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Characterization of a recurrent 15q24 microdeletion syndrome

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We describe multiple individuals with mental retardation and overlapping *de novo* submicroscopic deletions of 15q24 (1.7–3.9 Mb in size). High-resolution analysis showed that in three patients both proximal and distal breakpoints co-localized to highly identical segmental duplications (>51 kb in length, >94% identity), suggesting non-allelic homologous recombination as the likely mechanism of origin. Sequencing studies in a fourth individual provided base pair resolution and showed that both breakpoints in this case were located in unique sequence. Despite the differences in the size and location of the deletions, all four individuals share several major features (growth retardation, microcephaly, digital abnormalities, hypospadias and loose connective tissue) and resemble one another facially (high anterior hair line, broad medial eyebrows, hypertelorism, downslanted palpebral fissures, broad nasal base, long smooth philtrum and full lower lip), indicating that this represents a novel syndrome caused by haploinsufficiency of one or more dosage-sensitive genes in the minimal deletion region. Our results define microdeletion of 15q24 as a novel recurrent genomic disorder.

INTRODUCTION

With the widespread use of array-based techniques for the measurement of DNA copy number, the list of human diseases that result from recurrent DNA rearrangements is steadily increasing (http://www.sanger.ac.uk/PostGenomics/decipher/). Termed genomic disorders, these are usually mediated by flanking blocks of duplicated sequence which predispose specific chromosomal regions to high frequencies of rearrangement via non-allelic homologous recombination (NAHR), leading to the deletion, duplication or inversion of the intervening sequence (1). Previously, we defined a region of chromosome 15q24 as a probable site of recurrent microdeletion associated with mental retardation (2). Here we report detailed studies of four patients with 15q24 deletions. Significantly, we show that all patients share a set of common congenital

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anomalies and that three of these four patients also share common deletion breakpoints that map to clusters of highly identical sequence, defining 15q24 as a site of recurrent microdeletion.

RESULTS

All four patients were initially referred for clinical genetic testing, and the presence of 15q24 deletions were ascertained by CGH using either targeted (IMR349, IMR371) (2) or whole genome BAC (ID204) (3) or oligonucleotide arrays (C45/06, this study) (Agilent Technologies, Palo Alto, CA, USA), and subsequently confirmed by FISH (Supplementary Material, Fig. S1). On the basis of the resolution of BAC microarray and FISH studies, it was unclear whether these patients shared common breakpoints, constituting a recurrent microdeletion syndrome. We set out to characterize the breakpoints and the phenotypes of these four cases in greater detail.

In order to localize the breakpoints of each deletion, we designed a custom oligonucleotide array (NimbleGen Systems, Madison WI, USA) covering 7.5 Mb of 15q23–q25 (mean density, one probe per 147 bp). Results are shown in Figure 1A and Supplementary Material, Figure S2 and demonstrate that all four individuals carry overlapping deletions, defining a minimal region for this syndrome (hg17, chr15:72.15–73.85 Mb). Although the deletion in one individual appears atypical (IMR371, del chr15:70.40–74.21 Mb), the proximal breakpoints in the three other cases all map to a common region, which we designate breakpoint 1 (BP1). Two of these cases (IMR349 and C45/06, del chr15:72.15–76.01 Mb) also share a common distal breakpoint region (designated BP3), with an alternate distal breakpoint (BP2) in the third case (ID204, del chr15: 72.15–73.85 Mb). Comparison of the deletions with the reference assembly (http://genome.ucsc.edu/) shows that all three of these breakpoints occur in segmental duplication clusters (BP1, 32 pair-wise alignments spanning 68.5 kb; BP2, 74 pair-wise alignments spanning 174.3 kb; BP3, 66 pair-wise alignments spanning 141.9 kb, Supplementary Material, Fig. S2, http://humanparalogy.gs.washington.edu/). Notably, a shared 51–59 kb sequence is located precisely coincident with BP1, BP2 and BP3. Analysis of the reference assembly shows that while BP1 and BP3 share 51 kb of directly orientated sequence with 95% identity, the structure at BP2 is more complex, with a 59 kb sequence having split into multiple fragments in both direct and inverted orientation with an average of 94% identity to those at BP1 and BP3 (Fig. 1, Supplementary Material, Fig. S2).

In order to further characterize the deletion breakpoints, we designed a second ultra-high density oligonucleotide array targeted specifically to BP1 and BP3 (mean density, one probe per 4.3 bp) (Fig. 1B). Although cross-hybridization of probes within the segmental duplication cluster made it difficult to define the exact extent of the deletion in IMR349, the proximal breakpoint occurs in the interval chr15:72 145 000–72 180 000. This breakpoint coincides exactly with a polymorphic ~30 kb variable number tandem repeat (VNTR) which shows increased copy number in the mother of IMR349 (4,5).

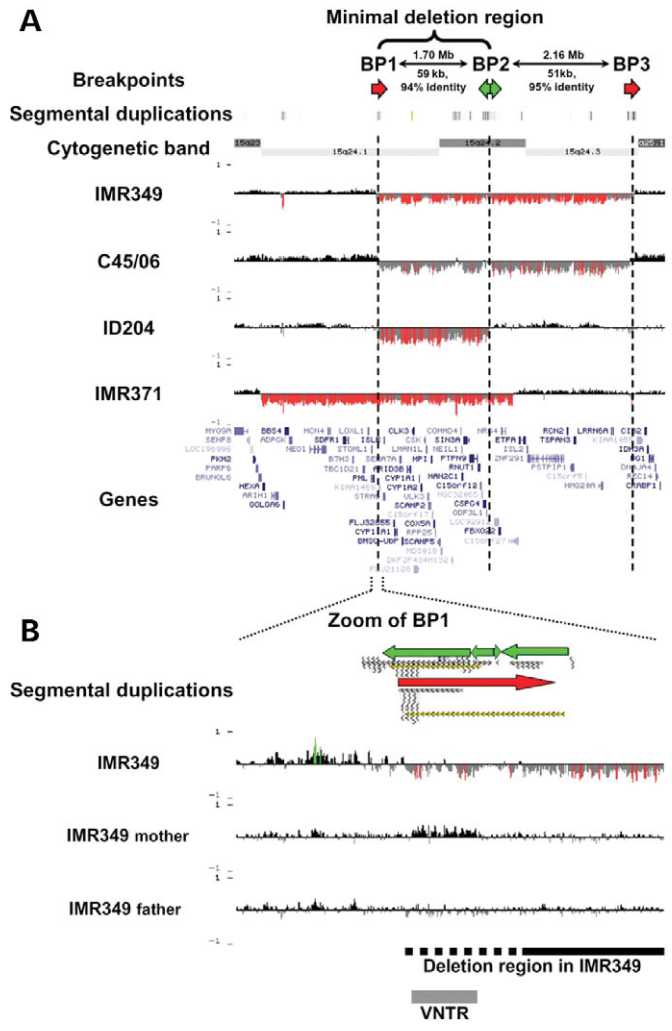

Figure 1. (**A**) Structural resolution of four 15q24 microdeletions using high-density oligonucleotide arrays (mean density, one probe per 147 bp). Each plot shows the $\log_2$ ratio (*y*-axis) for probes within hg17 (*x*-axis). The region shows a 6.5 Mb region of 15q23–q25.1 (chr15:70,000,000–76,500,000) containing overlapping deletions in four individuals, defining a minimal deletion region for this syndrome (hg17, chr15:72.15–73.85 Mb). For three of these rearrangements, the breakpoints map to clusters of flanking segmental duplications. A shared segmental duplication is present at BP1, BP2 and BP3 (>51 kb, >94% identity, represented by green/red arrows, indicating identity to BP2 and BP3, respectively). Although the repeats at BP1 and BP2 are in direct orientation, the copy at BP2 is split into multiple fragments of both direct and inverted orientation. (**B**) Ultra-high resolution oligonucleotide array analysis of 135 kb (hg17, chr15:72 095 000–72 230 000) surrounding the common proximal breakpoint BP1 of the 15q24 microdeletion in the family of IMR349 (mean probe density, one probe per 4.3 bp). Pair-wise segmental duplication relationships between BP1 and BP2/BP3 are represented by green and red arrows, respectively. Previous studies have demonstrated the presence of a polymorphic ~30 kb VNTR motif at BP1 (4,5) (gray bar). Increased copy number of this VNTR in the parent in whom the deletion arose (IMR349 mother) is evident. Because of the presence of this polymorphic repeat and cross-hybridization of probes within the segmental duplication cluster, the exact extent of the deletion in IMR349 is difficult to define (solid/dashed black bar), but occurs in the interval chr15:72 145 000–72 180 000. For each individual, deviations of probe $\log_2$ ratios from zero are depicted by gray/black bars, with those exceeding a threshold of 1.5 standard deviations from the mean probe ratio colored green and red to represent relative gains and losses, respectively. Tracks above each plot indicate segmental duplications (gray/yellow/orange bars representing duplications with 90–98%/98–99%/99–100% sequence identity, respectively).

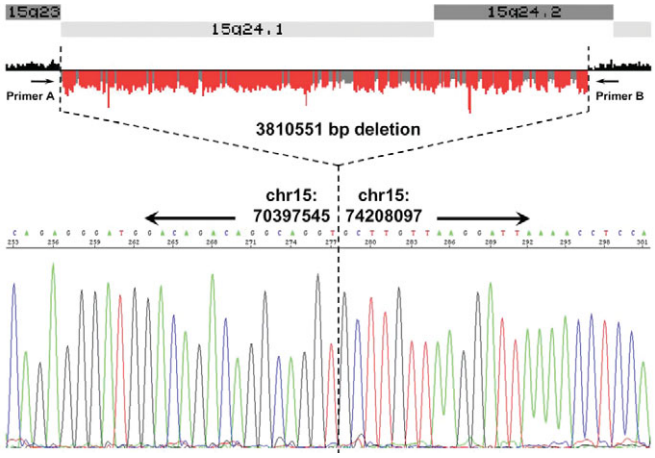

Figure 2. Sequencing of the breakpoint in patient IMR371 shows the deletion spans 3810551 bp in 15q24.1–q24.2 (hg17, chr15:70397546–74208096), with both breakpoints located in unique sequence with no apparent homology. Seven nucleotides (gagacag) 221 bp proximal to the deletion breakpoint were also deleted relative to the reference assembly, although the significance of this observation is unclear. Sequencing primers which spanned the microdeletion were designed directly from the results of the oligonucleotide array, which localized each breakpoint within 100–200 bp.

Oligonucleotide array analysis of the atypical deletion in IMR371 precisely localized both breakpoints, allowing PCR amplification and sequencing of the breakpoint junction (Fig. 2). This revealed that the deletion spans 3 810 551 bp (chr15:70 397 546–74 208 096) and that unlike the other three cases, both breakpoints were located within non-repetitive unique sequence with no apparent pair-wise homology.

Parental DNA samples were available for three of the four patients described. In each case, array CGH showed that the deletions were *de novo*. Microsatellite marker analysis also demonstrated that all three deletions were of maternal origin (Table 1, data not shown). FISH analysis in the mother of C45/06 using probes outside and within the deletion region did not show any evidence for inversions of 15q24 (data not shown).

Detailed clinical examination of each case revealed that they share several major phenotypic features, including mild/moderate developmental delay, growth retardation, microcephaly, digital abnormalities, hypospadias and loose connective tissue, and also resemble one another facially (Table 1, Fig. 3, Supplementary Material, Fig. S3).

DISCUSSION

Our analysis of several cases of 15q24 microdeletion defines a novel site of recurrent rearrangement associated with mental retardation and congenital anomalies. High-resolution mapping studies revealed that both proximal and distal breakpoints of three of these deletions co-localize to highly identical segmental duplications. The presence of a shared sequence located precisely at BP1, BP2 and BP3 suggests NAHR as the likely mechanism underlying these rearrangements. Thus, recurrent deletions of 15q24 are analogous to those of 15q11–q13 observed in Prader–Willi/Angelman syndrome, exhibiting a common proximal breakpoint and alternate distal breakpoints mapping to large, highly identical repeats (6).

A common phenotype is apparent for these 15q24 deletions, indicating that this could potentially represent a clinically identifiable syndrome (Table 1, Fig. 3). All cases presented with mild to moderate developmental delay, digital abnormalities and unusual facial features (high anterior hair line, broad medial eyebrows, hypertelorism, downslanted palpebral fissures, broad nasal base with flaring of alae nasi, long and smooth philtrum and full lower lip). Three of the four had a prenatal and postnatal growth deficiency, microcephaly, mild hypospadias, recurrent infections and loose connective tissue manifesting in joint laxity, scoliosis and inguinal hernia. Hearing loss, bowel atresia and growth hormone deficiency were also observed in two of the four individuals. We anticipate that this shared phenotypic spectrum will lead to the identification of additional cases of this syndrome.

Despite the differing extent of the deletions in our patients, the phenotypic similarities observed between all four cases suggest that the deletion of 15q24 may represent a clinically distinct entity and suggest that a haploinsufficient gene or genes within the minimal deletion region underlie this syndrome. This minimal region is gene rich, containing 32 RefSeq genes, making the identification of specific candidate genes difficult at this stage based on their currently known functions. Characterization of additional 15q24 deletion patients may help refine this critical region, potentially allowing the identification of the underlying gene(s) by mutation screening of phenotypically similar patients or mouse modeling approaches.

Array CGH and microsatellite analysis demonstrated that in all three cases where parental samples were available, the deletions were *de novo* and of maternal origin. Although the observation that all three deletions occur in the maternal lineage may simply be chance, our results do not exclude the possibility that genomic imprinting may underlie the deletion phenotype. However, no known imprinted genes reside within the deletions we describe (http://www.geneimprint.com/). Alternatively, if a parent-of-origin bias exists, it may indicate that the mechanism underlying deletions of 15q24 occurs preferentially in the maternal germline, as is observed for some other genomic disorders (7). Although it is not possible to accurately estimate the frequency of deletions of 15q24 from this study, the four cases we describe were ascertained by array CGH screening of ~1200 individuals with unexplained mental retardation and congenital anomalies.

There are several reports of deletions encompassing 15q24 in the literature (8), many of which show overlapping clinical features with the cases we describe here, including digital, genital, eye and ear abnormalities. However, from the available data, the breakpoints of these previously reported deletions appear distinct from the recurrent events that we describe. Although some deletions of 15q, such as that observed in IMR371, are likely sporadic events, chromosome 15q contains numerous clusters of highly identical segmental duplications, and we hypothesize that these likely mediate a number of different rearrangements of this region.

Table 1. Molecular and phenotype details of four 15q24 microdeletions

	IMR349	C45/06	ID204	IMR371
Deletion (hg17 coordinates)	72.15–76.01 Mb	72.15–76.01 Mb	72.15–73.85 Mb	70.40–74.21 Mb
Inheritance	*De novo*	*De novo*	Unknown	*de novo*
Parental origin	Maternal	Maternal	Unknown	Maternal
Age	14	14	33	15
Sex	Male	Male	Male	Male
Dev. delay (IQ level)	+ (65 points)	+ (69 points)	mild	+ (60 points)
Speech	Speaks well	Few words	Speaks well	Simple speech
Height	Less than third centile	Less than third centile	Less than first centile	25th centile
Weight	Low birth weight (less than third centile)	Low birth weight (less than fifth centile)	Low birth weight (less than second centile)	75th centile
OFC	Less than third centile	Less than third centile	Less than third centile	50th centile
Happy facial expression	−	+	+	+
Facial asymmetry	−	+	+	+
Facial features	Long, narrow face, high anterior hair line, floating forehead, broad medial eyebrows that taper laterally, hypertelorism, mildly downslanted palpebral fissures, high nasal bridge, broad nasal base with notched flaring alae nasi, long philtrum, full lower lip, highly arched palate and crowded teeth	High anterior hair line, broadening of the medial eyebrows, hypertelorism, downslanting palpebral fissures, broad nasal base with flaring of alae nasi, long, smooth philtrum and full lower lip	High forehead, broad medial eyebrows, deep set eyes with downslanting palpebral fissures, hypertelorism, epicanthic folds, small nose with hypoplastic alae nasi, long and smooth philtrum, full lower lip	Long, narrow face, high anterior hair line, floating forehead, broad medial eyebrows that taper laterally, hypertelorism, long palpebral fissures, high nasal bridge, broad nasal base with flared alae nasi, long philtrum, full lower lip
Eye abnormalities	−	Micropthalmia with strabismus	Strabismus, operated on at 10 years	Nystagmus
Ear abnormalities	+	+	Small mildly everted ears	−
Hands/feet	Long slender fingers, proximally implanted thumbs, sandal gap and deep plantar creases	Proximally implanted thumbs, simian crease	Small hands, simian crease, distal brachydactyly and mild cutaneous syndactyly of second to third and third to fourth fingers and second and third toes	Hypoplastic right thumb, contractures of fingers pes cavus, camptodactyly of toes with clawing and bunions,
Musculoskeletal abnormalities	Scoliosis, joint laxity	Scoliosis	Joint laxity	Joint laxity, valgus deformity at ankles
Hypospadias	−	+	Mild	Coronal with phimosis
Bowel atresia	+	+	−	−
Endocrine abnormalities	Growth hormone deficiency, delayed pubertal onset (induced at 14 years)	Growth hormone deficiency, hypogonadotropic hypogonadism	Not tested	Not tested
Brain abnormalities by MRI	Wide basal cisterna	Dysplastic corpus callosum and transected pituitary stalk, hypoplasia of the adenohypophysis and ectopic neurohypophysis	Not tested	Not tested
Hearing loss	Moderate conductive hearing loss and tinnitus	−	−	Deaf in left ear
Additional details	Hyperactive behavior with ADHD/autistiform traits, coarse hair of two different colors, hairy elbows, repeated middle ear infections causing cholesteatoma	Suffers both regular tonic and atonic seizures, often precipitated by sleep or fever - referred for epilepsy aged 13, hypotonia at birth, low-tone voice, edema of extremities	Feeding difficulties as child, recurrent upper airway infections	Very poor sleeper, recurrent chest infections and asthma, narrow chest, diaphragmatic, inguinal and hiatal hernias, trivial pulmonary stenosis

(+/−) denotes the presence/absence of abnormalities.

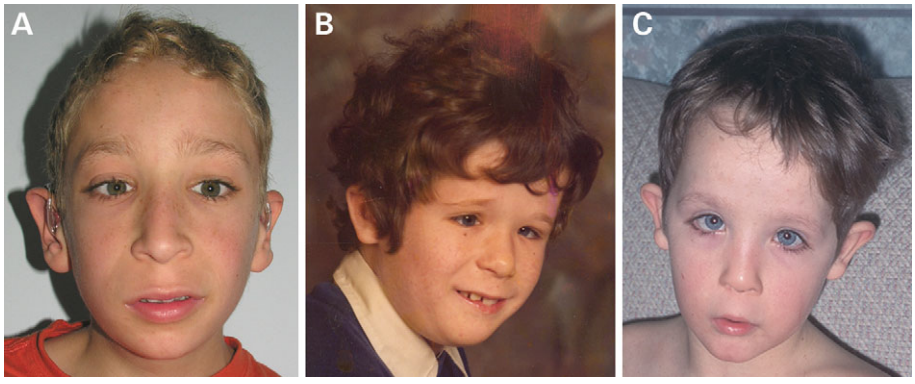

Figure 3. Patient images of (**A**) IMR349, (**B**) ID204 and (**C**) IMR371. All four deletion cases share several major features (growth retardation, microcephaly, hypospadias, loose connective tissue) and resemble one another facially (high anterior hair line, broad medial eyebrows, hypertelorism, downslanted palpebral fissures, broad nasal base, long and smooth philtrum and full lower lip).

There is growing evidence that a number of chromosomal deletions and translocations occur preferentially on chromosomes with a predisposing polymorphic architecture (reviewed in 9). FISH testing in the mother of patient C45/06 did not provide any evidence for inversion of the deletion region, as has been shown to occur in the transmitting parent for a number of other recurrent genomic disorders (2,10–16). However, our observations are consistent with the possibility of an alternate predisposing architecture for these microdeletions. Previous studies have shown the presence of a polymorphic ~30 kb VNTR coincident with the common proximal breakpoint, BP1 (4,5). Our oligonucleotide array studies indicated the presence of increased copies of this BP1 tandem repeat motif in the mother of IMR349 (Fig. 1B). Although our array data do not provide allelic discrimination of VNTR copy number, we hypothesize that the presence of additional copies of this repeat on the parental chromosome on which the deletion arose may facilitate NAHR by increasing the length of perfect homology between BP1 and BP2/BP3, leading to an increased propensity for generation of the 15q24 microdeletion. A similar phenomenon is observed for the recurrent 11q23;22q11 translocation, in which length variation of palindromic repeats at the breakpoints results in altered translocation frequencies during meiosis (17). As structural variation is also apparent at the breakpoints of many other recurrent genomic disorders (18), we speculate that an altered propensity for the generation of *de novo* microdeletions/duplications as a result of variation in the flanking repeat structures which mediate these events may represent a common theme at other genomic loci. Concerted efforts, such as the detailed characterization of multiple transmitting parents of genomic disorder patients or sperm studies to determine specific rates of *de novo* rearrangement in individuals with different genomic architecture, will be necessary to test this hypothesis.

Our results define a novel genomic disorder at 15q24 associated with a distinct clinical phenotype. Although not observed in our study, the homology between BP2 and BP3 suggests that deletions of the intervening sequence may also occur. Because of the recurrent nature of 15q24 deletions, we also predict the existence of the reciprocal duplication products, although the phenotype, if any, associated with these rearrangements awaits identification.

MATERIALS AND METHODS

In order to localize the breakpoints of each microdeletion, we designed a custom oligonucleotide array (NimbleGen Systems), consisting of 51 140 probes covering 7.5 Mb of 15q23–q25 (mean density, one probe per 147 bp). Probe length varied from 45 to 70 bp to yield an isothermal array design ($T_m = 76^\circ C$), and probes whose sequence mapped to non-unique genomic locations were excluded. A second ultra-high density isothermal array composed of 93 765 probes covering 400 kb at the BP1 and BP3 regions (mean density, one probe per 4.3 bp) was also designed, with probes only excluded from any 15 bp window with >100 identical genome-wide matches. All hybridizations were performed as described previously (19) and used the same reference individual as the BAC array hybridizations (GM15724, Coriell, Camden, NJ, USA). Oligonucleotide microarray data discussed in this publication are available at http://humanparalogy.gs.washington.edu/structuralvariation/.

Parental origin studies were performed using fluorescently labeled PCR of microsatellite markers mapping within the deletion region (*D15S160*, *D15S984*, *D15S965*; Operon Biotechnologies, Huntsville, AL, USA), resolved using an ABI3100 and analyzed using Genescan software. Sequencing primers (A: atgtggactagccgggatagag, B: gaaaaagtggcag cagtttcct) were designed using Primer3 (http://frodo.wi.mit.edu/cgi-bin/primer3/primer3_www.cgi) and used to amplify across the deletion breakpoints in IMR371. Sequencing reactions (ABI BigDye v3.0; Applied Biosystems, Foster City, CA, USA) were cleaned using Exonuclease I/Shrimp Alkaline Phosphatase (New England Biolabs, Ipswich MA), followed by precipitation with ethanol/EDTA prior to separation using an ABI3100.

FISH studies for confirmation of each deletion and inversion studies of 15q24 were performed on fixed stimulated T-lymphocytes by standard techniques using BAC

(RPCI-11 library) and fosmid (G248 library) clones mapping to 15q24.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at HMG Online.

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Conflict of Interest statement. P.S.E. and R.R.S. are employees of NimbleGen Systems, Inc. and have stock options in the company.

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