Identification of a Recurrent Microdeletion at 17q23.1q23.2 Flanked by Segmental Duplications Associated with Heart Defects and Limb Abnormalities

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Segmental duplications, which comprise ~5%–10% of the human genome, are known to mediate medically relevant deletions, duplications, and inversions through nonallelic homologous recombination (NAHR) and have been suggested to be hot spots in chromosome evolution and human genomic instability. We report seven individuals with microdeletions at 17q23.1q23.2, identified by microarray-based comparative genomic hybridization (aCGH). Six of the seven deletions are ~2.2 Mb in size and flanked by large segmental duplications of >98% sequence identity and in the same orientation. One of the deletions is ~2.8 Mb in size and is flanked on the distal side by a segmental duplication, whereas the proximal breakpoint falls between segmental duplications. These characteristics suggest that NAHR mediated six out of seven of these rearrangements. These individuals have common features, including mild to moderate developmental delay (particularly speech delay), microcephaly, postnatal growth retardation, heart defects, and hand, foot, and limb abnormalities. Although all individuals had at least mild dysmorphic facial features, there was no characteristic constellation of features that would elicit clinical suspicion of a specific disorder. The identification of common clinical features suggests that microdeletions at 17q23.1q23.2 constitute a novel syndrome. Furthermore, the inclusion in the minimal deletion region of TBX2 and TBX4, transcription factors belonging to a family of genes implicated in a variety of developmental pathways including those of heart and limb, suggests that these genes may play an important role in the phenotype of this emerging syndrome.

Segmental duplications comprise ~5%–10% of the human genome.1 Misalignment of segmental duplications during meiosis can mediate genomic instability by nonallelic homologous recombination (NAHR). Depending on the orientation of the segmental duplications, NAHR can generate microdeletions, microduplications, and inversions of the intervening genomic sequence.2–7 Chromosomal rearrangements associated with segmental duplications include microdeletions (MIM 609425) and their reciprocal microduplications (MIM 611936); Williams syndrome (MIM 194050) and deletions at 7q11.23; Angelman (MIM 105830) and Prader-Willi syndromes (MIM 176270) and maternally and paternally derived deletions, respectively, of 15q11-q13; microdeletions at 16p11.2p12.2 and their reciprocal microduplications; Smith-Magenis syndrome (MIM 182290) and deletions at 17p11.2; duplication at 17p12 in Charcot-Marie-Tooth disease type 1A (MIM 604563); and the reciprocal deletion at 17p12 resulting in hereditary neuropathy with liability to pressure palsies (HNPP [MIM 162500]) (reviewed in 4). Recently, a recurrent microdeletion at 17q21.3 mediated by segmental duplications was identified by screening individuals with idiopathic mental retardation and congenital anomalies with a microarray targeting potential segmental duplication-rich rearrangement “hot spots” in the genome5,6–7 suggesting that other such rearrangements may yet be identified.

Recent evidence suggests another segmental duplication “hub” on chromosome 17 at 17q23. Breakpoint analysis of a paracentric inversion that occurred in the human/chimpanzee/gorilla ancestor revealed that the distal breakpoint maps to the region syntenic to human 17q23, which suggests that the presence of this duplcon mediated the inversion in the Homo sapiens/Pan troglodytes/Gorilla gorilla ancestor.10 Furthermore, at least two insertions and deletions and one translocation have occurred within the past six million years since the divergence of chimpanzees and humans, indicating that these regions have continued to be subject to more-recent local rearrangements. Further data have demonstrated the structural complexity of the

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region, which has been shown to be polymorphic in the human population and associated with a multiple sclerosis susceptibility locus on 17q22-q24.\textsuperscript{11,12}

Here we report the clinical and molecular characterization of seven individuals with microdeletions at 17q23.1q23.2. Patients 1–3 in this study were ascertained by Signature Genomic Laboratories. Patients 4 and 5 were ascertained by Nationwide Children’s Hospital. Patient 6 was ascertained by Emory University School of Medicine. Patient 7 was ascertained by Baylor College of Medicine. Informed consent was obtained from patients 1, 4, 6, and 7 to publish photographs with consent forms approved by the Institutional Review Board of respective institutions.

All seven individuals with microdeletions at 17q23 were initially identified by microarray-based comparative genomic hybridization (aCGH) with various microarray platforms, one of which, patient 6, was previously reported (Figure 1).\textsuperscript{13} Whole-genome bacterial artificial chromosome (BAC)-based microarray analysis was originally performed on DNA from patients 1 and 2 with a &gt;4600 clone custom microarray as previously described.\textsuperscript{14} Oligonucleotide-based microarray analysis was originally performed on DNA from patients 3–5 with a custom 105K-feature whole-genome microarray (Agilent Technologies), as previously described.\textsuperscript{14} The deletion in patient 6 was identified with a custom 44K oligonucleotide-based microarray (Agilent Technologies), as previously described.\textsuperscript{13,15} The deletion in patient 7 was originally identified with a custom-designed 105K-feature whole-genome oligonucleotide microarray (Agilent Technologies), as previously described.\textsuperscript{16} In addition, all patients for whom DNA was available (1–4, 6, and 7) were reanalyzed at higher resolution with an off-the-shelf 244K-feature whole-genome microarray (Agilent Technologies), as previously described.\textsuperscript{14} One individual, patient 2, had a 2.8 Mb deletion (chromosome 17: 54.8–57.6 Mb); the remaining six individuals had 2.2 Mb deletions (chromosome 17: 55.4–57.6 Mb).

All seven deletions were confirmed and visualized by fluorescence in situ hybridization (FISH) with BAC clones, as previously described (Figure 2).\textsuperscript{17} Parental FISH testing in five of the seven cases confirmed an apparently de novo origin (patients 2 and 4–7). The deletions in patients 1–3 and 5 were confirmed by FISH with BAC probe RP11-289K16 from 17q23.1. For case 4, BAC RP11-119J7 was
used to confirm the deletion. The deletion in patient 6 was confirmed by FISH with BAC RP11-436E15, as previously described,\textsuperscript{13,15} and the deletion in patient 7 was confirmed by FISH with BAC clone RP11-615P24. Microsatellite marker analysis with the Identifier kit (Applied Biosystems) showed correct paternity in patient 6, confirming the de novo origin of the deletion (Rudd et al.\textsuperscript{13}). All other parental samples were unavailable.

Computational analysis of the 17q23.1q23.2 region with the hg18 build of the UCSC genome browser\textsuperscript{18} and the hg17 build of the Human Genome Segmental Duplication Database identified a complex arrangement of segmental duplications, some of which directly flank the 2.2 Mb deletion breakpoints and the distal 2.8 Mb breakpoint (Figure 1). These flanking segmental duplications are ~100 kb in size and have a complex evolutionary structure\textsuperscript{10} that includes an ~15 kb segment of >98% sequence identity present in the same orientation. In addition, there is an ~18 kb segment of >94% sequence identity that is inverted in orientation with respect to its duplication partner. The 2.2 Mb deletions are flanked by the homologous segmental duplications present in the same orientation. Highly identical (>98% sequence identity) segmental duplications in direct orientation flanking the deletion breakpoints are consistent with NAHR-mediated rearrangements (Figure 1). Although six of seven deletions were flanked by segmental duplications, the proximal breakpoint of the 2.8 Mb deletion falls between two segmental duplications (Figure 1). Atypical breakpoints have been reported for other recurrent rearrangements mediated by segmental duplications: for example, some of the rarer rearrangements of 17p11.2 associated with Smith-Magenis syndrome do not have breakpoints flanked by the typical paired segmental duplications and are not associated with known genomic architectural features,\textsuperscript{19} and some of the breakpoints in the recently identified 16p11.2p12.2 microdeletion syndrome are not flanked by segmental duplications.\textsuperscript{9}

Clinical characterization of the seven individuals with microdeletions at 17q23.1q23.2 revealed multiple common clinical features (Table 1; see also Supplemental Discussion available online). All individuals had mild to moderate developmental delay. A majority had low birth weight (5 of 7); microcephaly or relative microcephaly (5 of 7), including one with overall small growth parameters; postnatal growth retardation (5 of 7); heart defect(s) (6 of 7), in most cases either patent ductus arteriosus or atrial septal defect (ASD); hand and foot anomalies including long, thin fingers and toes (7 of 7); and musculoskeletal abnormalities of varying severity (4 of 7). Features identified in more than one individual include aggressive behavior (2 of 7) and hearing loss (2 of 7). Although five of seven individuals had eye anomalies such as chalazion, stellate pattern of the irises, retinopathy of prematurity, and strabismus, the anomalies affect different components of the eye and are unlikely to be related; therefore, these anomalies are likely incidental to the 17q23.1q23.2 microdeletion phenotype. Although all individuals had at least mild dysmorphic facial features, there was no characteristic constellation of features that would elicit clinical suspicion of a specific disorder (Figure 3). Nonetheless, the common clinical features in these individuals together with the common size and gene content of the deleted regions suggest that deletion at 17q23.1q23.2 is causative of the individuals’ phenotypes and may constitute a novel microdeletion syndrome.

From November 2007 to October 2009, Signature Genomic Laboratories tested 19,912 patients with whole-genome microarray platforms that had coverage over 17q23.1q23.2 and identified three microdeletions of 17q23.1q23.2, for a frequency of 0.015% among its patient population. By comparison, during this same period, the laboratory identified 23 Smith-Magenis syndrome (SMS) deletions (0.12% of patient population), which has a frequency in the general population of ~1 in 15,000,\textsuperscript{20} suggesting that the population frequency of 17q23.1q23.2 microdeletions may be ~1 in 115,000. This may be an overestimate of frequency because some cases of SMS are diagnosed by other methods, and therefore not all individuals with these syndromes will have aCGH testing, whereas 17q23.1q23.2 microdeletions would not be expected to be diagnosed by other methods that require clinical suspicion of a specific disorder.

Because the phenotype of the individual with the larger 2.8 Mb deletion does not appear to differ from that of the individuals with the smaller 2.2 Mb deletion, the critical region for this syndrome likely lies inside this 2.2 Mb region. Of the 11 OMIM and RefSeq genes within the 2.2 Mb smallest region of overlap (Figure 1), at least two, TBX2 (MIM 600747) and TBX4 (MIM 601719), are strong candidates that might play a role in some of the features of individuals with this microdeletion.

TBX2 and TBX4 belong to an ancient family of genes present in divergent multicellular organisms, such as sponges and humans, that encode transcription factors characterized by a strongly conserved, sequence-specific DNA-binding domain (or T-box domain). More specifically, TBX2 and TBX4 are members of two closely related
T-box subfamilies, TBX2/3 and TBX4/5. Interestingly, at least 17 evolutionary rearrangements, including gene cluster insertions and deletions, one inversion, and one local translocation, have occurred within the region since the divergence of humans and chickens ~300 million years ago. Despite the instability of the region in which the gene pair resides, TBX2 and TBX4 (as well as TBX3 and TBX5) have remained flanked by several loci present in all amniotes, BCAS33 and BRIP1 (MIM 605822) (THRA2P [MIM 608711] and RBM19 flank TBX3 [MIM 601621] and TBX5 [MIM 601620]).

The following abbreviations are used: +, feature present; −, feature absent; PDA, patent ductus arteriosus; ASD, atrial septal defect; DTR, deep tendon reflexes; NR, none reported.

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>1</th>
<th>2a</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3 yrs</td>
<td>5 yrs, 1 mo.</td>
<td>4 yrs</td>
<td>16 yrs, 6 mo.</td>
<td>8 mo.</td>
<td>4 yrs</td>
<td>1 yr, 10 mo.</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Low birth weight (&lt;25th percentile)</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Postnatal growth retardation</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Microcephaly (&lt;5th percentile)</td>
<td>+</td>
<td>+</td>
<td>+ (relative)</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Mild to moderate developmental delays</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Heart defects</td>
<td>PDA</td>
<td>ASD secundum</td>
<td>Pulmonary hypertension</td>
<td>PDA with pulmonary hypertension</td>
<td>PDA; bicuspid aortic valve</td>
<td>None; no echocardiography</td>
<td>ASD secundum with pulmonary hypertension</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Tibial torsion</td>
<td>Abnormally laterally positioned ossification centers of the patella, delayed for age</td>
<td>Underossified femoral heads; hips deeply seated in acetabula; mottled femoral epiphyses and metaphyses; small and abnormal lower-limb epiphyses</td>
<td>Short stature with leg length discrepancy; hypoplasia of patellae and tibial epiphyses; shallow acetabula; right side short femoral neck with coxa vara and magna; scoliosis</td>
<td>NR</td>
<td>None</td>
<td>Scoliosis; limited extension of knees and elbows</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Eyes</td>
<td>Chalazion</td>
<td>Left sided esotropia</td>
<td>Normal</td>
<td>Bilateral esotropia</td>
<td>Retinopathy of prematurity</td>
<td>Stellate pattern of irises</td>
<td>Normal</td>
</tr>
<tr>
<td>Facial features</td>
<td>High eyebrows; right epicanthal fold</td>
<td>Hypertelorism; flattened nasal bridge and midface; simple right ear</td>
<td>Plagioccephaly; bilateral inner epicanthal folds; bulbous, bifid nose; posteriorly rotated, prominent ears; long eyelashes</td>
<td>Prominence of forehead; moderate dental crowding requiring orthodontic appliances</td>
<td>Box-shaped cranium; open anterior fontanelle; prominent forehead; wide-set eyes, small nose with bulbous nasal tip; microstomia; small ears; recessed jaw</td>
<td>Mild frontal bossing; rounded nasal tip; wide space between front two teeth</td>
<td>Mild micromняthia; long eyelashes; protuberant ears; small mouth; long neck</td>
</tr>
<tr>
<td>Hands and feet</td>
<td>Thin fingers; deep, grooved space between first and second toes; familial 2–3 syndactyly</td>
<td>Long, thin fingers and toes</td>
<td>Long, thin fingers and toes; second toes longer than great toes</td>
<td>Long, thin fingers and toes; digital clubbing; bilateral pes planus; slightly shortened foot rays</td>
<td>Long fingers and toes; overlapping toes</td>
<td>Congenital contractures; long fingers and toes; overlapping toes 4 and 5; pes planus; fifth finger clinodactyly</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Behavioral abnormalities; intention tremors; asthma</td>
<td>NR</td>
<td>Tethered cord; sacral dimples; shawl scrotum</td>
<td>Mild increased DTR at knees and ankles; migraines</td>
<td>Cutis aplasia at birth; central hypotonia; brisk DTRs</td>
<td>Behavioral abnormalities</td>
<td>NR</td>
</tr>
</tbody>
</table>

The following abbreviations are used: +, feature present; −, feature absent; PDA, patent ductus arteriosus; ASD, atrial septal defect; DTR, deep tendon reflexes; NR, none reported.

* Patient 2 has an atypical ~2.8 Mb deletion. All other patients described in this table have ~2.2 Mb deletions.

* All growth parameters were at the fifth percentile.
Alternatively, the presence of large segmental duplications in the region of 17q23 may predispose the region to rearrangements that conserve the linkage of these genomic segments.

Targeted gene deletions in mouse have demonstrated that T-box genes play numerous roles in development; consequently, disruptions of many of these genes have been associated with human disease. Mutations in the coding sequence of *TBX1* (MIM 602054), which maps within the DiGeorge syndrome (DGS) region (MIM 188400) on chromosome 22q11.2,22 have been identified in individuals with sporadic DGS/conotruncal anomaly face syndrome/velocardiofacial syndrome (VCFS),23–25 which has a characteristic clinical feature of outflow tract heart defects. In addition, heterozygous mutations in *TBX3* cause ulnar-mammary syndrome (UMS [MIM 181450]),26,27 which has a characteristic feature of posterior upper-limb abnormalities; heterozygous loss-of-function mutations of *TBX4* in 15 individuals from five families and one sporadic patient were found to cause the autosomal-dominant Scott-Taor or small patella syndrome (SPS [MIM 147891]),28 heterozygous mutations in *TBX5* cause anterior limb abnormalities and ASD in Holt-Oram syndrome (MIM 142900);27 and mutations of *TBX20* (MIM 606061) have been associated with congenital heart disease and cardiac developmental anomalies, including defects in septation, chamber growth, and valvulogenesis and cardiomyopathy.29

The *TBX2/3* and *TBX4/5* subfamilies of genes are especially interesting as haploinsufficiency candidates in microdeletions at 17q23 because of their role in the evolution of novel vertebrate structures, including mouse limbs.30 *Tbx2* is expressed in the anterior and posterior margins of forelimbs and hindlimbs,31–33 and loss-of function and misexpression studies suggest a role for *Tbx2* in the anteroposterior patterning of digits.34 All individuals reported here had long fingers and toes, and some had additional digital anomalies (Table 1); patient 4, for example, had slightly shortened fourth and fifth rays of both feet (Figure 4). The presence of subtle digital anomalies in individuals with microdeletions at 17q23.1q23.2 suggests that haploinsufficiency of *TBX2* plays a role in the phenotype.

Expression studies in chicken and mice show limb-specific expression of *Tbx4* in forelimbs and hindlimbs, which suggests that *Tbx4* plays a role in lower-limb development.32,35–37 Although recent studies in mice have suggested that *Tbx4* expression does not confer limb-specific morphology to the limb that subsequently develops,38,39 it is clear that the gene plays a vital role in the maintenance of limb outgrowth.

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The association between mutations of *TBX4* and SPS further suggests that the gene plays a role in the musculoskeletal phenotypes of the patients reported here. SPS is better characterized as ischiopatellar dysplasia because clinical diagnosis includes essential features in addition to patellar aplasia or hypoplasia.40 These essential additional features are absent, delayed, or irregular ossification of the ischiopubic junctions and/or the infra-acetabular axe-cut notches.28 Individuals with SPS and known *TBX4* mutations may also have femur and foot anomalies.28 In contrast, some sporadic cases reported that predate *TBX4* mutation analysis had, in addition to dysplasia of the lower limbs and pelvis, dysmorphic facial features and digital anomalies.40–43 Thus, these sporadic cases may have *TBX4* mutations or, based on the features in addition to essential SPS features, may actually represent deletions at 17q23.1q23.2. Likewise, the musculoskeletal abnormalities identified in patients 3 and 4 of this study are reminiscent of, but not specific to, SPS (Figure 5). For example, patient 4 has lower limb abnormalities similar to patients with *TBX4* mutations28 including small patellae, infra-acetabular axe-cut notches, abnormal femoral heads, lesser trochanter hypoplasia, and pes planus. In contrast, patient 4 has shortened rather than elongated femoral neck and no ischiopubic ossification abnormality. It is unknown whether the absence of SPS-like musculoskeletal abnormalities in the other individuals in this study is because...
detailed skeletal surveys were not performed, although patient 6 was specifically noted to lack any patellar, pelvic, or foot anomalies characteristic of SPS. Therefore, deletions of TBX4 may show incomplete penetrance for SPS. Concerning the dysmorphic features, there does not seem to be a common constellation of features among the SPS patients in the literature and our patients, although this does not rule out the possibility of the previously reported sporadic cases being deletions at 17q23.1q23.2.

Interestingly, it has been suggested that an ancestral function of Tbx4/Tbx5 in chordates involved heart cell specification and that, during the evolution of vertebrates, the genes were co-opted to play a role in the initiation of limb outgrowth. Furthermore, studies of Tbx2 in the developing mouse heart show that Tbx2 is expressed in areas complementary to that of Anf, expression of which is specific to formation of the ventricular and atrial chambers; Tbx2 also cooperatively functions with Nkx2.5 on the Anf promoter to repress Anf activity. The presence of “heart-hand” syndromes in human, including Holt-Oram syndrome, the characteristic features of which are thumb anomalies and ASD, provide further evidence that...
T-box genes play dual roles in limb outgrowth and heart specification. Such a mechanism may also explain the presence of heart and limb anomalies in individuals with microdeletions at 17q23.1q23.2.

We have identified a previously unknown microdeletion syndrome at 17q23.1q23.2 by analyzing individuals with mental retardation, developmental delay, or dysmorphic features by array CGH. The common clinical features of these individuals and the presence of segmental duplications flanking the deletion breakpoints suggest that deletions at 17q23.1q23.2 represent a novel recurrent microdeletion. The identification of additional cases with microdeletions at 17q23.1q23.2 should further elucidate the clinical features of this emerging syndrome.

Supplemental Data

Supplemental Data include Supplemental Discussion and can be found with this article online at http://www.ajhg.org.

Acknowledgments

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Web Resources

The URLs for data presented herein are as follows:
UCSC Genome Browser, http://genome.ucsc.edu/
Human Genome Segmental Duplication Database, http://projects.tcag.ca/humandup/

Accession Numbers

The GEO accession numbers for the probands in this study are GSM498356 (patient 1), GSM498357 (patient 2), GSM498358 (patient 3), GSM498359 (patient 4), GSM506250 (patient 5), GSM498360 (patient 6), and GSM498361 (patient 7).

References