Recurrence Rearrangements of Chromosome 1q21.1 and Variable Pediatric Phenotypes


The authors’ affiliations are listed in the Appendix. Address reprint requests to Dr. Eichler at the University of Washington and Howard Hughes Medical Institute, Foege Bldg. S413A, Box 355065, 1705 NE Pacific St., Seattle, WA 98195, or at eee@gs.washington.edu.

Drs. Mefford and Sharp contributed equally to this article.

*The full names and degrees of the authors are listed in the Appendix.

Abstract

Background
Duplications and deletions in the human genome can cause disease or predispose persons to disease. Advances in technologies to detect these changes allow for the routine identification of submicroscopic imbalances in large numbers of patients.

Methods
We tested for the presence of microdeletions and microduplications at a specific region of chromosome 1q21.1 in two groups of patients with unexplained mental retardation, autism, or congenital anomalies and in unaffected persons.

Results
We identified 25 persons with a recurrent 1.35-Mb deletion within 1q21.1 from screening 5218 patients. The microdeletions had arisen de novo in eight patients, were inherited from a mildly affected parent in three patients, were inherited from an apparently unaffected parent in six patients, and were of unknown inheritance in eight patients. The deletion was absent in a series of 4737 control persons ($P = 1.1 \times 10^{-7}$). We found considerable variability in the level of phenotypic expression of the microdeletion; phenotypes included mild-to-moderate mental retardation, microcephaly, cardiac abnormalities, and cataracts. The reciprocal duplication was enriched in nine children with mental retardation or autism spectrum disorder and other variable features ($P = 0.02$).

Conclusions
We identified three deletions and three duplications of the 1q21.1 region in an independent sample of 788 patients with mental retardation and congenital anomalies.
Recent advances in technologies such as comparative genomic hybridization (CGH; see Glossary) allow for the routine detection of submicroscopic deletions and duplications. Several studies of persons with mental retardation or congenital anomalies of unknown cause have led to the identification of new genomic disorders.\textsuperscript{1-10} Classically, criteria that have been applied to determine whether a given rearrangement is causative include de novo appearance of the deletion or duplication in an affected individual (i.e., it is not present in unaffected parents), recurrence of the same or an overlapping event in similarly affected persons, and absence of the deletion or duplication in a control population. Examples of genomic disorders with these features include the Williams–Beuren syndrome, the 17q21.31 microdeletion syndrome, and the Prader–Willi and Angelman syndromes.

As more patients are identified with a given unbalanced microrearrangement, it has become clear that some genomic disorders have high penetrance but a wide range of phenotypic severity. For example, although 90% of persons with the 22q11 deletion syndrome have the same 3-Mb deletion on chromosome 22, the phenotypic features are highly variable. Congenital heart disease is found in most (74%) but not all carriers of the 22q11 deletion, and cleft palate is found in 27% of carriers (reviewed in Robin and Shprintzen\textsuperscript{11}). More recently, reports of microdeletions or duplications with apparently incomplete penetrance and variable expressivity have been identified in mental retardation–multiple congenital anomalies, autism, and other psychiatric disorders.\textsuperscript{12-16} The 1q21.1 microdeletions associated with the thrombocytopenia–absent radius syndrome are necessary but not sufficient to cause disease.\textsuperscript{17} As these reports accumulate, it is becoming clear that the phenotypes associated with imbalances of some regions of the genome can be variable, and modifiers probably play an important role. The ascertainment and description of patients with a specific chromosomal rearrangement critically affects the spectrum of phenotypes associated with it.

### Methods

#### Populations of Patients

DNA samples were obtained from the series described in Tables 1A and 1B in the Supplementary Appendix (available with the full text of this article at www.nejm.org) after approval by local institutional review boards at each of the participating centers in Europe and the United States. Series 1 and 2, 4 through 11, 13 through 15, and the Dutch series of 788 patients came from diagnostic referral centers to which the majority of patients (95%) were referred for mental retardation with or without other features. Series 3 and 12 comprise probands with a diagnosis of autism according to Autism Diagnostic Interview–Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) criteria. Written informed consent was provided by all patients or, if children, by their parent or guardian.

#### Determining Variation in Copy Number

##### Affected Persons

The method of screening for changes in copy number for each series is included in Table 1A in the Supplementary Appendix. The Dutch series of patients was screened using array-based CGH involving a bacterial artificial chromosome microarray, as described in Table 1B in the Supplementary Appendix. Rearrangements of 1q21.1 were further analyzed with the use of custom oligonucleotide arrays (NimbleGen Systems). Details are given in the Methods section of the Supplementary Appendix.\textsuperscript{18-20}

##### Unaffected Persons

We evaluated 2063 unaffected persons, using HumanHap 300, HumanHap 550, or HumanHap 650Y Genotyping BeadChips (Illumina) (Table 2...
in the Supplementary Appendix; 91, 206, or 212 probes used, respectively, within the critical region. Hybridization, data analysis, and copy-number analysis, with particular reference to chromosome 1q21.1 (mapping between genome coordinates 143,500,000 and 145,000,000 on chromosome 1, according to National Center for Biotechnology Information [NCBI] build 35), were performed according to published protocols.21 We also evaluated 300 unaffected persons, using a quantitative real-time polymerase-chain-reaction (PCR) assay for changes in copy number at five loci within the region of minimal deletion (primer list available on request). Details about this assay, as well as information about the TaqMan quantitative PCR, DNA-methylation studies, sequence analysis, and fluorescence in situ hybridization (FISH), are given in the Supplementary Appendix.

RESULTS

CHROMOSOME 1Q21.1 REARRANGEMENTS IN AFFECTED PERSONS

We previously described one person with a deletion of 1q21.1 and another with an overlapping duplication in a series of 390 persons screened by array-based CGH involving a bacterial artificial chromosome microarray.2,8 These persons had global delay, growth retardation, and seizures (Patient 1) (Table 1) and mental retardation, growth retardation, and facial dysmorphism (Patient 2) (Table 3 in the Supplementary Appendix). In a collaborative study of 3788 patients from 12 centers in Europe and the United States using array-based CGH (Table 1A in the Supplementary Appendix), we identified an additional 22 probands with deletion and 8 probands with duplication. Targeted screening of another 1040 persons with unexplained mental retardation, by means of two TaqMan quantitative PCR assays within the commonly deleted region, resulted in detection of a deletion in two additional patients. Thus, from a total of 5218 persons with idiopathic mental retardation, autism, or congenital anomalies, we have a series of 25 unrelated probands with overlapping deletions of 1q21.1 (0.5%) (Fig. 1A) and 9 persons with the apparently reciprocal duplication (0.2%) (Fig. 1B). Five persons (four with a 1q21.1 deletion and one with a duplication) also carried one or more additional chromosome abnormalities that could have contributed to their phenotype and were therefore excluded from further analysis (see Table 4 in the Supplementary Appendix for their phenotypic features).

The minimally deleted region spans approximately 1.35 Mb (on chromosome 1, 143.65 to 145 Mb [according to NCBI build 35], or 145 to 146.35 Mb [according to NCBI build 36]) and includes at least seven genes. The majority of persons studied have deletions with breakpoints (BP) in segmental-duplication blocks BP3 and BP4 (see Glossary and Fig. 1). Patient 12 has a larger, atypical deletion approximately 5.5 Mb in size that extends more proximally toward the centromere than the common deletion (on chromosome 1, 142.5 to 148.0 Mb [NCBI build 36]) (Fig. 1 in the Supplementary Appendix). Of the 21 probands without secondary karyotype abnormalities, the 1q21.1 deletion was de novo in 7 (3 with maternal origin, 1 with paternal origin, and 3 with undetermined parental origin), maternally inherited in 3, paternally inherited in 4, and of unknown inheritance (parents unavailable for study) in 7 (Table 1).

The phenotypes of persons with 1q21.1 deletions are described in Table 1 (21 patients without additional chromosomal abnormalities) and Table 4 in the Supplementary Appendix (4 patients with additional chromosomal abnormalities). Pedigrees of eight probands are shown in Figure 2. The majority of persons with a deletion have a history of mild-to-moderate developmental delay (16 of 21 (76.2%)) and dysmorphic features (17 of 21 (81.0%)), consistent with their ascertainment criteria. Three parents are also mildly affected; however, five probands had normal cognitive development, and four apparently unaffected parents have the same deletion. In addition, 14 of the 21 patients (66.7%) and 2 parents with the deletion have microcephaly or relative microcephaly. Other phenotypic features noted in more than one patient with the deletion include ligamentous laxity or joint hypermobility (five patients), congenital heart abnormality (six patients), hypotonia (five patients), seizures (three patients) and cataracts (three patients). There are no notable phenotypic differences among carriers of a deletion with different breakpoints. Consistent with variability of phenotypic outcome, we noted that the same region was recently described in an adult patient with schizophrenia22 (Table 4 in the Supplementary Appendix). We obtained DNA from this patient to map the breakpoints; our results show that the deletion in this patient with adult-onset schizophrenia is apparently identical to the common 1.35-Mb deletion found in...
Table 1. Phenotypic Features of Probands with a Deletion in Chromosome 1q21.1.*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Inheritance</th>
<th>Parental Origin</th>
<th>Cognitive Features</th>
<th>Growth Features</th>
<th>Facial Features</th>
<th>Skeletal Features</th>
<th>Features of Heart</th>
<th>Features of Eyes</th>
<th>Neurologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>De novo</td>
<td>M</td>
<td>Severe global delay, autism, self-harming behavior, stereotypy</td>
<td>Height, 3rd percentile for age; weight, 3rd percentile for age; in childhood, 25th percentile for age from adolescence (truncal obesity); OFC normal</td>
<td>Prominent nasal bridge, prominent columella, grimacing smile</td>
<td>Marked ligamentous laxity</td>
<td>Normal</td>
<td>Normal</td>
<td>Hypermetropia, convergent squint</td>
</tr>
<tr>
<td>2</td>
<td>De novo</td>
<td>M</td>
<td>Mild DD</td>
<td>Height, 25th–50th percentile for age; weight, 50th percentile for age; OFC, &lt;0.4th percentile for age</td>
<td>Epicanthic folds, full lower lip, wide-spaced teeth</td>
<td>Single palmar crease in left hand</td>
<td>Patent ductus arteriosus (diagnosed at 4 yr of age)</td>
<td>Subtle nuclear pulverulent cataracts (diagnosed at 4 yr of age)</td>
<td>No seizures</td>
</tr>
<tr>
<td>3</td>
<td>De novo</td>
<td>M</td>
<td>Normal cognition, mild speech delay</td>
<td>At birth: Normal height, weight, OFC At 7.5 yr: Height, 3rd percentile for age; weight, &lt;3rd percentile for age; OFC, &lt;3rd percentile for age</td>
<td>Prominent nose with long columella, flat philtrum</td>
<td>Normal</td>
<td>Normal</td>
<td>Strabismus in left eye</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>De novo</td>
<td>P</td>
<td>Moderate MR</td>
<td>Height, 50th percentile for age; weight, &gt;97th percentile for age; OFC, 50th–75th percentile for age</td>
<td>Brachycephaly, large and deep nasal bridge, thin lips, prognathism, short neck</td>
<td>Brachydactyly, single palmar crease in left hand, small feet</td>
<td>Normal</td>
<td>Hypermetropia in right eye</td>
<td>Seizures since 8 mo of age, hypotonia, deep sulci in cortex on brain MRI</td>
</tr>
<tr>
<td>5</td>
<td>De novo</td>
<td>Unknown</td>
<td>Mild MR</td>
<td>Height, 50th percentile for age; weight, &gt;97th percentile for age; OFC, 10th percentile for age</td>
<td>Brachycephaly, large and deep nasal bridge, synophrys, long philtrum, thin lips, high palate, wide-spaced teeth, short neck</td>
<td>Mild joint hypermobility, short distal phalanges on 2nd, 4th, and 5th fingers</td>
<td>Normal</td>
<td>Normal</td>
<td>Mild hypotonia, slow waves over the anterior and central areas of both hemispheres on EEG</td>
</tr>
<tr>
<td>No.</td>
<td>Inheritance</td>
<td>Sex</td>
<td>Clinical Features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>-------------</td>
<td>-----</td>
<td>------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Inherited (mother with BIF; grandfather also carries deletion)</td>
<td>M</td>
<td>Mild MR (IQ 55)</td>
<td>Height, &lt;3rd percentile for age; weight, &lt;10th percentile for age; OFC, &lt;3rd percentile for age; Brachycephaly, prominent ears, long columella, fine upper lip, pointed chin; Wide thumbs, duplicated left hallux; Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Inherited (mother normal)</td>
<td>M</td>
<td>Severe DD</td>
<td>At birth: Height and weight normal; In childhood: Microcephaly; Fine features, triangular face; hypotelorism, low-set ears; Severe scoliosis, severe ligamentous laxity; Truncus arteriosus, multiple muscular VSDs of moderate size requiring early intervention; Microphthalmia, strabismus; Tonic–clonic seizures since 4 mo of age; absence seizures since 3 yr of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Inherited (mother normal)</td>
<td>M</td>
<td>Mild global delay</td>
<td>Height, weight, and OFC all &lt;0.4th percentile for age; Epicanthic folds, mild micrognathia, high palate, bifid uvula, turricephaly; Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Inherited (father with growth 2nd–9th percentile for age and no cataracts; affected sister carries same 1q21.1 deletion)</td>
<td>P</td>
<td>Normal</td>
<td>Growth measures, 9th percentile for age (sister’s growth measures, 2nd–9th percentile for age)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Inherited (father mildly affected, with OFC &lt;3rd percentile for age)</td>
<td>P</td>
<td>Mild MR (IQ 65)</td>
<td>Height and OFC, &lt;3rd percentile for age; Long columella, wide-spaced teeth; Broad thumbs, great toes, and fetal pads; Normal echocardiogram; Exophoria; Normal neurologic examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Mild DD at 1 yr of age, resolved by 4 yr of age</td>
<td>OFC normal at 4 yr of age; Deep-set eyes, flat nasal bridge; Bilateral bifid great toes (required surgery); Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Unknown (son with speech delay)</td>
<td>Unknown</td>
<td>Mild MR (IQ 59)</td>
<td>OFC, 80th–85th percentile for age; Round facies; Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The image contains a table summarizing the clinical features of individuals with recurrent 1q21.1 rearrangements. The table includes details such as inheritance, sex, IQ scores, clinical features, and medical conditions. The information is presented in a structured format, making it easier to compare and analyze the data.
Table 1. (Continued.)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Inheritance</th>
<th>Parental Origin</th>
<th>Cognitive Features</th>
<th>Growth Features</th>
<th>Facial Features</th>
<th>Skeletal Features</th>
<th>Features of Heart</th>
<th>Features of Eyes</th>
<th>Neurologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Severe MR (IQ, 33)</td>
<td>Height, weight, and OFC all &lt;3rd percentile for age</td>
<td>Micrognathia, full nose, fine lips, simple ears</td>
<td>Bilateral clinodactyly of 5th finger</td>
<td>Normal</td>
<td>Strabismus</td>
<td>Fine tremor, heel stomping, stereotypic behaviors</td>
</tr>
<tr>
<td>14</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Developmental delay; ADHD</td>
<td>Failure to thrive, microcephaly</td>
<td>Prominent occiput, high palate, micrognathia</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>15</td>
<td>Inherited (father and brother with deletion both have OFC &lt;3rd percentile for age, mild learning disability, and similar facies)</td>
<td>P</td>
<td>Mild MR; schoolwork 2 yr behind that for chronologic age</td>
<td>At birth: Weight, 10th–25th percentile for age At 8 yr: Height and weight, 0.4th percentile for age; OFC, &lt;3rd percentile for age</td>
<td>Prominent metopic suture, up-slanting palpebral fissures, thin upper lip, full lower lip</td>
<td>Normal</td>
<td>Normal echocardiogram</td>
<td>Normal</td>
<td>Normal brain CT</td>
</tr>
<tr>
<td>16†</td>
<td>Unknown</td>
<td>Unknown</td>
<td>BIF</td>
<td>Height, 75th–90th percentile for age, weight, 97th percentile for age</td>
<td>Up-slanting palpebral fissures, malar hypoplasia, arched palate, orthodontic correction</td>
<td>Joint laxity, pes planus</td>
<td>Bicuspid aortic valve, dilation of ascending aorta, aortic insufficiency</td>
<td>Cataracta complicata</td>
<td>Behavioral abnormalities</td>
</tr>
<tr>
<td>17</td>
<td>De novo</td>
<td>Unknown</td>
<td>Mild MR (IQ, 63) and ADHD</td>
<td>Height and OFC, &lt;3rd percentile for age; weight, 50th percentile for age</td>
<td>Frontal balding, arched eyebrows, deeply set eyes, thin upper lip</td>
<td>Fingers with mild campodactyly, mild interdigital webbing</td>
<td>Aortic coarctation diagnosed at 1 wk of age, surgically repaired at 8 yr of age</td>
<td>Strabismus (surgical intervention at 2 yr of age)</td>
<td>Normal</td>
</tr>
<tr>
<td>18</td>
<td>Inherited (father normal)</td>
<td>P</td>
<td>Normal at 9 mo of age</td>
<td>Height, weight, and OFC all &lt;3rd percentile for age</td>
<td>Hypotelorism, short palpebral fissures, low nasal bridge</td>
<td>Mesaxial polydactyly of right foot</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>19</td>
<td>De novo</td>
<td>Unknown</td>
<td>Moderate MR, aggressive behavior</td>
<td>Height, 3rd–10th percentile for age; weight, 10th–25th percentile for age; OFC, 3rd–10th percentile for age</td>
<td>High, prominent forehead, long eyelashes, low nasal bridge</td>
<td>Overlapping toes</td>
<td>Patent ductus arteriosus</td>
<td>Normal</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
our sample of patients with primarily childhood-onset phenotypes (Fig. 3).

We also detected the reciprocal 1q21.1 duplication in nine persons (Fig. 1B), one of whom carried an additional large chromosomal abnormality and was thus excluded from further analysis (Table 4 in the Supplementary Appendix). Of the remaining eight patients with duplication, two had inheritance from an unaffected father, two had de novo duplication (parent of origin not known), and four did not have parental DNA available for analysis. Four of the eight patients with duplication (50.0%) had autism or autistic behaviors (Table 3 in the Supplementary Appendix). Other common phenotypic features of the eight duplication carriers include mild-to-moderate mental retardation (in five [62.5%]), macrocephaly or relative macrocephaly (in four [50.0%]), and mild dysmorphic features (in five [62.5%]).

In an independent sample of 788 patients with mental retardation and congenital anomalies from an unknown developmental delay (DD) cohort, autistic features were seen in 13 patients (1.6%). Among these patients, the mean age was 6.7 years (range, 5 months to 32 years), and six were males (46.2%). The majority (84.6%) had additional phenotypes indicating an autism spectrum disorder; of these, the most common were hypotonia (100%), hyperactivity (76.9%), and sensory hypersensitivity or aversion (61.5%). Other features included seizures (53.8%), feeding problems (46.2%), and joint hypermobility (30.8%).

The results for Patients 17 through 20 with deletions and Patient 8 with a duplication are shown in Figure 3 in the Supplementary Appendix. Patient 21 with a deletion and Patient 6 with a duplication were evaluated only by means of the screening platform listed in Table 1A in the Supplementary Appendix, because of insufficient DNA for additional oligonucleotide-array analysis (data not shown).
A Deletions

AUTHOR: FIGURE: JOB: 4-C H/T RETAKE SIZE ICM CASE EM

Figure has been redrawn and type has been reset. Please check carefully.

Copyright © 2008 Massachusetts Medical Society. All rights reserved.
RECURRENT 1Q21.1 REARRANGEMENTS

B Duplications

Patient
1, with deletion

1, with duplication

2, with duplication

3, with duplication

4, with duplication

5, with duplication

6, with duplication

Gaps

Genes

Copyright © 2008 Massachusetts Medical Society. All rights reserved.

Downloaded from www.nejm.org at IREL on November 26, 2009.
the Netherlands, we identified deletion in 3 patients (0.4%) and duplication in another 3 patients (0.4%). The phenotypic features and inheritance patterns of these patients are listed in Table 1B in the Supplementary Appendix.

DELETIONS AND DUPLICATIONS IN UNAFFECTED PERSONS

To assess the frequency of 1q21.1 rearrangements in the general population, we evaluated data on copy number from three control populations: 2063 persons evaluated by means of single-nucleotide polymorphism (SNP)–genotyping bead arrays21 (Itsara A: personal communication), 300 persons evaluated by means of quantitative PCR performed on specimens from five different locations within the minimal-deletion region, and 2374 persons from previously published studies for which the copy-number variation of the 1q21.1 region was genotyped (Table 2 in the Supplementary Appendix).25,27 In this series of 4737 controls, we found no deletions of the 1q21.1 minimal-deletion region. Two controls each had one small duplication (117 kb and 184 kb) at the distal end of the minimal-deletion region, and only one control had confirmed duplication of the entire minimal 1q21.1 rearrangement region29 (Feuk L: personal communication). Thus, the frequency of the 1.35-Mb deletion is clearly enriched in affected persons as compared with controls (25 of 5218 patients vs. 0 of 4737 controls, \( P=1.1\times10^{-7} \) by Fisher’s exact test). Although detected at a lower frequency in our series, the reciprocal duplication also appears to be enriched in affected persons (9 of 5218 patients, vs. 1 of 4737 controls; \( P=0.02 \) by Fisher’s exact test).

GENOMIC STRUCTURE OF THE 1Q21.1 REGION

The genomic structure of the 1q21.1 breakpoint regions is extremely complex, with at least four large segmental-duplication blocks ranging in size from 270 kb to 2.2 Mb (Fig. 1, and Fig. 1 in the Supplementary Appendix), most of which exhibit copy-number polymorphism in the general population25,27 (see also the Database of Genomic Variants, http://projects.tcag.ca/variation/). A large inversion polymorphism that spans the recurrent deletion–duplication region, a feature associated with many other recurrent genomic disorders, has also been described.27,30 The complexity of 1q21.1 is underscored by the fact that there are still 15 assembly gaps, representing approximately 700 kb of missing sequence, in the most recent NCBI genome build (build 36). Of the 5.4 Mb of sequence within 1q21.1, only 25% represents unique (i.e., nonduplicated) sequence.

Although the complexity of the region complicates mapping efforts, our high-density array-based CGH results show that the proximal and distal breakpoints of the deletion–duplication events map within large segmental-duplication blocks. Our analysis reveals four possible break-

Figure 2. Pedigrees of Eight Probands with a 1q21.1 Deletion. Squares indicate males, and circles females. Additional phenotypic information is available in Table 1. CHD denotes coronary heart disease, DD developmental delay, and MR mental retardation.
point regions, BP1 and BP4 (Fig. 1, and Fig. 1 in the Supplementary Appendix), as well as BP2 and BP3, which correspond to the previously described breakpoints associated with the thrombocytopenia–absent radius syndrome. Breakpoints of the most common 1.35-Mb deletion map to BP3 and BP4, which share 281 kb of sequence with more than 99.9% identity (Table 5 in the Supplementary Appendix). The structure of the 1q21.1 region (with multiple large blocks of highly homologous segmental duplication), the frequency of recurrent deletions or duplications, and the additional observation of reciprocal deletion and duplication events strongly suggest nonallelic homologous recombination as the mechanism that generates the deletion and duplication.

The presence of numerous assembly gaps in the 1q21.1 region hinders precise mapping of the chromosomal breakpoints that flank each duplication or deletion. Moreover, these gaps may contain genes that are absent from the current reference sequence and could potentially contribute to phenotypic differences between deletion carriers. One example is a partially duplicated copy of the hydrocephalus-inducing homologue (mouse) 2 gene HYDIN2, recently mapped to 1q21.1. We confirmed the presence of a HYDIN homologue within 1q21.1 by using FISH analysis involving two chromosome 16g22 fosmids containing the chromosome-16 HYDIN sequence (Fig. 2 in the Supplementary Appendix). Analysis of two deletion carriers (Patient 7 and her unaffected mother) revealed that the HYDIN2 locus lies within the commonly deleted region and therefore may reside in one of the gaps between BP3 and BP4. Because probes designed to detect HYDIN also hybridize with HYDIN2 sequence, data obtained through CGH studies, involving a whole-genome array, of persons with the 1q21.1 deletion suggest the existence of an approximately 35-kb deletion at 16q22 (Fig. 2 in the Supplementary Appendix) — that is, a false positive for the 16q22 deletion. FISH studies revealed only the 1q21.1 deletion and did not confirm the apparent 16q22 deletion.

ANALYSIS OF POTENTIAL MODIFIERS OF PHENOTYPE
Given associations between GJA5 (the gene encoding connexin 40) and cardiac phenotypes and between GJA8 (the gene encoding connexin 50) and eye phenotypes, we hypothesized that coding variants on the remaining GJA5 or GJA8 allele of deletion carriers may contribute to the cardiac or eye phenotypes, respectively, seen in some patients. However, we sequenced the coding and upstream regions of both genes in 11 deletion carriers and found no mutations (Table 6 in the Supplementary Appendix). We also investigated the possibility that epigenetic differences on the single remaining 1q21.1 allele might underlie the variable phenotype of those with 1q21.1 deletions. We analyzed the CpG (cytidine–phosphate–guanosine) methylation status within the deletion region in an affected 1q21.1 deletion carrier (Patient 7) and in her mother, who also carries the deletion but is unaffected. We found no significant differences between them (data not shown).

DISCUSSION
Our data show that 1q21.1 deletions are associated with a broad array of pediatric developmental abnormalities. There is considerable phenotypic diversity associated with haploinsufficiency of 1q21.1, consistent with previous reports of apparently identical 1q21.1 deletions in patients with different phenotypes, including isolated heart defects, cataracts, mullerian aplasia, autism, and schizophrenia. We identified several unaffected deletion carriers; however, it is possible that apparently unaffected parents who have a 1q21.1 deletion could also have subtle phenotypic features consistent with the deletion that would become evident on further clinical evaluation. In one of our patients (Patient 2), for example, subtle cataracts and a patent ductus arteriosus were detected only after directed studies were performed after discovery of the 1q21 deletion (Table 1).

The reciprocal duplication was detected less frequently in our series, a finding that is consistent with recent studies showing that rates of duplication mediated by nonallelic homologous recombination are higher than that for duplications in the male germ line. Nonetheless, the duplication is also enriched in affected persons as compared with controls (P = 0.02). Seven of the eight duplication carriers have learning or developmental delay or mental retardation. Four of the eight duplication carriers have autistic behaviors or autism, consistent with previously reported 1q21.1 duplications in patients with autism. Two patients were initially identified among 141 patients with autism, a finding that suggests even greater
Figure 3. High-Density Oligonucleotide-Array Comparative Genomic Hybridization of Chromosome 1q21.1 Deletions in Three Study Patients.

There were nearly identical breakpoints in the three patients, with the minimal 1.35-Mb deletion in chromosome 1 in the region of 142,000,000 to 146,500,000 bp (according to National Center for Biotechnology Information build 35). For each patient, deviations from 0 of probe log₂ ratios are depicted by vertical bars, with those exceeding a threshold of 1.5 SD from the mean probe ratio shown in red to represent relative losses; bars below this threshold are black (gains) or gray (losses). Additional phenotypic information is available in Table 1 (for Patients 7 and 9) and in Table 4 in the Supplementary Appendix (available with the full text of this article at www.nejm.org) (for Patient S5).
show that a specific variant is pathogenic. Al-
samples of patients and controls are required to
structural variants in human disease; they also

eases, with 1q21.1 deletions in studies of specific dis-
though there have been several reports of patients
reveal both maternal and paternal transmission
1q21.1 locus does not contribute to the variabil-
ences in the methylation status of the nondeleted
deletion but was unaffected, suggest that differ-
gation of genetic and environmental modifiers
will occur in any given person. Further investi-
abnormalities, the identification of a 1q21 re-
association with 1q21 rearrangements will com-
trance, and lack of distinct syndromic features
associated with 1q21 rearrangements will com-
clinicians caring for patients with developmental
abnormalities, the identification of a 1q21 re-
between 1q21 deletions and 1q21 rearrangements
patient with a 1q21.1 rearrangement, current knowledge
does not allow us to predict which abnormalities
will occur in any given person. Further investiga-
may explain such variable expressivity but requires
characterization of an even larger number of pa-
tients with a 1q21 deletion. Data on rare, de novo
structural variants are collectively beginning to
explain an increasingly greater fraction (approxi-
ately 15%) of patients with developmental de-
ments, such persons should be monitored in the
long term for learning disabilities, autism, or
schizophrenia or other neuropsychiatric disor-
ders. Counseling in the prenatal setting will pre-
the greatest challenge: although the likeli-
hood of an abnormal outcome is high in a person
with a 1q21.1 rearrangement, current knowledge
does not allow us to predict which abnormalities
will occur in any given person. Further investi-
gation of genetic and environmental modifiers
may explain such variable expressivity but requires
characterization of an even larger number of pa-
tients with a 1q21 deletion. Data on rare, de novo
structural variants are collectively beginning to
explain an increasingly greater fraction (approxi-
ately 15%) of patients with developmental de-

the Wellcome Trust and the Health Research Board (a grant to Drs. Gallagher and Gill). Dr. Poot was supported by a grant from the Dutch Foundation for Brain Research (Hersenstichting grant 2008(1) 34); Drs. Regan and Knight, by the Oxford Partnership Comprehensive Biomedical Research Centre; Dr. Willatt, by the Cambridge Biomedical Research Centre, with funding from the United Kingdom Department of Health’s National Institute for Health Research Biomedical Research Centres funding scheme; Drs. Huang and Maloney, as part of the National Genetics Reference Laboratory (Wessex) by the United Kingdom Department of Health; Ms. Buyse, as a research assistant of the Research Foundation—Flanders (FWO—Vlaanderen); and Dr. Eichler, as an investigator of the Howard Hughes Medical Institute. The views expressed in this publication are those of the authors and not necessarily those of the United Kingdom Department of Health.

APPENDIX

The full names and degrees of the authors are as follows: Heather C. Mefford, M.D., Ph.D., Andrew J. Sharp, Ph.D., Carl Baker, B.S., Andy Itsara, B.A., Zhaoshi Jiang, M.D., Karen Buyse, M.S., Shuwen Huang, Ph.D., Viv K. Maloney, B.Sc., John A. Crolla, Ph.D., Diana Baralle, M.B., B.S., Amanda Collins, B.M., Catherine Mercer, B.M., Koen Norga, M.D., Ph.D., Thorny de Ravel, M.D., Koen Devriendt, M.D., Ph.D., Ernie M.H.F. Bongers, M.D., Ph.D., Nicole de Leeuw, Ph.D., William Reardon, M.D., Stefania Gimelli, Ph.D., Frederique Bena, Ph.D., Raoul C. Hennekam, M.D., Ph.D., Alison Male, M.R.C.P., Lorraine Gaunt, Ph.D., Jill Clayton-Smith, M.D., Ingrid Simon-nic, Ph.D., Soo Mi Park, M.B., B.S., Ph.D., Sarju G. Mehta, M.D., Serena Nik-Zainal, M.R.C.P., C. Geoffrey Woods, F.R.C.P., Helen V. Firth, D.M., Georgia Parkin, B.Sc., Marco Ficheria, Ph.D., Santina Reitano, M.D., Marianna Giudice, B.S., Kelly E. Li, Ph.D., Iris Casuga, B.S., Adam Broomer, M.S., Bernard Conrad, M.D., Markus Schernwanz, M.D., Lorenz Räber, M.D., Sabina Gallati, Ph.D., Pasquale Striano, M.D., Ph.D., Antonietta Coppola, M.D., John L Tolmie, F.R.C.P., Edward S. Tobias, F.R.C.P., Chris Lilley, M.R.C.P., Lluis Armengol, Ph.D., Yves Spyschaert, M.D., Patrick Verloor, M.D., An Dae Coene, M.D., Linde Goossens, M.D., Geert Morit, M.D., Ph.D., Frank Speleman, Ph.D., Ellen vanBinsbergen, M.Sc., Marcel R. Nelen, Ph.D., Ron Hochstenbach, Ph.D., Martin Poot, Ph.D., Louise Gallagher, M.D., Ph.D., Michael Gill, M.D., Jon McClellan, M.D., Mary-Claire King, Ph.D., Regina Regan, Ph.D., Cindy Skinner, R.N., Roger E. Stevenson, M.D., Stylianos E. Antonarakis, M.D., Ph.D., Caifu Chen, Ph.D., Xavier Estivill, M.D., Ph.D., Björn Menten, Ph.D., Giorgio Gimelli, Ph.D., Susan Gribble, Ph.D., Stuart Schwartz, Ph.D., James S. Sunliffe, Ph.D., Tom Walsh, Ph.D., Samantha J.L. Knight, Ph.D., Charlotte Steer, Ph.D., Paul M. Davis, M.D., Michelle Tenboehl, Ph.D., Ewelina A. Wawrzyniec, M.D., Ph.D., Joris C.B. Barber, Ph.D., Lionel Willatt, Ph.D., May Tassahebji, Ph.D., and Evan E. Eichler, Ph.D.

The authors’ affiliations are as follows: the University of Washington School of Medicine (H.C.M., C.B., A.I., Z.J., M.-C.K., E.E.E.), University of Washington (J.M., M.-C.K., T.W.), and Howard Hughes Medical Institute (E.E.E.) — all in Seattle; University of Geneva Medical School (A.J.S., S.E.A.) and Geneva University Hospitals (S. Gimelli, F.D.) — both in Geneva; Center for Medical Genetics (K.B., G.M., F.S., B.M.) and Division of Pediatric Neurology and Metabolism (Y.S., P.V., A.D.C., L. Goossens), Ghent University Hospital, Ghent, Belgium; National Genetics Reference Laboratory (S.H., J.A.C., J.C.K.B.) and Wessex Regional Genetics Laboratory (V.K.M., J.A.C., J.C.K.B.), Salisbury National Health Service Trust Foundation Trust, Salisbury; Wessex Clinical Genetics Service, Southampton University Hospitals Foundation Trust, Southampton (D.B., A.C., C.M.); University College London (R.C.H.) and Great Ormond Street Hospital for Children NHS Trust (A.M.); London; Department of Clinical Genetics (L. Gaunt, J.C.-S.) and Academic Unit of Medical Genetics, University of Manchester (M.T.), St. Mary’s Hospital, Manchester; Addenbrooke’s Hospital NHS Trust Foundation Trust, Cambridge; and the Wellcome Trust Centre for Human Genetics, Churchill Hospital, Oxford (R.R., S.J.L.K.) — all in the United Kingdom; Children’s Hospital and Vlaams Interuniversitair Instituut Voor Biotechnologie (K.N.) and Center for Human Genetics (T.K., K.D., J.R.V.), Catholic University of Leuven, Leuven, Belgium; Radboud University Nijmegen Medical Center, Nijmegen (E.M.H.F.B., N.L., J.A.V., B.B.A.V.); University Medical Center, Utrecht (F.R., M.R., R.H., M.P.); and Academic Medical Center, Amsterdam (R.C.H.) — all in the Netherlands; Our Lady’s Hospital for Sick Children (W.R.) and St. James’s Hospital (L. Gallagher, M.G.) — both in Dublin; Istituto di Ricovero e Cura a Carattere Scientifico IRCCS Associazione Oasi Maria Santissima, Troina (M.F., S.R., M.L.G., C.R.); Università Federico II, Naples (A.C.); and Unità di Genetica Medica (W.R.) and St. James’s Hospital (L. Gallagher, M.G.) — both in Dublin; Istituto di Ricovero e Cura a Carattere Scientifico IRCCS Associazione Oasi Maria Santissima, Troina (M.F., S.R., M.L.G., C.R.); Università Federico II, Naples (A.C.); and Unità di Genetica Medica (W.R.) and St. James’s Hospital (L. Gallagher, M.G.) — both in Dublin; St. Marks Hospital, London; and Wellcome Trust Sanger Institute (S. Gribble), Cambridge; and the Wellcome Trust Centre for Human Genetics, Churchill Hospital, Oxford (R.R., S.J.L.K.) — all in the United Kingdom; Children’s Hospital and Vlaams Interuniversitair Instituut Voor Biotechnologie (K.N.) and Center for Human Genetics (T.K., K.D., J.R.V.), Catholic University of Leuven, Leuven, Belgium; Radboud University Nijmegen Medical Center, Nijmegen (E.M.H.F.B., N.L., J.A.V., B.B.A.V.); University Medical Center, Utrecht (F.R., M.R., R.H., M.P.); and Academic Medical Center, Amsterdam (R.C.H.) — all in the Netherlands; Our Lady’s Hospital for Sick Children (W.R.) and St. James’s Hospital (L. Gallagher, M.G.) — both in Dublin; Istituto di Ricovero e Cura a Carattere Scientifico IRCCS Associazione Oasi Maria Santissima, Troina (M.F., S.R., M.L.G., C.R.); Università Federico II, Naples (A.C.); and Unità di Genetica Medica (W.R.) and St. James’s Hospital (L. Gallagher, M.G.) — both in Dublin; Istituto di Ricovero e Cura a Carattere Scientifico IRCCS Associazione Oasi Maria Santissima, Troina (M.F., S.R., M.L.G., C.R.); Università Federico II, Naples (A.C.); and Unità di Genetica Medica (W.R.) and St. James’s Hospital (L. Gallagher, M.G.) — both in Dublin; St. Marks Hospital, London; and Wellcome Trust Sanger Institute (S. Gribble), Cambridge; and the Wellcome Trust Centre for Human Genetics, Churchill Hospital, Oxford (R.R., S.J.L.K.) — all in the United Kingdom; Children’s Hospital and Vlaams Interuniversitair Instituut Voor Biotechnologie (K.N.) and Center for Human Genetics (T.K., K.D., J.R.V.), Catholic University of Leuven, Leuven, Belgium; Radboud University Nijmegen Medical Center, Nijmegen (E.M.H.F.B., N.L., J.A.V., B.B.A.V.); University Medical Center, Utrecht (F.R., M.R., R.H., M.P.); and Academic Medical Center, Amsterdam (R.C.H.) — all in the Netherlands; Our Lady’s Hospital for Sick Children (W.R.) and St. James’s Hospital (L. Gallagher, M.G.) — both in Dublin; Istituto di Ricovero e Cura a Carattere Scientifico IRCCS Associazione Oasi Maria Santissima, Troina (M.F., S.R., M.L.G., C.R.); Università Federico II, Naples (A.C.); and Unità di Malattie Muscolari e Neurodenerative, Istituto G. Gaslini (P.S.) and Istituto G. Gaslini (G.G.), Genoa — all in Italy; Applied Biosystems, Foster City, CA (K.E.L., I.C., A.B., C.C.); Bern University Children’s Hospital (B.C., S. Gallati) and Department of Cardiology, University Hospital Bern (M.S., L.R.) — both in Bern, Switzerland; Royal Hospital for Sick Children, Glasgow, Scotland (J.L.T., E.S.T., C.L.); Biomedical Research Center for Epidemiology and Public Health (CIBERESP) and Pompeu Fabra University, Barcelona (L.A., X.E.); Greenwood Genetic Center, Greenwood, SC (C.S., R.E.S., C.E.S.); University of Chicago, Chicago (S.S.); Vanderbilt University, Nashville (J.S.S.); and Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (J.S.S.).

REFERENCES


22. Walsh T, McClellan JM, McCarthy SE, et al. Risk of schizophrenia is increased with multiple genes in neurodevelopmental pathways in schizophrenia. Science 2008;320:539-43.


