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Dok1 Encoding p62^{dok} Maps to Mouse Chromosome 6 and Human Chromosome 2 in a Region of Translocation in Chronic Lymphocytic Leukemia

Keats Nelms,*,[1] Andrew J. Snow,* and Konrad Noben-Trauth†

**Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892-1892; and †Section on Murine Genetics, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Rockville, Maryland 20850*

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The small GTPase Ras plays a critical role in normal cell growth, and mutations in Ras can contribute to cellular transformation (1, 3). Ras GTPase activating protein (RasGAP) modulates Ras activation (1). Recently the protein p62^{dok} has been identified as the highly phosphorylated 62 kD protein that interacts with RasGAP in chronic myelogenous leukemia (CML) progenitor cells and v-*abl* transformed preB cells (2, 13). The elevated kinase activity resulting from the expression of v-*abl* or the chimeric protein p210$^{bcr\text{-}abl}$ in CML cells has been shown to lead to constitutive p62^{dok} phosphorylation (2, 13). The downstream effects of p62^{dok} phosphorylation in CML has yet to be elucidated but it has been suggested that constitutive p62^{dok} phosphorylation may contribute to cellular transformation (2, 13). Previous studies have suggested that p62^{dok}, which is expressed in a wide range of tissues, is a target for the p210$^{bcr\text{-}abl}$ and v-*abl* proteins as well as for other receptor and cytosolic tyrosine kinases including, v-*src*, the EGF receptor, the insulin/IGF-1 receptors, and the PDGF receptor (2, 4, 6, 13).

We mapped the gene encoding p62^{dok} (referred to here as *Dok1*) to mouse chromosome 6 using the BSS backcross panel [(C57BL/6JEi × SPRET/Ei) F_1 females × SPRET/Ei males] obtained from The Jackson Laboratory (Bar Harbor, ME) (9). Sequence analysis of *Dok1* from C57BL/6J and SPRET/Ei DNA revealed a polymorphism in the SPRET/Ei allele that resulted in the loss of a *Bss*SI restriction site at nucleotide position 1311 (numbering according to GenBank Accession

Sequence data from this article have been deposited with the Mouse Genome Database under Accession No. MGD-JNUM-43522.

[1] To whom correspondence should be addressed at LI, NIAID, NIH, Building 10, Room 11N311, 10 Center Drive, MSC 1892, Bethesda, MD 20892-1892. Telephone: (301) 496-8864. Fax: (301) 480-7352.

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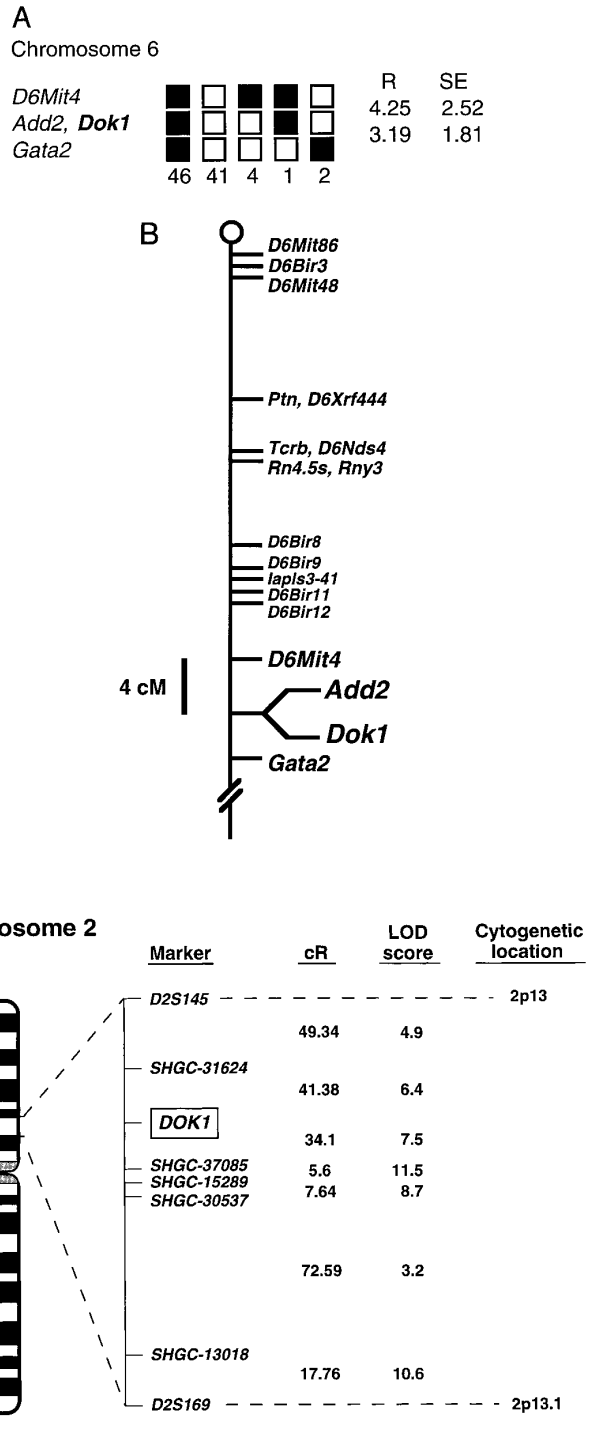

FIG. 1. The *Dok1* gene maps to the central region of mouse chromosome 6 and to human chromosome 2. (**A**) Haplotype figure from The Jackson BSS backcross showing part of chromosome 6 with loci linked to *Dok1*. Loci are listed in order with most proximal at the top. The black boxes represent the C57BL6/JEi allele, and the white boxes represent the SPRET/Ei allele. The number of animals with each haplotype is given at the bottom of each column of boxes. The percentage recombination (*R*) between adjacent loci is given to the right of the figure, with the standard error (SE) for each *R*. Missing typings were inferred from surrounding data where assignment was ambiguous. Data from The Jackson Laboratory were obtained from the World Wide Web address http://www.jax.org/resources/documents/cmdata. (**B**) Map figure from The Jackson Laboratory BSS backcross showing part of mouse chromosome 6 containing the *Dok1* locus and representative flanking markers. The map is depicted with the centromere at the top. Relative distances between markers are indicated by a 4-cM scale bar. (**C**) The location of *DOK1* on human chromosome 2. The chromosome 2 idiogram is depicted on the left, followed by an excerpt of the Stanford G3 Radiation Hybrid map, the distance between individual markers as given in cR, the lod score, and the cytogenetic location of the flanking markers *D2S145* and *D2S169*. Marker order, distances, and lod scores were computed using the MapManager program and are in agreement with the Stanford Radiation Hybrid map.

No. U78818). A 770-bp PCR fragment encompassing the region between nucleotides 690 and 1460 of *Dok1* was amplified from the 94 BSS backcross panel DNA samples using the primers 5′GGGACCTTCACCTTCCAGACTTCTCAGGGA (forward) and 5′CTGTCTCAGGTGGAACCCTCAGACTTGACCCCCGCC (reverse) (annealing temperature 68°C). Resultant PCR fragments were digested with *Bss*SI (New England Biolabs, Beverly, MA). Fragments amplified from the SPRET/Ei allele were not cut, whereas fragments amplified from the C57BL6/JEi allele were cut, resulting in a diagnostic 620-bp fragment.

The typing analysis indicated that *Dok1* maps to the central region of mouse chromosome 6 and cosegregated with β-adducin (*Add2*) (Figs. 1A and 1B) (12). *ADD2* and other markers from this region of mouse chromosome 6 have been mapped to human chromosome 2p13 including transforming growth factor α (*TGFA*) and γ 2 actin (*ACTG2*) [Mouse Genome Informatics (MGD), The Jackson Laboratory, http://www.informatics.jax.org]. Thus it seemed likely that human *DOK1* would also map to 2p13. We confirmed the location of *DOK1* to be on human chromosome 2p13 using the Stanford G3 Radiation Hybrid panel. Oligonucleotides specific to the 3′ end of *DOK1* [5′GTGGCACTAGGGATCAAAGAAGATGGTTAGAACCAG (forward) and 5′AGAACAATGCAGGAGTAAGGATCCAGGCACAGTCC (reverse); anealing temperature 72°C] amplifed a gene-specific 330-bp fragment, and data were entered into the online database (rhserver@shgc.stanford.edu). *DOK1* was localized in close proximity to *SHGC-37085* at 2p13 (Fig. 1C). Using MapManager, *DOK1* was placed between markers *SHGC-31624* and SHGC-30785 (Fig. 1C).

Human chromosome 2p13 has previously been shown to be involved in a unique chromosomal translocation t(2;14) associated with chronic lymphocytic leukemia (CLL) and B-cell acute lymphoblastic leukemia (B-ALL) (5, 10, 11, 14). Translocations to 2p13 have been implicated in other tumors including basal cell papilloma and keratoacanthoma (7). The t(2;14) translocation has been hypothesized to disrupt the structure or expression of a gene, which then leads to malignant transformation of cells (8, 11). Since the $p62^{dok}$ protein is hyperphosphorylated in CLL and v-*abl* transformed cells, it has been suggested to contribute to the transformed phenotype of these cells. It is interesting to speculate that the expression or function of the human *DOK1* gene may be altered by chromosomal translocations to chromosome 2p13 that lead to tumor formation.

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