-22,871,077
	CTC-786K20	B31653	chr16:22,863,502-23,065,655
	RP11-893G15	AQ666465	chr16:23,057,796-23,257,941
	CTD-2270L9	AC008915.11	chr16:23,250,417-23,386,384
RP11-713L8	RP11-713L8	AQ517764	chr16:23,677,161-23,865,452
	CTC-484E17	AC010268.10	chr16:23,851,472-24,017,251
	RP11-1012J5	AQ715578	chr16:23,996,766-24,202,781
	CTC-625P11	B50730	chr16:24,163,925-24,357,913
	CTD-2313J23	AC008938.9	chr16:24,343,199-24,442,685
	RP11-281K7	AQ505868	chr16:24,481,288-24,660,676
	CTD-2547G23	AC008741.7	chr16:25,059,106-25,265,387
	RP11-478K1	AQ633981	chr16:25,532,212-25,718,737
	RP11-185O21	AC093524.4	chr16:25,660,176-25,795,346
	CTD-2537L13	AC093516.5	chr16:25,757,694-25,944,540
	CTD-2507C6	AC093511.4	chr16:25,979,727-26,168,977
	RP11-208I19	AZ517750	chr16:26,265,451-26,426,422
	RP11-1146L14	AQ752085	chr16:26,448,719-26,610,425
	RP11-142A12	AC009035.9	chr16:26,595,063-26,727,359
	RP11-1105E14	AQ677437	chr16:26,679,517-26,865,413
	RP11-71G15	AQ239222	chr16:26,743,787-26,891,949
	RP11-62O3	AQ199810	chr16:26,789,897-26,953,747
	RP11-673P17	AQ457615	chr16:26,927,251-27,132,642
RP11-15I10		AC092330	chr16:27,643,681-27,695,993
RP11-264B17		AC109460	chr16:28,786,259-28,949,693
RP11-74E23		AC023831	chr16:29,550,782-29,724,963

<sup>1</sup> Based on the UCSC May 2004 draft of the human genome

**Supplementary Table 3.** Candidate genes in 16p11.2p12.2 and their functions (if known).

<b>Gene</b>	<b>OMIM No.</b>	<b>Disease Associations (if known)</b>	<b>Function (if known)</b>	<b>References</b>
<i>OTOA</i>	607038	Autosomal recessive deafness	Inner ear protein restricted to the interface between the apical surface of sensory epithelia and their overlying acellular gels	1
<i>SCNN1G</i>	600761	Autosomal dominant Liddle syndrome (human hypertension); may also play a role in cystic-fibrosis-like lung disease	Structural subunit of the amiloride-sensitive epithelial sodium channel expressed in the distal nephron; constitutive activation or overexpression results in Liddle syndrome	2,3
<i>SCNN1B</i>	600760	Autosomal dominant Liddle syndrome (human hypertension); homozygous loss of function results in pseudohypoaldosteronism type I (opposite phenotype)	Structural subunit of the amiloride-sensitive epithelial sodium channel expressed in the distal nephron; constitutive activation or overexpression results in Liddle syndrome; homozygous loss of function results in pseudohypoaldosteronism type I	4,5
<i>COG7</i>	606978	Autosomal recessive congenital disorder of glycosylation type IIe	Component of the conserved oligomeric Golgi (COG) complex involved in intracellular transport and glycoprotein modification	6,7
<i>PRKCB1</i>	176970	Homozygous knockout mice develop immunodeficiency	Member of the protein kinase C gene family; Mediates prevention of mouse neural tube defects by inositol	8,9
<i>SLC5A11</i>	610238	Candidate gene for seizure phenotype	Member of the sodium/glucose cotransporter gene family	10
<i>JMJD5</i>	NA	Unknown	Novel member of jumonji gene family; jumonji gene family members function in transcriptional repression and/or chromatin regulation during development of the heart and liver, neural tube fusion, and hematopoiesis in mice	11
<i>IL4R</i>	147781	Specific haplotypes associated with atopy	Component of the interleukin 4 receptor which plays a major role in interleukin-4 signal cascade to produce immunoglobulin E	12
<i>IL21R</i>	605383	Knockout mice suggest IL21R plays a role in the transition from innate to adaptive immunity	Type I cytokine receptor for hematopoietic growth factors and interleukins	13
<i>CLN3</i>	607042	Autosomal recessive Batten disease (severe neurodegeneration)	Unknown	14
<i>ATP2A1</i>	108730	Autosomal recessive Brody myopathy (disorder of skeletal muscle function)	Calcium-transporting ATPase	15
<i>ALDOA</i>	103850	Autosomal recessive aldolase deficiency resulting in hemolytic anemia and possibly mental retardation and dysmorphic features	Glycolytic enzyme; Sole adolase isozyme expressed during embryonic development and one of two isozymes expressed in adult brain and nervous tissue	16,17
<i>TBX6</i>	602427	Knockout mice develop paraxial neural tube-like structures	Transcription factor that specifies paraxial mesoderm formation	18

NA=Not available

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