Assignment of the Human Dihydropyrimidine Dehydrogenase Gene (*DPYD*) to Chromosome Region 1p22 by Fluorescence *in Situ* Hybridization

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Dihydropyrimidine dehydrogenase (DPD, EC 1.3.1.2) is the initial and rate-limiting enzyme in the three-step pathway of uracil and thymine catabolism leading to the formation of β-alanine and β-aminobutyric acid, respectively (13). Several studies have demonstrated the importance of DPD in cancer patients, particularly in those lacking or having only low levels of activity (2). Patients exhibiting severe toxicity when administered 5-fluorouracil were shown to have low DPD activity (4, 11). Studies of affected families demonstrated that the deficiency was inherited in an autosomal recessive pattern (1). DPD deficiency is one of several inherited disorders of pyrimidine metabolism, clinically termed thymine-uraciluria.

DPD has been purified from livers of rats (8), pigs (6), cattle (7), and humans (3). We have cloned and sequenced cDNAs encoding the pig and human dihydropyrimidine dehydrogenase and found that the human gene for dihydropyrimidine dehydrogenase (*DPYD*) is localized to the centromeric region of chromosome 1 between 1p22 and q21 by using Southern analysis of panels of human/rodent somatic cell hybrid DNAs (14). In the present study, we used fluorescence *in situ* hybridization (FISH) with R-banded chromosomes to gain finer assignment of the human *DPYD* gene.

R-banded chromosomes were prepared by standard methods (12) with some modifications (9). A 1.97-kb cDNA fragment containing the main portion of the coding sequence (from nucleotide 1070 to 3040) (14) for the human *DPYD* cDNA was used as a probe for FISH. The probe was labeled by nick-translation with biotin-16-dUTP (Boehringer). Hybridization and the signal detection with amplification procedure were carried out as reported before (5, 9, 10). Chromosomes were observed and photographed using a Nikon OPTIPHOT-2-EFD2 microscope (B-2A filter).

The *DPYD* gene was mapped to human chromosome 1 on the short arm at p22. Fifty (pro)metaphase chromosome cells with R-bands were analyzed. Twenty-four of the cells had completely symmetrical double spots at chromosomal region 1p22. No symmetrical double spots were detected on any other chromosomes (Fig. 1). These data precisely restricted the *DPYD* gene locus in the region 1p22–q21 reported in our previous paper (14). These results conclusively establish that the locus of the human *DPYD* gene is chromosome 1p22. It is possible that the *DPYD* gene could be involved in chromosome translocations and/or loss, resulting in DPD deficiency. Further studies to understand the cause of this deficiency are currently underway.

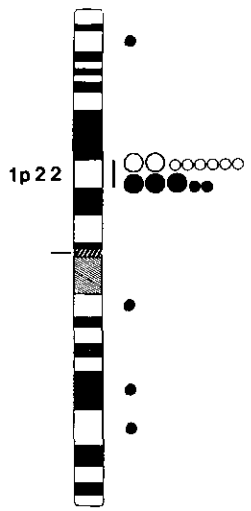

FIG. 1. Idiogram of human chromosome 1 showing the distribution of signals after fluorescence *in situ* hybridization (FISH) with the biotinylated human *DPYD* cDNA probe. Open circles, symmetrical double spots. Solid circles, single spot. Large circles, 10 counts. Small circles, 1 count. Signals were counted in 50 (pro)metaphases observed.

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