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A 2-Mb Critical Region Implicated in the Microcephaly Associated With Terminal 1q Deletion Syndrome

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Patients with distal deletions of chromosome 1q have a recognizable syndrome that includes microcephaly, hypoplasia or agenesis of the corpus callosum, and psychomotor retardation. Although these symptoms have been attributed to deletions of 1q42-1q44, the minimal chromosomal region involved has not been identified. Using microsatellite and single nucleotide polymorphism (SNP) markers, we have mapped the deleted regions in seven patients with terminal deletions of chromosome 1q to define a 2.0 Mb microcephaly critical region including the 1q43-1q44 boundary and no more than 11 genes. © 2007 Wiley-Liss, Inc.

Key words: terminal 1q deletion syndrome; microcephaly and hypoplasia of the corpus callosum; deletion 1q43-1q44

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INTRODUCTION

In the 29 years since the first report by Mankinen et al. [1976], more than 30 patients with terminal chromosome 1q deletions have been described. Based upon these patients, Juberg et al. [1981] and others [Johnson et al., 1985; Watson et al., 1986; Meinecke and Vogtel, 1987] have defined a 1q deletion syndrome that includes microcephaly, growth and psychomotor retardation, as well as craniofacial and other somatic abnormalities.

Advances in imaging techniques and cytogenetics have allowed progressively more precise characterizations of both the disease manifestations and the underlying genetic causes. Initial studies were limited to those aspects of the syndrome that are evident upon physical or neurological exam. Likewise, only microscopically visible chromosome rearrangements could be identified using Giemsa-banding techniques. The use of imaging techniques including computed tomography (CT) and magnetic resonance imaging (MRI) have allowed for the identification of additional disease characteristics, such as hypoplasia of the corpus callosum. Recently, fluorescent in situ hybridization (FISH) of DNA has been used to identify submicroscopic deletions of the terminal end of 1q in patients with mental retardation [Bezrookove et al., 2000; De Vries et al., 2001; Baker et al., 2002]. We sought to extend these studies by using abundant, polymorphic DNA markers to more precisely define the region deleted in six microcephalic patients with terminal chromosome 1q deletions, and to correlate the DNA analysis with brain imaging results for these patients. This allows a more precise radiological definition of the 1q43-44 deletion syndrome and the identification of a 2.0 Mb genomic region associated with microcephaly. This critical region is bordered by single nucleotide polymorphism (SNP) markers rs2754471 and rs1330695 and encodes no more than eleven genes.

MATERIALS AND METHODS

Seven previously unreported patients with terminal chromosome 1q deletions were recruited

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from multiple medical centers and examined by pediatric neurologists. Detailed medical histories, physical and neurological examinations, and occipito-frontal circumferences (OFC) were obtained when possible. Informed consent was obtained, and all work was conducted in accordance with protocols approved by the Institutional Review Board of Children's Hospital Boston.

Brain MRI was performed on Patients 1, 2, 4, and 5 according to standard clinical protocols of each patient's referring medical institution. In general, T1-weighted and T2-weighted spin-echo images were obtained in multiple planes using a 1.5-T magnet. All images were reviewed with particular attention to the complexity of cortical gyral pattern and associated abnormalities of the corpus callosum and posterior fossa structures. Clinical and MRI data were evaluated to determine whether each patient had the characteristic features of terminal 1q deletion syndrome.

Blood samples were obtained from all seven patients as well as 13 of 14 parents, and DNA was extracted from the lymphocytes using standard methods. Microsatellite markers were amplified and analyzed on an ABI Prism 3100 DNA analyzer (Applied Biosystems, Foster City, CA). SNP analysis was also performed on genomic DNA from these patients. Genomic DNA was amplified and then hybridized to Affymetrix 50k HindIII and XbaI chips. SNP genotypes and copy number were determined using dCHIP array analysis software [Lin et al., 2004].

RESULTS

Karyotypes and clinical findings for the seven patients are listed in Table I. Six (Patients 1–6) had clinical features consistent with the 1q deletion syndrome, including microcephaly, seizures, and psychomotor delay. Patient 7 was normocephalic and had no history of seizures but does have dyspraxia, learning difficulties and a heart condition.

CLINICAL REPORTS

Patient 1

Patient 1 is an 8-year-old girl born at full term by vaginal delivery. A prenatal sonogram performed at 33 weeks' gestation revealed hydrocephalus, microcephaly, and growth retardation. At 7 weeks of age, brain MRI demonstrated severe hypoplasia of the corpus callosum with moderate enlargement of the atria and occipital horns of the lateral ventricles. At 10 months of age she experienced a generalized tonic–clonic seizure. EEGs performed at 2 and 3 years demonstrated multifocal epileptiform discharges. At 4 years of age, she was still experiencing recurrent seizures; she lacked speech but was

TABLE I. Comparison of Deletion Size and Clinical Findings Between this Study and Published Deletion Cases

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Subtelomeric deletions	Larger 1q deletions
Karyotype	del(1)(q43)	der(1)t(1;9)(q44;p11.2)mat	del(1)q43q44	del(1)(q44)	del(1)(q44)	del(1)(q44)	del(1)q44		
Measured size (Mb)	<8.3	<6.7	<7.2	<7.2	<6.7	5.9–7.8	<4.9		
Mental retardation	+	+	+	+	+	+	Learning, verbal	6/6	20/20
Growth retardation	+ +	ND	ND	+ +	ND	+ +	ND	17/19	5/6
Microcephaly	+ +	+	+ +	+ +	+ +	+ +	–	21/23	3/5
Seizures	+	+	+ +	+	+	+	–	16/20	5/5
Corpus callosum	Hypoplasia	Hypoplasia	ND	Agenesis	Agenesis	Hypoplasia	ND	8/11	4/4
Skeletal	+	ND	+	ND	ND	+	ND	3/3	
White matter	ND	+	+	ND	ND	+	ND		
Cerebellum	ND	Hypoplastic vermis	ND	Hypoplastic vermis	ND	ND	ND		
Gyration	ND	Simplified	ND	Mildly simplified	ND	ND	ND		
Lateral ventricles	Moderately enlarged	Enlarged	Enlarged	Enlarged	Enlarged	Enlarged	ND		

Karyotypes, deletion size ranges, and findings for the seven patients in this study along with a summary from the literature adapted from van Bever et al. A "+" or "–" denotes the presence or absence, respectively, of a clinical or radiological sign. ND indicates that such information was not available. Six patients have features of 1q deletion syndrome, including mental retardation, microcephaly, seizures and hypoplasia of the corpus callosum. The ratios shown are the number of patients in whom a given clinical or radiological sign was present over the number of patients for which information on the sign was available.

learning to sign. OFC at this age was 42 cm (<2nd centile).

Karyotyping performed at 6 months revealed a de novo deletion of chromosome 1q43. Microsatellite markers were amplified from blood lymphocyte genomic DNA to more precisely map the region deleted in Patient 1. Alleles amplified from this patient for seven microsatellite markers spanning the terminal 6.7 Mb of chromosome 1q43-44 are shown in Figure 1. Only one allele was observed for each of these markers and all markers distal to D1S2785. A distinct allele was inherited from each parent for D1S2785 (physical location 238,943,306), located 8.3 Mb from the end of chromosome 1. Based upon these data, we conclude that Patient 1 has a <8.3 Mb deletion of the distal long arm of chromosome 1.

Patient 2

Patient 2 is a 10-year-old boy born at full term by Caesarean. After delivery he showed poor feeding and required a nasogastric tube. Head sonogram performed at birth revealed slight prominence of the third and fourth ventricles. At 18 months of age he had a generalized tonic–clonic seizure in the setting of fever. Brain MR images showed microcephaly, enlarged ventricles, simplified gyral pattern and hypoplasia of the corpus callosum and cerebellar vermis (Fig. 2A,B).

Karyotype testing revealed an unbalanced translocation resulting in trisomy of chromosome 9p11.2-pter and monosomy of 1q44, giving a karyotype of 46,XY,-1,+der(1)t(1;9)(q44;p11.2). The patient's mother had a balanced translocation involving these loci. Like Patient 1, Patient 2 showed clear uniparental inheritance for microsatellite markers distal to D1S404. The most distal heterozygous marker in this patient, D1S1634 is located at 240,396,930, 6.9 Mb from the end of chromosome 1. SNP analysis confirmed this finding with normal allele copy number for rs2754471 and more proximal SNPs (Fig. 3 and data not shown). Based upon the position of this SNP at 240,519,849, we conclude that Patient 2 has a deletion covering <6.7 Mb of chromosome 1q.

Trisomy of 9p has been associated with a variant of Dandy–Walker syndrome that includes ventriculomegaly, thinning of the corpus callosum and hypoplasia of the cerebellar vermis and cerebellar peduncles [Hannam et al., 1999; Chen et al., 2002, 2005]. It is therefore likely that the enlarged ventricles and hypoplastic corpus callosum and cerebellar vermis observed in this patient are at least partially attributable to trisomy 9p. However, microcephaly has not been reported in previous cases of trisomy 9p [Hannam et al., 1999; Chen et al., 2005], suggesting that this patient is hemizygous for one or more genes required for normal brain growth. Interestingly all of the other 1q deletion syndrome patients in this study have enlarged ventricles, suggesting that this may be a common or at least frequently occurring feature of this syndrome.

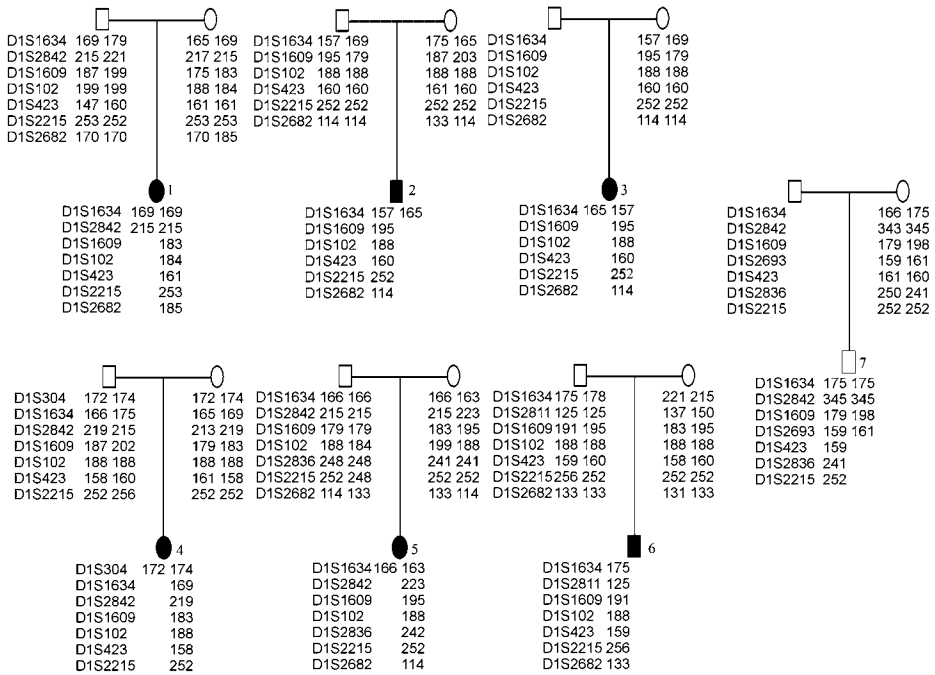

FIG. 1. Microsatellite alleles for Patients 1–7 and their parents. Clearly hemizygous alleles are indicated by a single number, and alleles that could be either hemizygous or homozygous are indicated by repeating the allele number. Affected individuals with microcephaly and hypoplasia of the corpus callosum are indicated by filled symbols.

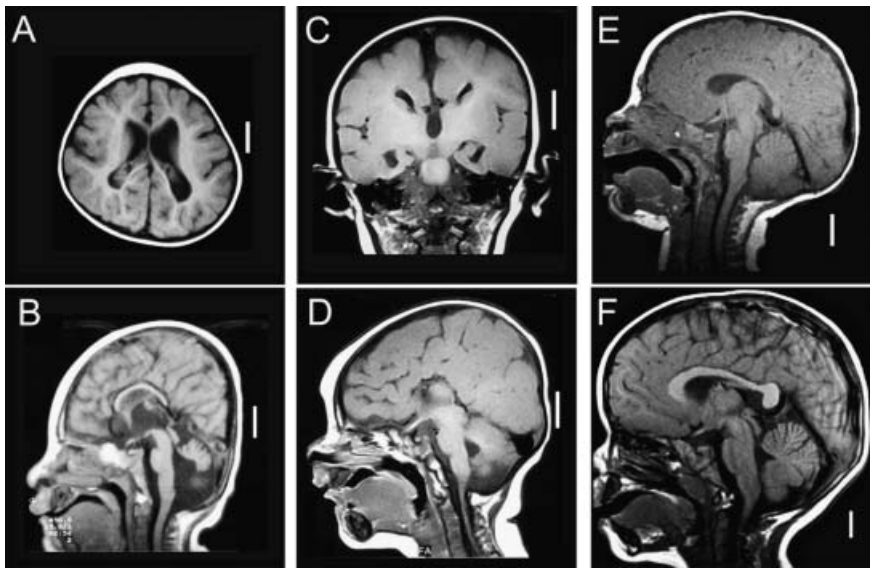

FIG. 2. T1-weighted brain MRI of Patient 2 at 6 months (**A**,**B**) and Patient 4 at 18 months (**C**,**D**) obtained in the axial (A), coronal (C) and sagittal (B,D) planes. MR images of Patient 2 (A,B) show reduced brain size, enlarged ventricles and a thin corpus callosum when compared to an age and gender matched control (**E**). The dramatic hypoplasia of the cerebellum and the thin corpus callosum are evident in (B). The striking absence of the corpus callosum in Patient 4 is evident in (C,D). Panels E,F show sagittal images of an unaffected 6-month-old boy (E) and an unaffected 18-month-old girl (**F**) for comparison. Scale bars = 2 cm.

Patient 3

Patient 3 was an 18-year-old woman with a history of developmental delay and mental retardation. Communication skills were limited to a few simple words, and she was learning to sign. She could ambulate with a walker. Patient 3 suffers from myoclonic seizures. Head CT scan performed at 2 years of age revealed microcephaly, reduced white matter volume, and enlarged lateral ventricles.

FISH at 16 years of age using telomere-specific probes demonstrated a terminal deletion of chromosome 1q. Consistent with this FISH result, all of the microsatellite markers distal to D1S304 showed

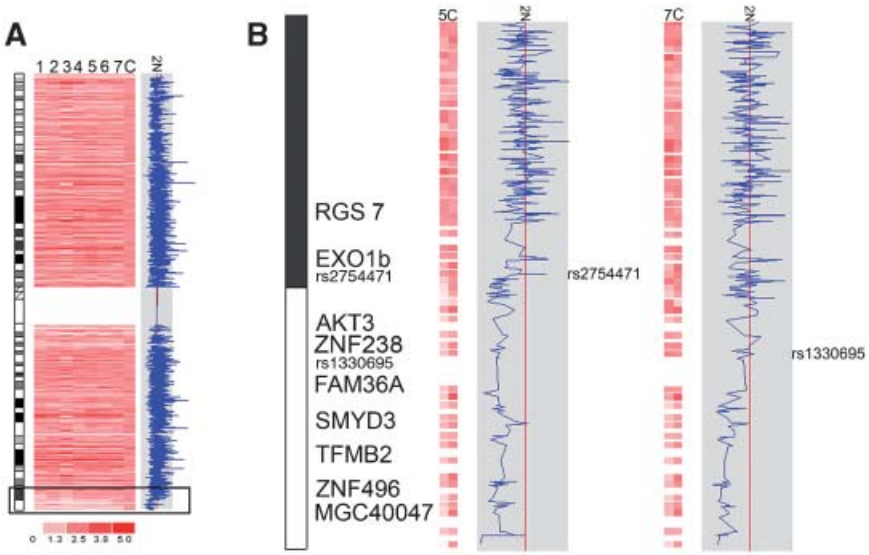

FIG. 3. SNP hybridization intensities and copy number. Cytobands, hybridization intensity, and representative calculated copy number are shown for (**A**) the entire chromosome 1 or (**B**) the boxed region in (A). A: When SNP hybridization intensities are plotted along a schematic of chromosome 1, lightly shaded boxes indicate regions of reduced copy number in each patient. In a graph of calculated copy number (blue graph at right of panel A) for Patient 2, the deleted region is evident as a drop in average signal below 2N. Patient number is shown at the top of each intensity plot. C: Control reference DNA. B: Hybridization intensity and calculated copy number are shown for Patients 5 (on the left) and 7 (right side of panel) along with a schematic showing affected cytobands and the relative locations of some potentially deleted genes. In Patient 5 hybridization intensity and calculated copy number are reduced for SNPs distal to rs2754471. Patient 7 shows normal hybridization signal for rs1330695 and more proximal SNPs, while SNPs distal to rs1330695 show reduced copy number.

only a single allele. However, the absence of paternal DNA for this patient made it impossible to determine which of these markers were hemizygous. In order to unambiguously determine the deleted region in this patient, SNPs were amplified from DNA from Patient 3, and analyzed using the dCHIP program. Reduced copy number relative to controls was evident for all SNPs distal to rs2754471 at position 240,519,849. Normal copy number was noted for SNPs proximal to rs10495477 at position 239,096,859. Based upon the positions of these SNPs, the deletion in Patient 3 was determined to be between 6.7 and 8.1 Mb.

Patient 4

Patient 4 was a 6-year-old girl born at full term by Caesarean. At birth, this patient had an OFC of 32 cm (<3rd centile). She began experiencing recurrent seizures at 11 months of age. By 36 months she could walk with assistance but showed no speech. Her head circumference was 39 cm (<3rd centile). MRI showed microcephaly, complete agenesis of the corpus callosum, reduced white matter volume and delayed myelination (Fig. 2C,D) in addition to agenesis of the anterior and habenular commissures.

Giemsa-banding and FISH with telomere-specific probes revealed a de novo deletion of 1q44. Microsatellite analysis confirmed that 6.9 Mb of chromosome 1q were deleted between D1S1634 and the telomere. A distinct allele was inherited from each parent for D1S547, located 7.4 Mb from the telomere. Normal copy number was observed for rs952084, a SNP located at position 240,012,917. The deletion in this patient therefore covers <7.2 Mb of chromosome 1.

Patient 5

Patient 5 was a 9-year-old girl. OFC at birth was 31 cm (<3rd centile) and at 4 years 8 months was 45 cm (<2nd centile). Seizures began during the neonatal period. By the age of 5 she was having 10–20 seizures per month. She could walk with assistance, understand several commands, and was attempting to say a few words. MRI at seven weeks of age revealed agenesis of the corpus callosum.

Giemsa banding and FISH revealed a de novo deletion of chromosome 1q44. Microsatellite markers between D1S2842 and the telomere were hemizygous in this patient. D1S1634 and proximal markers were heterozygous in this patient. Normal copy number was observed for rs2754471, which is located 6.7 Mb from the telomere at 240,519,849 (Fig. 3). Based upon the locations of these markers Patient 5 has a deletion covering <6.7 Mb of chromosome 1.

Patient 6

Patient 6 is an 11-year-old girl. She had seizures with and without fever beginning at the age of 3 years 10 months. By age 8, Patient 6 had an OFC of 44.6 cm (<3rd centile). She could say a few words and walk 25–30 feet unsupported. She weighed 31 lbs (<3rd centile) and stood 95.5 cm tall (<3rd centile).

Karyotyping and FISH analysis revealed a de novo 1q44 deletion in this patient. Patient 6 did not inherit a maternal allele for D1S2811, which is 5.5 Mb from the telomere. An additional 2.4 Mb of markers, between D1S304 and D1S2811 were homozygous but not informative. Normal copy number was observed for the SNP marker rs10495477, which resides 8.1 Mb from the telomere at 239096859. Unambiguously reduced copy number was observed for SNP marker rs1796846 at 241373547. The deletion in this patient covers between 7.8 and 5.9 Mb of 1q43-44.

Patient 7

Patient 7 is a 17-year-old boy. He had oral and motor dyspraxia and mental retardation but normal OFC (47 cm at 15 months, 50th centile) and no history of seizures. An EEG performed at 8 years of age also failed to show any evidence of seizure activity. At the age of 5 years 5 months he was able to express himself using simple two word sentences and some signs. By 14 years he could follow simple commands and express himself in sentences, though he continued to have difficulty discriminating among and producing sounds. These findings suggest improved language development relative to patients with deletions extending more proximally.

Microsatellite analysis showed a deletion of the long arm of chromosome 1, including D1S423 at position 243,612,280 but not D1S2693. This deletion covers the terminal 3.6–4.9 Mb of chromosome 1. SNP analysis confirmed this deletion. Reduced copy number was observed for all SNPs distal to rs1330695, which is located 4.9 Mb from the telomere at 242,374,397 (Fig. 3). The absence of microcephaly in this case suggests that this patient is disomic for an interval whose deletion causes microcephaly in the other patients.

DISCUSSION

A refined critical region for microcephaly associated with 1qter deletion syndrome van Bever et al. [2005] reported a case of a terminal 1q deletion in a patient with microcephaly, hypoplasia of the corpus callosum, growth retardation, convulsions, and absent language. The breakpoint in this case mapped between D1S2785 and D1S304. These authors defined a 4.5 Mb critical region based upon this patient, previously reported deletions, and the

observation that the terminal 1.5-Mb of chromosome 1 is comprised of pseudogenes. Although the deletion in this case covered 6.5 Mb, the authors ruled out the terminal most 1.5 Mb of the deleted region on the assumption that this pseudogene-rich region should not be required for normal growth and development. In the current study we refine this critical region to define a 2.0 Mb region associated with microcephaly. The 4.9 Mb telomeric deletion in Patient 7 confirms van Bever's hypothesis that two copies of the distal most 1.5 Mb of chromosome 1 are not required for normal head growth, since this patient has normal head circumference. Additionally, the deletion seen in Patient 7 allows us to extend the region excluded from the microcephaly critical region proximally to rs1330695. We hypothesize that the region deleted in Patients 1–6 but not in Patient 7 contains one or more genes required for normal brain growth and development.

There have been several reports of individuals with microcephaly and 1q44 deletions [Hathout et al., 1998; Bezrookove et al., 2000; Villa et al., 2000]. However, none of these deletions have been precisely mapped, making it impossible to determine if these deletions are truly restricted to 1q44. Our analysis has shown that what appear to be 1q44 deletions by Giemsa-banding can actually include a significant part of 1q43 (this is the case for Patients 2, 4, 5, and 6 of the present study, for instance).

Gentile et al. [2003] proposed correlations between clinical phenotype and the extent of deletion in patients with 1q deletion syndrome. They observed a specific correlation between hand and foot abnormalities and deletions including the 1q42 region. Consistent with this observation, no hand or foot abnormalities were reported in the patients in this study, all of whom have deletions that are restricted to 1q43-44. Clinodactyly was observed in Patient 2, but that is attributable to this patients duplication of chromosome 9p [Hannam et al., 1999]. Hip dysplasia was observed in the three patients with the largest potentially deleted regions, Patients 1, 3, and 6; as well as a patient with a similarly sized deletion [van Bever et al., 2005]. Additional studies will be needed to determine if this points to a gene or genes between D1S304 and D1S1634 that is required for normal hip development.

Analysis of Deleted Genes

The refined microcephaly critical region (Fig. 4), bounded by rs2754471 and rs1330695, contains five RefSeq genes according to the UCSC Bioinformatics website. The NCBI Human Genome Mapviewer build 3.6 lists an additional six hypothetical genes within this region. The identified genes within this region are *PLD5*, *CEP170*, *SDCCAG8*, *AKT3*, and *ZNF238*. Some of these are logical candidate genes

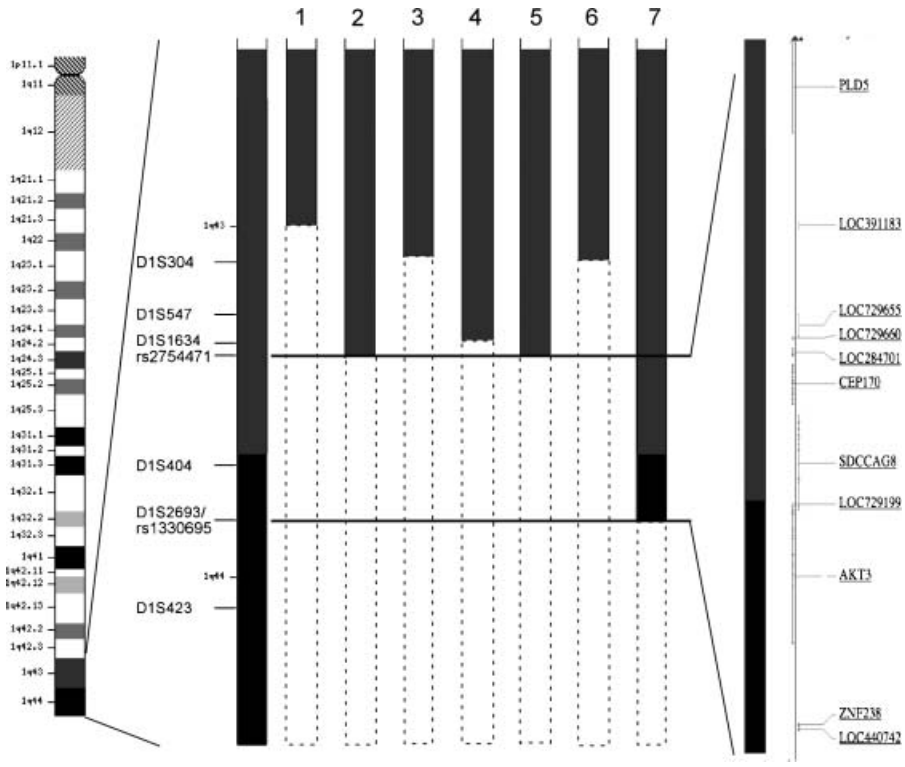

FIG. 4. Summary of deleted regions in all seven patients. Cytobands for 1q are shown to the left, along with an enlargement of 1q43-1q44. Dotted lines surround potentially deleted regions in each patient. The critical region, defined by the deletions present in Patients 5 and 7, is expanded to the right. This region contains all or part of 11 genes, which are listed at the far right.

for the control of brain size. CEP170 is a centrosomal protein that contains a forkhead-associated domain and is phosphorylated during mitosis [Guarguaglini et al., 2005]. SDCCAG8 is a coiled-coil domain containing protein that also localizes to the centrosome [Kenedy et al., 2003]. Centrosomal proteins have been shown to regulate brain size in mice and humans [Feng and Walsh, 2004; Bond et al., 2005], presumably by regulating cell division and/or spindle orientation. AKT3 is a member of a family of serine/threonine kinases that has been shown to control cell and organ size in flies, mice, and humans [Verdu et al., 1999; Shioi et al., 2002; Potter et al., 2003]. Interestingly, the brain and corpus callosum are significantly reduced in AKT3 knock out mice [Easton et al., 2005], making this a strong candidate gene for human microcephaly and hypoplasia of the corpus callosum.

We have defined a 2.0 Mb critical region for microcephaly surrounding the 1q43-1q44 boundary. FISH analysis with probes specific to this minimal deleted interval may help identify patients with small interstitial deletions of chromosome 1q43-44 in the future. Identification of the precise set of genes responsible for this syndrome will require the identification of patients with smaller interstitial deletions, or point mutations if this microcephaly is caused by haploinsufficiency for one gene.

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