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An Integrated Genetic Map of the Pearl Locus of Mouse Chromosome 13

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We have used a *Mus domesticus/spretus* congenic animal and two interspecific backcross panels to map genetically 30 sequence-tagged sites (STSs) and 13 genes to the vicinity of the pearl locus on mouse chromosome 13. The STSs defining the mapped region are from D13Mit9 to D13Mit37, spanning 10.6 cM. Genes mapped to this region include Versican (Cspg2), GTPase activating protein (Rasa), dihydrofolate reductase (Dhfr), arylsulfatase (As-1), thrombin receptor (Cf2r), hexosaminidase b(Hexb), 3-hydroxy-3-methylglutaryl coenzyme A reductase (Hmgcr), microtubule associated protein 5/1b (Mtap5), phosphodiesterase (Pde), phosphatidylinositol 3′ kinase (Pik3r1), rat integrin a1-subunit (Itga1), collagen receptor a2-subunit (Itga2), and 5-hydroxytryptamine 1a receptor (Htr1a). This high resolution genetic map of the pearl region of chromosome 13 establishes the order of multiple markers, including genes whose human homologs are located within a limited region of human chromosome 5, with respect to the phenotypic anchor marker pearl.

The mouse pearl mutation is a recessive, hypopigmentation mutation that affects retinal development and function, and causes inherited platelet storage pool deficiencies (Balkema et al. 1983; Linden and Pinto 1985; O'Brien et al. 1995). Pearl has been studied as a model of human inherited congenital stationary night blindness and the inherited human Hermansky-Pudlak Syndrome. Originally identified in 1954 in a C3H strain, it has subsequently been transferred into a C57Bl/6J line, C57Bl/6J PIN pe/pe (Avner et al. 1988). The pearl locus was first localized to chromosome 13 by linkage to *Arylsulfatase B* and *Lth1* (Elliott et al. 1985). Because of its heritable visual phenotype, pearl served as an anchor locus for other genes and markers that have been mapped to chromosome 13 (Holcombe et al. 1991; O'Brien et al. 1995; Xu et al. 1996).

In an effort to further localize the pearl locus, a congenic strain, B6/*spretus* pe^{+PIN}N12F6, was developed to introduce a highly polymorphic region suitable for the mapping of new markers to the pearl region (Rikke et al. 1993). The selective breeding of a region of *Mus spretus* containing the pearl locus into a C57Bl/6J background allowed for the binning of genes and other markers to within or outside a 10.0-cM interval that contains the pearl locus.

Interspecific backcross panels have been developed to allow high resolution recombinant mapping (Copeland and Jenkins 1991). Markers that are in the pearl region have been localized partly by using a 96-mouse interspecific backcross panel of C57Bl/6J and *M. spretus* from Jackson Laboratories. A 528-mouse backcross panel segregating pearl, muted, and satin phenotypes mapped pearl to within a 1.4-cM region (O'Brien et al. 1995). This panel has subsequently been propagated to 1250 mice and the pearl region is now localized to within 0.5 cM.

We have integrated mapping data from these sources as part of our efforts to define the critical pearl region with respect to the closest flanking markers. This integrated map establishes the or-

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der of multiple genes and microsatellite markers on chromosome 13.

RESULTS

The congenic B6/*spretus* pe^{+PIN}N12F6 mouse strain contains a 10-cM genomic region of *M. spretus* DNA surrounding the pearl locus with a small flanking region of C3H genomic DNA from the original pearl strain. The remainder of its genome is derived from C57Bl/6J. Forty microsatellites and sequence-tagged sites (STSs) with nine expressed genes were typed in *M. spretus* C57Bl/6J and C3H strains to determine the boundaries of the *spretus* genomic region containing the pearl gene. STS markers PL2, PL3, D13SH1, D13Gor2, D13Gor3, D13Gor4, D13Mit27, D13Mit28, D13Mit29, D13Mit105, D13Mit106, D13Mit107, D13Mit160, D13Mit161, D13Mit169, D13Mit258, D13Mit104, D13Mit69, D13Mit145, D13Mit191, D13Mit36, D5S39 (human), and mouse genes *Dhfr, Hexb, As-1, Hmgcr, Rasa,* and *Mtap5* were binned within the 10-cM interval. *Htr1a* and *Ctla3* were binned telomeric to the 10-cM interval.

Southern hybridization with the probe for *Srd5 alpha* revealed a 1.7-kb informative allele in the congenic that matched the C3H parental strain. We were unable to distinguish whether the position of *Srd5 alpha,* based on the Southern blot data, was centromeric or telomeric to the *M. spretus* region. We have placed it in the proximal C3H region based on the 1993 and 1994 consensus maps (Justice and Stephenson 1993, 1994) and a previous study that localized *Srd5 alpha* centromeric with respect to *As-1* and *Rasa* (Jenkins et al. 1991), which we have binned into the *M. spretus* region.

The strain of origin of most alleles could be determined by directly comparing the products of the appropriate parental DNAs. D13Mit36, however, identified an allele in the congenic B6/*spretus* pe^{+PIN}N12F6 mouse that could either be attributed to *M. spretus* or C57Bl/6J. Examination of the locus in the original C57Bl/6J PIN pe/pe mouse showed that the D13Mit36 allele corresponded to the C3H allele rather than to the C57Bl/6J allele. We concluded that the observed allele for D13Mit36 in the congenic was specific for *M. spretus.* In contrast, D13Mit37, which is telomeric to D13Mit36, identified a C3H allele in both the congenic and C57Bl/6J PIN pe/pe. Taken together, this indicates that the boundary of the *M. spretus* region in this congenic strain must lie between D13Mit36 and D13Mit37.

We mapped *Dhfr, Pik3rl,* and several microsatellites onto the Jackson [(c57B1/6J × *spretus*) F_1 × *M. spretus*] (BSS) interspecific backcross panel. These data are shown in Figure 1. The marker positions were calculated using Map manager v. 2.6. Marker order was determined by minimizing the number of multiple recombination events. *Dhfr* showed a band shift when analyzed by single-strand conformation polymorphism (SSCP); C57Bl/6J revealed a higher mobility band than *M. spretus. Pik3rl* revealed a T–C polymorphism at nucleotide 2833 in the untranslated region between C57Bl/6J and *M. spretus,* respectively. This single-base polymorphism was not consistently informative by SSCP analysis, therefore a PCR-based sequence analysis was performed to determine its segregation throughout the backcross panels. The resolution of this panel is 7.9 cM at the 95% confidence level.

We further localized the pearl region with the interspecific backcross panel described by O'Brien et al. (1995). This panel, originally de-

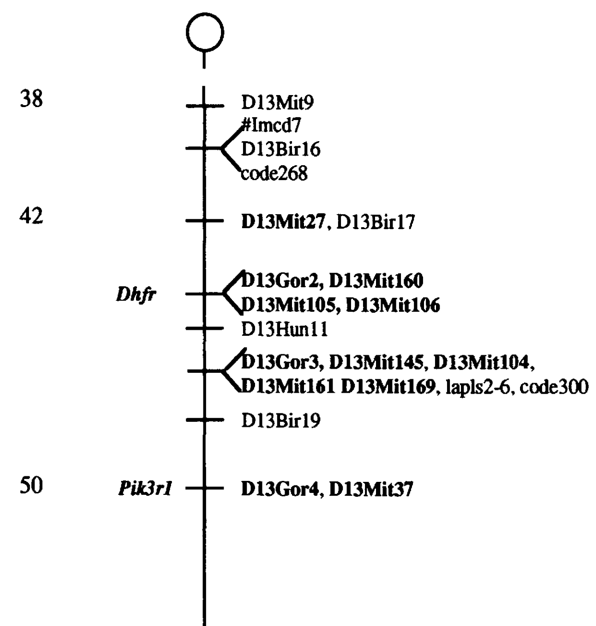

Figure 1 Genetic map of mouse chromosome 13 configured by Jackson Laboratories, showing the positions and relative distances of STS markers and two genes in the pearl region. Highlighted markers were mapped in our laboratory. Numbers at *left* indicate distances in centimorgans. Information regarding these markers can be obtained from Jackson Laboratories.

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scribed with 528 mice, has been expanded to 1250 mice. It has a resolution of 0.08 cM with a 95% confidence interval up to 0.2 cM. The results from this backcross panel are summarized in Figure 2. These data place the pearl critical region to within a 0.5-cM region with the closest flanking markers being Centromere–D13Mit28, D13Mit29–(0.3cM)–Pearl–(0.0cM)–D13Mit160, D13Mit258, D13Mit104, D13Mit161, D13Mit169, D13Mit108–(0.2cM)–Cf2r–Telomere. The T–C polymorphism detected in *Pik3rl* between *M. spretus* and C57Bl/6J, using the Jackson panel, was also observed between Satin-Muted-Pearl (SaMuPe) and PWK, respectively. *Dhfr* analysis by SSCP produced higher mobility bands in the PWK DNA when compared with SaMuPe DNA. The *Cf2r* PCR product differed by 20 bp between PWK (340 bp) and SaMuPe (320 bp), using primers that flank a GA repeat within the (n-2) intron.

DISCUSSION

High resolution genetic mapping is an essential step in the positional cloning of any disease gene. With the concentration of highly polymorphic microsatellites increasing rapidly, this approach becomes increasingly powerful. The specific breeding of mice with visual heritable phenotypes has provided the meiotic events necessary to genetically map markers using the visual phenotype as an anchor locus (Holcombe et al. 1991; O'Brien et al. 1995; Xu et al. 1996). We have used two mapping tools that take advantage of the heritable pearl phenotype and the integration of an interspecific backcross panel of C57Bl/6J and *M. spretus* to construct a genetic map of the pearl region of chromosome 13.

The congenic B6/*spretus* pe^{+PIN}N12F6 enabled us to bin genes and other markers into a limited region including and flanking the pearl locus. The 96-mouse BSS interspecific backcross panel increased the resolution and aided in the ordering of the markers. However, because of the low number of informative meioses, the resolution was only 7.9 cM at the 95% confidence level. The 1250-mouse interspecific backcross panel of PWK and SaMuPe has increased the resolution to 0.2 cM at the 95% confidence level.

This integrated map identifies a number of potential discrepancies with the published consensus map (Justice and Stephenson 1994), primarily not with the order of marker sets, but with the alignment of the pearl locus and genes with

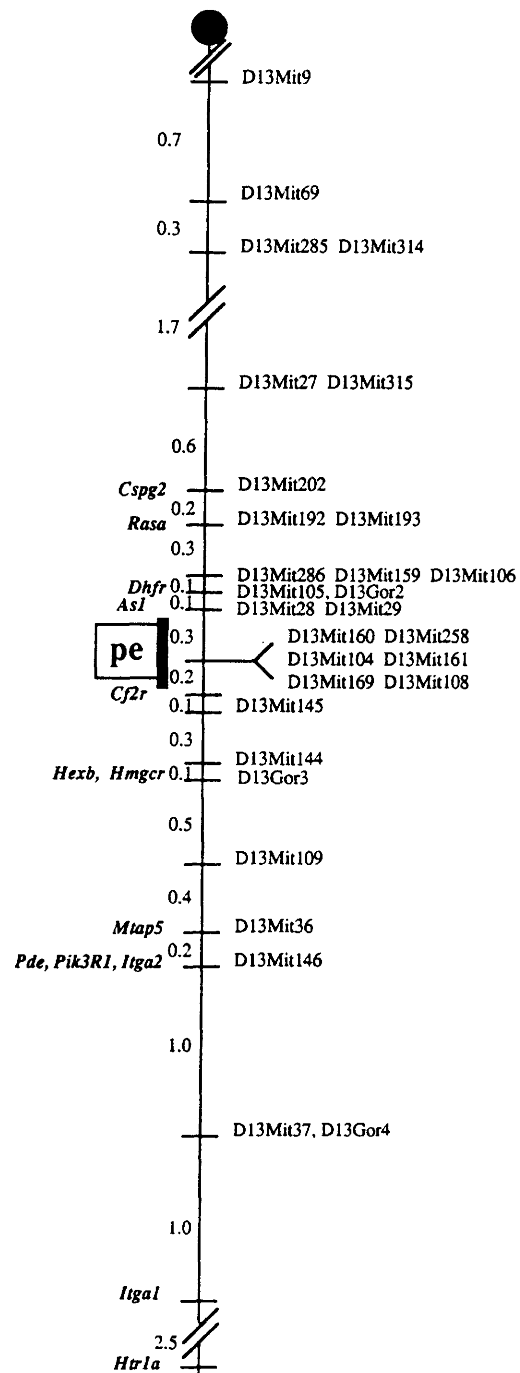

Figure 2 Genetic map of the pearl region of mouse chromosome 13 developed by using the PWK × SaMuPe interspecific backcross panel of 1250 mice. Numbers at *left* indicate distances in centimorgans.

respect to the microsatellite markers. We mapped *Hexb* telomeric to the pearl locus by 0.7 cM, and nonrecombinant with D13Gor3. We have further refined the initial mapping of *Pik3r1* (Hoyle et al.

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1994) to 1.8 cM telomeric to the set of markers nonrecombinant with the pearl locus. D13Mit28 and D13Mit29 are nonrecombinant with each other in this panel and D13Mit105 and D13Mit106 are 0.1 cM and 0.2 cM centromeric to D13Mit28/29, respectively. D13Mit104 has been placed telomeric to D13Mit105 by 0.4 cM and telomeric to D13Mit106 by 0.6 cM. The positions of D13Mit145, D13Mit144, and D13Mit109 have been localized to 0.3, 0.6, and 1.2 cM, respectively, telomeric to D13Mit161. In the Jackson backcross panel we identified a recombination between D13Mit160 and the pearl locus. A similar recombination event has not been observed in the 1250-mouse interspecific backcross panel. Because of the higher resolution of this panel, we have placed D13Mit160 centromeric but closer to D13Mit258, D13Mit104, D13Mit161, D13Mit169, and D13Mit108.

Many of the genes that we placed on this map were potential candidate genes for the pearl mutation, specifically *Cspg2, Rasa, Itga2,* and *Pik3r1*. The mapping results have eliminated these, as well as the other mapped genes, as candidate genes based on recombination events from the pearl locus.

All of the genes that we have placed in the region of the pearl locus on mouse chromosome 13 have been associated with a limited region of human chromosome 5. The orders of these genes and their respective genetic distances on the human genome have not been established. Although it is likely that this region of mouse chromosome 13 is syntenic with human 5q13, further human genome physical mapping efforts will be necessary to establish if small rearrangements distinguish these regions of the two genomes.

The human spinal muscular atrophy (SMA) locus is telomeric to the syntenic pearl region of mouse chromosome 13 based on the human chromosome 5 mapping data. MAP1B, the human homolog of *Mtap5,* which shows linkage to the human SMA locus is 1.6 cM distal to the pearl region. It has been reported that this region of the genome is very unstable with regards to genomic rearrangements (Selig et al. 1995). One pearl lineage has been reported to have a spontaneous reversion rate of 0.5% (Pinto et al. 1985), suggesting that, at least for one pearl allele, the disease phenotype could be caused by a DNA insertion. Elucidation of the actual pearl gene and the characterization of the different pearl mutations may clarify this potential genomic instability with respect to this gene.

The high resolution mapping and the abundance of markers in this region allow the initiation of physical mapping techniques to identify the gene responsible for the pearl phenotype as well as providing a set of markers that can be used in the mapping of other genes to this region of mouse chromosome 13.

METHODS

The interspecific backcross panel of PWK and SaMuPe has been described previously (O'Brien et al. 1995). The pearl (pearl $PIN^{pe/pe}$) and congenic B6/*spretus* $pe^{+PIN}N12F6$ have been described previously (Avner et al. 1988; Rikke et al. 1993). The C3H, C57Bl/6J mice and the 96-mouse backcross panel of BSS, were purchased from Jackson Laboratories.

Genomic DNA was isolated from mouse spleen and kidney according to standard protocols (Sambrook et al. 1989; Taylor and Rowe 1989). For Southern blotting, 10 μg of mouse genomic DNA was digested with *Eco*RI, *Pst*I, *Bam*HI, *Bgl*II, or *Hin*dIII according to manufacturer's conditions. The digests were electrophoresed on 1.0% agarose (FMC), stained with EtBr, and transferred to Hybond N+ filters (Amersham). The DNA was immobilized at 80°C for 2 hr. The hybridizations were performed as described previously (Xu et al. 1996). Markers were determined to be within the pearl-containing *M. spretus* region of the congenic animal if the hybridization patterns of the congenic animal were identical to those of *M. spretus* and distinct from the C57Bl/6J background.

Candidate genes that have been mapped previously to mouse chromosome 13 or localized to a presumed syntenic region of human chromosome 5 were used to determine their position with respect to the pearl locus. The probes are described in Table 1. All probes were excised from the vector with the appropriate enzyme, separated by gel electrophoresis on 1.0% agarose, excised, and purified with Geneclean (Bio 101, Inc.). The DNA Probes were labeled by the random hexamer method with [α-^{32}P]dCTP (Feinberg and Vogelstein 1983; NEN/Dupont).

D13Mit series primer sets were purchased from Research Genetics. The forward primer for each set was end-labeled with T4 kinase (GIBCO) and [γ-^{32}P]ATP (NEN/Dupont). The PCR conditions were 94°C for 2 min followed by 35 cycles of 94°C for 30 sec, 55°C for 1 min, and 72°C for 1 min with 1 unit of *Taq* polymerase in 25 mM TAPS (pH 9.3), 1.5 mM $MgCl_2$, 50 mM KCl, 1 mM DTT, and 0.2 mM each of dATP, dCTP, dGTP, and dTTP in a final volume of 20 μl. Products were electrophoresed on a 6.0% polyacrylamide, 7 M urea denaturing sequencing gel, dried, and analyzed by autoradiography.

The D13Gor primers were described previously (Xu et al. 1996). The *Pik3r1* primers are specific for nucleotides 2752–2935 in the 3′ untranslated region of phosphatidylinositol 3′ kinase regulatory subunit resulting in a product of 184 bp. The primer sequences are as follows. Pik3r1F 5′-TTCCTCACCTTCAAGCCACCCAAG-3′; Pik3r1R 5′-AGGTTAGAAACGTCTGGTCATCCAAC-3′. The *Dhfr* primers were OD3PF 5′-ACAGGAAGATGCTTTCAAGTTC-3′ and OD3PR 5′-GAGGTCTCATGGGAGGGG-3′. *Thrombin receptor* (*Cf2r*), D13SH1, PL2, and PL3 primer sequences

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Table 1. Genes Mapped to the Pearl Region of Mouse Chromosome 13

Gene	Probe name	Enzyme[a]		Informative alleles[d]		Reference
		congenic[b]	PWK[c]	congenic	PWK	
Versican	Cspg2	N.D.[e]	*Kpn*I	N.D.	14.5, 9.4	Zimmermann and Ruoslahti (1988)
GTPase-activating protein	Rasa	*Eco*RI	*Hin*dIII	19.1	4.8	Hsieh et al. (1989)
Arysulfatase B	As1	*Bam*HI	*Eco*RI	12.3	22, 9.0, 7.5	Schuchman et al. (1990)
Hexosaminidase B	HexB	*Bam*HI	*Pst*I	16.4, 5.4	4.5	Bapat et al. (1988)
3-hydroxy-3-methylglutaryl coenzyme A reductase	Hmgcr	N.D.	*Kpn*I	N.D.	6.4	Sundaresan et al. (1989)
Microtube-associated protein 5/1B	Mtap5	*Eco*RI	*Xba*I	4.5	9.6	Garner et al. (1990)
Cyclic nucleotide phosphodiesterase	Pde	N.D.	*Hin*dIII	N.D.	12.0	Milatovich et al. (1994)
Collagen receptor a2 subunit	Itga2	N.D.	*Bgl*II	N.D.	6.0	Takada and Hemler (1989)
Rat integrin a1-subunit	Itga1	N.D.	*Pst*I	N.D.	9.6	Ignatius et al. (1990)
5-hydroxytryptamine (serotonin) 1a receptor	Htr1a	*Eco*RI	*Bgl*II	1.2	4.9	Kobilka et al. (1987)
Steroid 5α-reductase	Srd5alpha	*Bgl*II	N.D.	1.7	N.D.	Jenkins et al. (1991)
Cytotoxic T lymphocyte-associated sequence 3	Ctla3	*Eco*RI	N.D.	24.5, 13.5	N.D.	Gershenfeld and Weismann (1986)

[a]Enzyme used to digest genomic DNA to identify polymorphism.
[b]Genomic DNA from the congenic strain was compared to that of C57 and Spretus as described in the text.
[c]Genomic DNA from PWK was compared to SaMuPe to observe crossovers in the backcross panel.
[d]Allele sizes in kilobases (kb).
[e](N.D.) Not determined.

have been described previously (Casavant and Hardies 1993; Rikke et al. 1993; Poirier et al. 1996). The PCR conditions for *Dhfr* were identical to those for the D13Mit series. The PCR conditions for *Pik3r1* required an annealing temperature of 60°C.

SSCP analysis for *Dhfr* was done per standard protocol with a few modifications (Dracopoli et al. 1994). Samples were denatured in 98% formamide/0.025% bromphenol blue/0.025% xylene cyanol and 0.65 mM NaOH at 95°C for 5 min and electrophoresed on a 0.5× MDE gel (Hydrolink) overnight at 4.0°C. The gel was dried and analyzed by autoradiography.

DNA sequencing of PCR products was performed using a cycle sequencing kit (Epicentre). Primers were end-labeled as described above. The products were separated on a 6.0% 7 M urea denaturing sequencing gel, dried, and analyzed by autoradiography.

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