

was confirmed by cohybridization with a chromosome 11-specific cosmid, ICRFc107CO1178 (8), which contains the potassium channel Kv1.4 and maps to 11p14.1 (5), or with a chromosome 11-specific plasmid library (2).

Several large families have been described in which human psychiatric disorders such as schizophrenia and bipolar affective disease segregate with cytogenetic abnormalities involving chromosome 11 (6, 14, 15). In this context, mapping of the human HTR3 receptor gene to a subregion within chromosome 11 close to a 11q22.3–9p22 translocation breakpoint seen in a family with bipolar affective disorder deserves attention (14). Further molecular studies should elucidate the proximity of the translocation breakpoint relative to the HTR3 gene.

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Assignment of DAP1 and DAPK—Genes That Positively Mediate Programmed Cell Death Triggered by IFN- γ —to Chromosome Regions 5p12.2 and 9q34.1, Respectively

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DAP-kinase (DAPK) and DAP1 were recently identified as positive mediators of IFN- γ -induced programmed cell death (1). The inactivation of these genes by antisense RNA expression reduced the susceptibility of HeLa cells to IFN- γ -induced apoptosis. DAP1 is expressed as a single 2.4-kb mRNA that codes for a basic proline-rich 15-kDa protein. DAPK is transcribed into a single 6.3-kb mRNA and codes for a structurally unique 160-kDa calmodulin-dependent serine-threonine kinase that carries eight ankyrin repeats and two putative P-loop consensus sites (1). Since genes involved in control of cell death can, when dysregulated, behave as oncogenes or growth suppressor genes, DAPK and DAP1 as positive mediators of IFN- γ -induced cell death may be candidate tumor suppressor genes. Thus, knowledge of the chromosome locations of the DAP1 and DAPK genes might be useful in initial assessment of involvement in neoplasia or other diseases.

Chromosome locations for the DAP1 and DAPK genes

Sequence data from this article have been deposited with the EMBL/GenBank Data Libraries under Accession Nos. X76104 and X76105.

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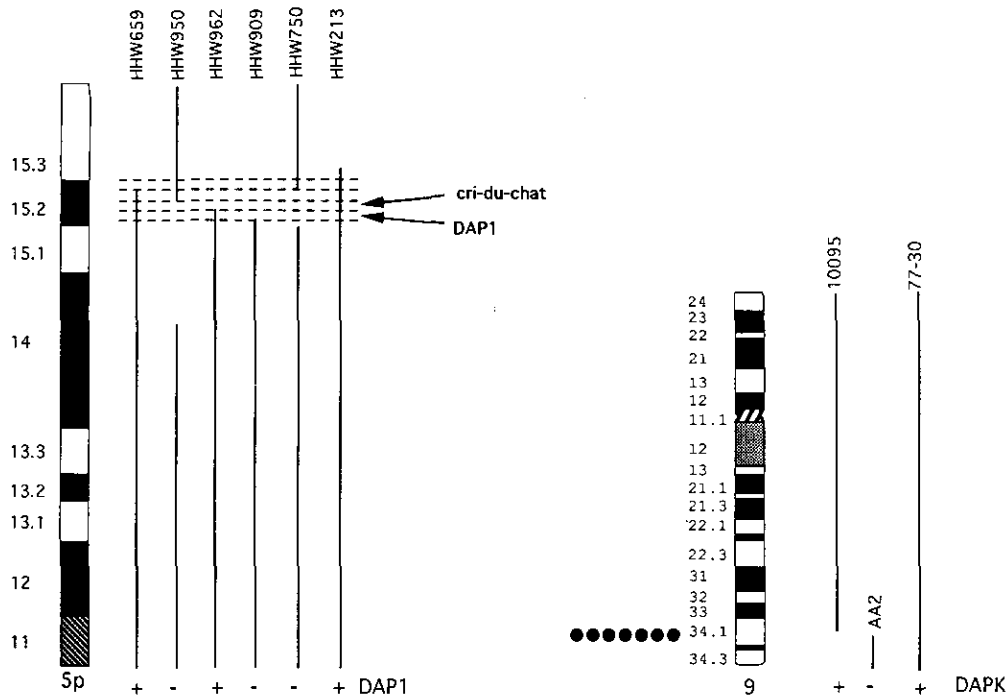


FIG. 1. Regional localization of the DAP1 and DAPK genes in rodent-human hybrids carrying partial 5 and 9 chromosomes. (**Left**) The portion of chromosome 5p present in specific hybrids is represented by the solid line to the right of the chromosome 5p ideogram with the presence or absence of the DAP1 gene indicated below. (**Right**) Hybrids carrying partial chromosomes 9 are illustrated to the right of the 9 ideogram with results of filter hybridization to the DAPK-specific probe indicated below. Results of fluorescence *in situ* hybridization to normal human metaphases are illustrated to the left of the chromosome 9 ideogram; each filled circle represents six fluorescent signals.

were determined by testing for the presence of the genes in panels of rodent-human hybrids carrying specific human chromosomes. Many of the hybrids used are available through the Human Genetic Mutant Cell Repository (Coriell Institute, Camden, NJ). Other hybrid DNAs were from previously described rodent-human hybrid cell lines (2, 7). The radiolabeled human DAP1 cDNA probe was hybridized to a panel of restriction enzyme-cleaved DNAs from 15 rodent-human hybrids. Hybrids carrying human chromosome 5 in common retained the DAP1 gene; those without chromosome 5 were negative for the DAP1 gene restriction fragment (data not shown). A chromosome 5 hybrid mapping panel in which each hybrid DNA retained a specific portion of chromosome 5 was similarly tested. Hybrids carrying 5p15.2 in common retained the DAP1 gene as illustrated in Fig. 1, and the gene was further sublocalized within region 5p15.2 using hybrid DNAs that define four subregions of 5p15.2 (6). Results of the sublocalization are illustrated to the right of the 5p ideogram and show that the DAP1 gene maps to the subregion adjacent and centromeric to the subregion to which the *cri-du-chat* syndrome has been mapped (6).

Similarly, the radiolabeled DAPK cDNA probe was hybridized to a panel of restriction enzyme-cleaved DNAs from 16 rodent-human hybrids, and hybrids carrying human chromosome region 9pter-9q34 in common contained the DAPK gene (Fig. 1). The DAPK gene was localized to a specific chromosome band by fluorescence *in situ* hybridization of the cDNA probe to human metaphases as described previously (4). Biotinylated DAPK cDNA was hybridized to metaphase chromosomes, and signal was detected with fluorescein-conjugated avidin; 42 fluorescent spots were observed at band 9q34.1 (most likely centro-

meric to the ABL locus) on a total 12 metaphases from peripheral blood of a normal male, as illustrated in Fig. 1, where each filled circle to the left of chromosome 9 represents 6 fluorescent spots. Clustering of signals on other chromosome regions was not observed. Loss of heterozygosity studies in bladder carcinoma have suggested the presence of a suppressor gene between 9q33 and 9q34.2 (3, 5) for which DAPK may be a candidate.

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Mouse Hepatitis Virus-3 Induced Prothrombinase (*Fgl2*) Maps to Proximal Chromosome 5

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Infection with mouse hepatitis virus-3 (MHV-3), a member of the coronavirus family, leads to a strain-dependent spectrum of liver disease (2). Mice of the BALB/cJ, C57BL/6J, and DBA strains are fully susceptible, exhibiting 100% mortality when infected with as little as 0.1 PFU of MHV-3, while A/J mice are resistant, as defined by complete survival and normal liver histology after infection with 2×10^4 PFU. All of these strains are permissive for viral replication, suggesting that host immune factors, rather than viral cytopathology, are responsible for the observed difference in mortality (2). While the pathogenesis of MHV-3-induced liver disease is not fully understood, several lines of evidence indicate that local activation of the coagulation cascade prior to detectable viral replication plays an important role in liver cell injury. First, microscopy performed early in the infection of susceptible mice has shown sinusoidal thrombosis and foci of coagulation necrosis associated with varying degrees of inflammatory cell infiltration (14). Second, a correlation between disease severity and the induction of macrophage procoagulant activity (PCA) has been established, with susceptible mice developing an earlier and heightened PCA response relative to resistant strains (12). Finally, treatment of mice with a monoclonal antibody to MHV-3-induced PCA prevents

the lethality associated with infection (13). Genetic linkage in the form of an identical strain distribution pattern was established between susceptibility to infection with MHV-3 and inducible macrophage PCA, using the set of AXB/BXA recombinant inbred strains derived from resistant (A/J) and susceptible (C57BL/6J) progenitors (3).

Macrophage PCA is mediated by a protein of approximately kDa that may exist in dimeric form (5). Its expression by cells of monocyte and macrophage lineage is specifically induced by MHV-3 (17). Functional assays and monoclonal antibody analysis have shown macrophage PCA to be a direct prothrombinase, distinct from other known procoagulants, including tissue factor. The gene coding for this inducible macrophage PCA has recently been cloned and sequenced from a cDNA library derived from BALB/cJ macrophages infected with MHV-3 (16). Comparison with known sequences revealed that, except for one basepair leading to a conservative amino acid substitution, it was identical to another gene constitutively expressed by cytotoxic T-lymphocytes that encodes a fibrinogen-like protein (*Fgl2*) (10). The COOH-terminal half of the predicted amino acid sequence showed significant homology (36%) to the β and γ subunits of fibrinogen, although it did not have a thrombin-sensitive site for release of a fibronopeptide or a site for cross-linking or interaction with platelets.

The gene encoding inducible macrophage procoagulant activity was mapped using DNA from two recombinant inbred strain (RIS) panels, BXD (derived from female C57BL/6J and male DBA/2J progenitor strains) and AKXD (derived from female AKR and male DBA/2J progenitor strains). Blots were made from genomic DNA samples obtained from progenitor strains, digested with various restriction enzymes, and hybridized with a partial cDNA fragment of 1250 bp corresponding to a portion of exon 2 of the *Fgl2* cDNA. An informative RFLP was observed using the restriction enzyme *HindIII*; fragments of 1.8, 2.9, and 1.6 kb were specific to C57BL/6J, DBA/2J, and AKR DNA, respectively. Hybridization was carried out at 42°C in 50% formamide, 10% dextran sulfate, 1% sodium dodecyl sulfate (SDS), 5× SSC (0.75 M NaCl, 75 mM Na citrate), 2 mM Tris (pH 7.5), 1× Denhardt's solution (0.1% BSA, 0.1% Ficoll, 0.1% polyvinyl pyrrolidone), and 200 μ g/ml denatured salmon sperm DNA. Washing was carried out to a final stringency of 0.5× SSC/1.0% SDS at 60°C. The strain distribution pattern of the polymorphic fragments was compared with the inheritance of marker loci (BXD, 932 markers; AKXD, 281 markers) previously typed and genetically mapped in these panels using the program Map Manager v2.6 (see Table 1). The results indicate that *Fgl2* maps to the proximal region of chromosome 5; a highly significant lod score of 7.2 was calculated in AKXD RIS between *Fgl2* and the two mouse chromosome 5 markers *D5Bir2* and *Mpmv23* and a lod score of 4.8 in BXD RIS between *Fgl2* and two other mouse chromosome 5 markers, *Xmv45* and *Pmv40*. The gene order was established by minimizing the number of double crossover events between *Fgl2* and mouse chromosome 5 loci. The most likely gene order and recombination fraction (cM \pm SE), using information from both panels, is *D5Mit1/Pmv40*–2.3 \pm 1.8–*Rmcf*–1.1 \pm 1.1–*D5Bir2/Fgl2*–1.2 \pm 0.9–*Mpmv23/Xmv17/Xmv45*–2.9 \pm 1.5–*Xmv34*.

Three mouse mutant phenotypes have been localized to the proximal region of mouse chromosome 5 carrying *Fgl2*, includ-

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