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Dedicator of cytokinesis 8 is disrupted in two patients with mental retardation and developmental disabilities

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Abstract

We have identified disruptions in the dedicator of cytokinesis 8 gene, *DOCK8,* in two unrelated patients with mental retardation (MR). In one patient, a male with MR and no speech, we mapped a genomic deletion of approximately 230 kb in subtelomeric 9p. In the second patient, a female with mental retardation and ectodermal dysplasia and a balanced translocation, t(X;9) (q13.1;p24), we mapped the 9p24 breakpoint to a region overlapping with the centromeric end of the 230-kb subtelomeric deletion. We characterized the *DOCK8* gene from the critical 9p deletion region and determined that the longest isoform of the *DOCK8* gene is truncated in both patients. Furthermore, the *DOCK8* gene is expressed in several human tissues, including adult and fetal brain. Recently, a role for *DOCK8* in processes that affect the organization of filamentous actin has been suggested. Several genes influencing the actin cytoskeleton have been implicated in human cognitive function and thus a possibility exists that the rare mutations in the *DOCK8* gene may contribute to some cases of autosomal dominant mental retardation.

Keywords: Subtelomere; Mental retardation; Chromosome translocation; DOCK8; Autosome

Mental retardation (MR) is the most common developmental disability, affecting intellectual and adaptive functions in approximately 1–3% of the population. Yet, the underlying cause of MR is established in fewer than half the cases [1,2]. Genetic factors in MR likely include mutations in genes distributed throughout the genome and are already well established for the genes on the X chromosome [1,2]. The finding of MR among almost all patients with autosomal microdeletions and the association of MR with submicroscopic alterations in the subtelomeric region of the autosomes further indicate the ubiquitous distribution of autosomal genes that influence intelligence [3–5].

Chromosomal abnormalities have been found in a significant number (10–15%) of individuals with mental retardation and developmental disabilities (MR/DD) [6]. About 5% of idiopathic MR can be explained by deletions or rearrangements of the subtelomeric regions of the autosomes [5–9]. A large number of subtelomeric deletions have been observed in patients with MR, suggesting that these deletions are likely to harbor a gene(s) responsible for the observed phenotypes in these patients. Furthermore, analysis of patients with submicroscopic deletions has facilitated identification of small regions of overlap linked to specific phenotypic characteristics and subsequent isolation of the causative genes. Recently, disruption of the *EHMT1* gene has been shown to be associated with the 9q34 subtelomeric deletion syndrome [10,11].

Here we characterized, at the DNA level, chromosomal rearrangements involving 9p24 in two unrelated patients with mental retardation and developmental disabilities. We have characterized the *DOCK8* gene from the critical 9p subtelomeric region, determined the expression of the *DOCK8* gene in fetal and adult human brains, and demonstrated that the longest isoform of the gene is physically disrupted in both patients.

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Results

Molecular analysis of the subtelomeric deletion in a patient with mental retardation and developmental disability

Subtelomeric FISH analysis revealed deletion of a probe from the 9p subtelomeric region (ish 9pter (305J7-T7 x1)) in patient CMS6482 (Figs. 1a and b). This probe was found to map within a genomic contig (NT_008413; NCBI) in 9p24.3 (Fig. 1a). We identified physically mapped genomic clones from the contig and used them systematically in FISH analyses to determine the extent of the subtelomeric 9p deletions in this patient (Fig. 1a and Table 1). A part of the 9p subtelomeric region has previously been shown to share sequence homology with other regions of chromosome 9 [12]. Consistent with that report, probes RP11-143M1 and RP11-174M15 gave three FISH signals on a normal chromosome 9: one at the 9p subtelomere and two others in 9p12 and 9q21.2 regions. However, the 9p subtelomere-specific FISH signal with clone RP11-174M15 was absent in CMS6482, indicating a deletion of this region in the patient (Supplementary Fig. 1 and Table 1). Probe RP11-59O6 gave a signal on the normal chromosome 9 but not on the deleted chromosome 9 (Fig. 1c). Probe RP11-910H2 gave signals on the normal chromosome 9, as well as a reduced signal on the derivative chromosome 9, suggesting this probe is partially deleted (Fig. 1d). All FISH probes gave expected signals on the normal chromosome 9 in a control sample (not shown). These results determined the deletion in patient CMS6482 to be between genomic clones RP11-143M1 (telomeric) and RP11-910H2 (centromeric) (Fig. 1a).

Mapping of the 9p chromosomal breakpoint in a female patient with MR, anhidrotic ectodermal dysplasia, and a de novo t(X;9) (q13;p24) translocation

We previously mapped the Xq13 chromosome breakpoint of patient CMS1485 within intron 1 of the anhidrotic ectodermal dysplasia (*EDA*) gene (Xq13) and determined that the

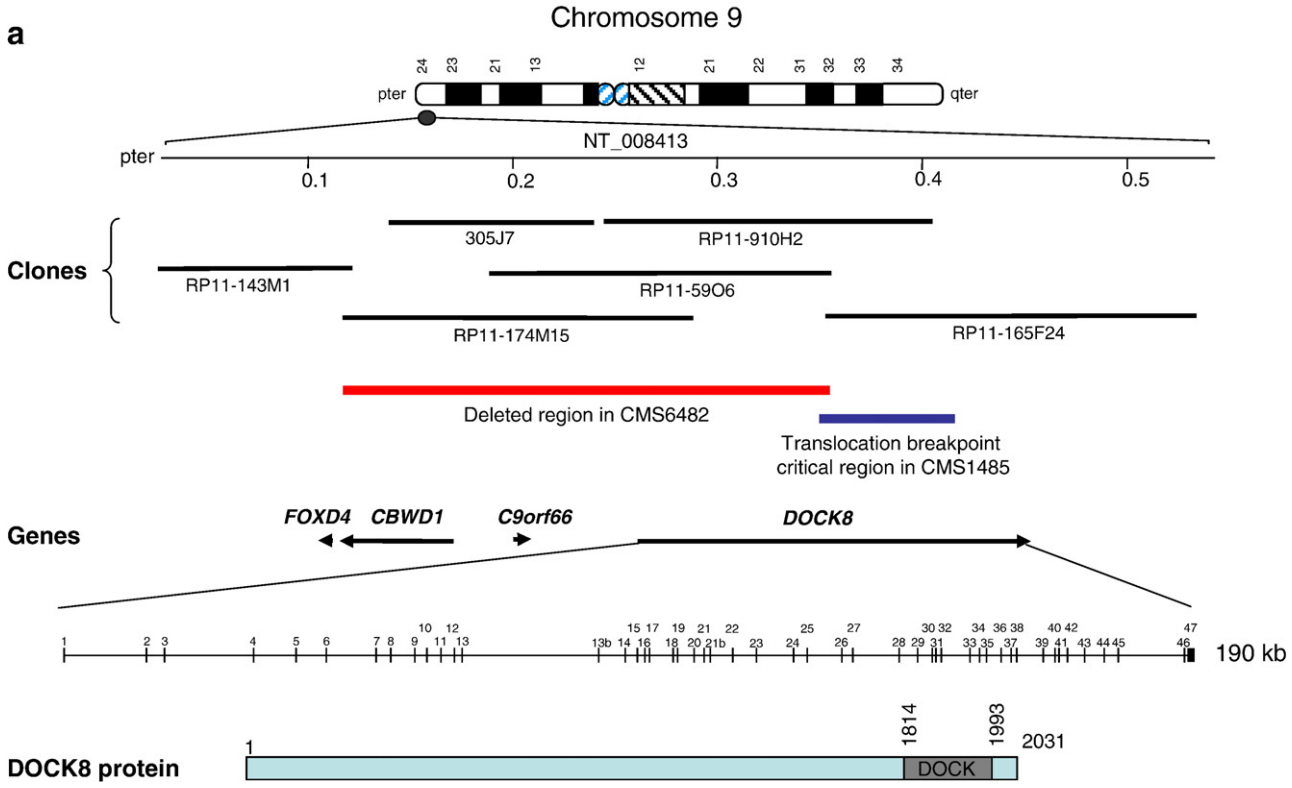

Fig. 1. Mapping of the subtelomeric 9p chromosomal rearrangements. (a) An idiogram of chromosome 9 with a partial physical map of the subtelomeric 9p24.3 region, the BAC clones used in FISH analysis, and known genes (in italics) are shown. Black arrows indicate the direction of the transcription. FISH analyses determined a critical deletion region (red bar) in patient CMS6482 and a region (blue bar) harboring the 9p24 translocation breakpoint in CMS1495. The genomic structure of the *DOCK8* gene and a schematic of the 2031 amino acids DOCK8 variant are shown. The predicted DOCK domain in the C-terminal region is indicated. (b–d) FISH analyses in CMS6482. (b) Chromosome 9 subtelomeric probes (9p, green; 9q red) produced a green signal only on one chromosome 9 and not the other, indicating a 9p subtelomeric deletion in CMS6482. Red signal was present on both the normal and the deleted chromosomes 9. (c) RP11-59O6 (red) gave a signal (dark red) only on the normal chromosome 9 and not on the deleted chromosome 9 (arrow), indicating deletion of this probe in CMS6482. The chromosome 9 centromeric probe is in light red color. (d) Probe RP11-910H2 (green, arrowheads) is partially deleted on the derivative chromosome 9 and gave signals on both the normal and the derivative chromosome 9. The chromosome 9 centromeric probe is in light red color. (e) FISH analysis in CMS1485. Probe RP11-910H2 (green) is distal to the 9p24.3 translocation breakpoint in CMS1485. The probe is present on the normal chromosome 9 as well as the derivative X chromosome. The chromosome 9 centromeric probe is in light red color. (f) PFGE analysis with a probe located in the 3′ portion of *DOCK8* reveals an abnormally migrating fragment in CMS1485 but not in the control sample. (g) Fine mapping of the 9p critical region with quantitative genomic PCR in CMS6482, CMS1485, and three controls (CMS11195, CMS5865, and CMS6265) reveals that the 9p subtelomeric deletion in CMS6482 extends at least through exon 23 of the *DOCK8* gene. CMS1485 has a deletion presumably associated with the translocation located between exon 23 and exon 34 with exon 29 deleted. The values represent the average of three replicates used in each case.