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P1 and cosmid clones define the organization of 280 kb of the mouse *H-2* complex containing the *Cps-1* and *Hsp70* loci

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Abstract. A 280 kilobase (kb) contig was isolated from mouse genomic P1 and cosmid libraries, using as probes human cDNA and genomic DNA fragments that map in the interval between the second component of complement and tumor necrosis factor genes of the *HLA* complex. The clone contig demonstrates synteny of eleven mouse genes that are homologous to genes initially mapped within the human major histocompatibility complex. These include the mouse homologs of *BAT2* (*HLA-B*-associated transcript 2) through *BAT9* and also three *HSP70*-related genes. Five P1 clones form a contig of 240 kb that spans from *BAT9* through *BAT3*. Twelve cosmid clones are arranged in three contigs that confirm most of the structure of the P1 contig and link the mouse *BAT3* homolog to the *BAT2* homolog approximately 15 kb farther telomeric. Polymorphic DNA markers within the cloned region were used to map the cleft palate susceptibility-1 (*Cps-1*) locus to the interval between *Hsp70.1* and *BAT6* (valyl-tRNA synthetase). This refines the location of the *Cps-1* locus to a 45 kb region contained in the H2-124 P1 insert.

Introduction

The portion of the human major histocompatibility complex (MHC) that extends from the MHC class III complement genes telomeric to the class I gene *HLA-B* is notable for its extremely high density of functional genes (Trowsdale et al. 1991). This region has been analyzed, using overlapping cosmid clones, and found to contain a duplicated locus encoding *Hsp70* (Sargent et al. 1989b), tumor necrosis factor α and β; (Spies et al. 1986), and a number of additional genes designated *BAT1* through *BAT9* (*HLA-B* associated transcripts: Spies et al. 1989) or *G1-G10* (Sargent et al. 1989a). Although most of the mouse MHC has been cloned by chromosome walking using cosmid vectors (Steinmetz et al. 1982a, b; Goodenow et al. 1982; Chaplin et al. 1983; Fisher et al. 1985; Flavell et al. 1986; Stephan et al. 1986), much of the region between *H-2S* and *H-2D*, which is homologous to the *HLA* region cited above, has not yet been isolated in molecular clones. This region is of particular interest because the genes controlling several phenotypic traits appear to map within it. A gene that affects the antibody response to TNP-Ficoll (Shapiro et al. 1985), the locus that controls the hematopoietic histocompatibility antigen, *Hh-1* (Daley et al. 1987), a gene that affects susceptibility to cortisone-induced cleft palate, *Cps-1* (Gasser et al. 1988), and a gene that affects susceptibility to experimental autoimmune orchitis, *Orch-1* (Teuscher et al. 1990; Snoek et al. 1993), have all been localized to this interval. The isolation of this portion of the mouse *H-2* complex in molecular clones will facilitate the identification of these functionally defined genes. Cloning of this region of the mouse will also permit comparison of the structure of this portion of the human and mouse MHCs to define the extent to which it has been evolutionarily conserved. In this study, we have cloned the region surrounding the *Hsp70* loci and used polymorphisms in this region to refine the location of the *Cps-1* locus.

Materials and methods

Isolation of cosmid clones. Two cosmid libraries were constructed, using high relative molecular mass DNA purified from MOPC-321

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