The Common Shrew Gene Map

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REASONS FOR MAPPING THIS SPECIES

Among mammals, gene mapping efforts have concentrated mainly on humans and house mice. However, although studies of these 2 species can add much to our understanding of eutherian genome evolution (for example, Ehrlich and others 1997), it is important to expand the range of species to be examined for a more complete picture of the genomic changes that have occurred during the eutherian radiation (O’Brien and others 1997). Gene mapping studies much more modest than those conducted on humans and mice can add enormously to our knowledge of eutherian genome evolution, especially if (1) species from a wide range of different eutherian orders are analyzed, and (2) the same set of comparative anchor loci are examined (O’Brien and others 1993, 1997). Because the relationship of many of the orders of eutherian mammals is difficult to infer (Novacek 1992), gene mapping studies on species from as many eutherian orders as possible are needed both to help clarify the relationships between the orders and to properly deduce the structure of the ancestral eutherian genome.

The order Insectivora includes shrews, hedgehogs, moles, and tenrecs. It is the third most speciose eutherian order (after Rodentia and Chiroptera), of which the shrew family (Soricidae) is particularly large. Morphologically, insectivores appear to be closer to the ancestral eutherian condition than other orders (Nowak 1991), and mitochondrial DNA sequences also suggest that insectivores are more basal within the eutherian phylogenetic tree than cetaceans, artiodactyls, primates, and rodents (Krettek and others 1995). Insectivores date back to the late Cretaceous in the fossil record (Stahl 1974). Given their status as a large group of "primitive" eutherians, insectivores are clearly an important model for gene mapping.

Among the Insectivora, the common shrew (Sorex araneus L. 1758) has been subjected to particularly detailed population genetic analysis, both with respect to chromosomes (see below) and to other genetic markers (Heikkila 1989; Taberlet and others 1994). (For recent studies see also Fredga and Searle 1996; Wójcik and Wolsan 1998.) This species has a huge range throughout much of the northern Palearctic region and a population size estimated at 3 billion (Searle 1996). Given its ubiquity, its abundance, its early description by Linnaeus, and its population genetic characteristics, the common shrew is the obvious "type" species of the Insectivora for which to construct a gene map. Such a map will not only be useful for comparative genomics, but it will also be invaluable to the many population geneticists studying the species.

SPECIAL FEATURES OF THE COMMON SHREW KARYOTYPE

The karyotype of the common shrew is notable in at least 2 respects: an XX/XY2 system of the sex chromosomes (Pack and others 1993; Sharman 1956) and an extremely variable complement of autosomes (Searle and Wójcik 1998). The ancestral karyotype of the species consisted of acrocentric chromosomes (Wójcik and Searle 1988), but there have been repeated Robertsonian fusions in which pairs of these acrocentrics have joined at their centromeres to form single metacentric chromosomes. (These metacentrics may, in some instances, have been further modified by whole arm reciprocal translocations: Searle and Wójcik 1998.) Each chromosome arm within the common shrew karyotype is designated by a letter of the alphabet so that “a” is the largest arm and “v” is the smallest (Searle and others 1991). The biarmed chromosomes af, bc, de (X), dv (Y2), and tu are invariable in all populations studied so far; the uniarmed chromosome s (Y1) is also not involved in the Robertsonian variation. The other arms are found combined in different ways as metacentrics in different populations; they may also occur as ancestral acrocentrics. Thus, the common shrew is subdivided into 50 different karyotypic races, each characterized by a particular set of metacentrics and acrocentrics (Searle and Wójcik 1998).

In our study, we used specimens of the Novosibirsk karyotypic race, taken from a natural population of the common shrew from the vicinity of the city of Novosibirsk (West Siberia, Russia). This race was first described by Král and Radjabli (1974) and confirmed by Volobouev and Aniskin (1981) and Polyakov and others (1996). On the basis of these observations, the chromosomes of the Novosibirsk race are designated according to the standard nomenclature as follows: XX/XY2, af, bc, hn, go, j,l,j1,l, ik, mp/m, p, q/r/q, r, tu. A high-resolution GTG-banded (Giemsa-banded with
(trypsin) karyotype of the Novosibirsk race has been published by Pack and others (1993).

**APPROACHES USED TO DEVELOP THE MAP**

The mapping data presented in this article were obtained mainly from the analysis of segregating biochemical markers and shrew chromosomes in the panel of shrew-rodent hybrid clones constructed by Pack and others (1995). The following cell lines were used: (1) mouse LMTK, deficient in thymidine kinase (TK) activity; (2) Chinese hamster Ag17 cells, deficient in hypoxanthine phosphoribosyltransferase (HPRT) activity; and (3) splenocytes and bone marrow cells derived from 2 adult female shrews of the Novosibirsk karyotypic race. Shrew-mouse (C series) and shrew-Chinese hamster (SAS and SAB series) hybrid clones were obtained by cell fusion following a protocol similar to that of Davidson and Gerald (1976).

Altogether 119 primary clones were potentially available for our clone panel: 70 shrew-mouse and 49 shrew-Chinese hamster. The preliminary cytogenetic analysis demonstrated that only the shrew chromosomes were segregating. Unfortunately, only 13 of 70 shrew-mouse clones could be considered for the panel, because shrew-mouse clones tended to display too much segregation of shrew chromosomes and too many chromosomal rearrangements. In the end, only 5 shrew-mouse clones were selected for the panel (Pack and others 1995).

Shrew-Chinese hamster hybrid clones were more suitable for the panel. They demonstrated a low rate of chromosome rearrangement and a satisfactorily moderate rate of chromosome loss; most shrew-Chinese hamster clones had at least 5 shrew chromosomes. However, the segregation of the shrew chromosomes was not random. For example, af, ik, qr, and tu tended to segregate together with de, which carried the gene for the selective marker (HPRT), whereas go and hn tended to be absent. These cosegregations created difficulty in setting up a suitable clone panel for gene mapping so that finally only 14 shrew-Chinese hamster hybrid clones were selected for the panel. An additional, noteworthy feature of the panel is that some shrew chromosomes were present at low frequency in certain hybrid clones. For example, qr was present in only 7% of SAS3 cells, and be in 47% of SAS37 cells. This feature might have resulted in some instances of artificial discordance because the sensitivity of the assay for some shrew DNA or enzyme markers might have been insufficient in these clones (Pack and others 1995).

In Figure 1, the distribution of chromosomes among the clones chosen for the panel is shown. The hatched squares

![Figure 1: Distribution of shrew chromosomes in the panel of shrew-Chinese hamster (SAS) and shrew-house mouse (C) clones. Designation for shrew chromosomes: filled squares, presence; open squares, absence of the chromosome. Chromosome s (= the Y1 chromosome) is not included in the figure because the clones were derived from an adult female.](image-url)
show the presence of the chromosome in the clone. We usually observed that the clones contained the shrew chromosome in more than 50% of cells; however, a few clones with a smaller fraction of positive cells were special cases, as discussed below. When the chromosome arms a-l, n, o, t, and u were present in the clones, they always occurred as the metacentrics de, bc, af, ik, go, jl, hn, and tu. The chromosome arms m, p, q, and r were present in some clones as acrocentrics and in others as the metacentrics mp and qr, respectively. This distribution allowed us to localize some genes to particular chromosome arms.

The clone panel was selected on the basis of the statistical criteria developed by Wijnen and others (1977). It can be seen in Figure 1 that at least 2 discriminant clones (11% discordance) appear for any pair of chromosomes being compared, but the level of discordance was usually much higher (up to 89% when 17 clones were discordant: Pack and others 1995). Biochemical markers were detected using protein electrophoresis with histochemical staining according to Harris and Hopkinson (1976).

**CURRENT MAP STATUS**

The genetic map of the common shrew currently contains 38 genes (Figure 2). These genes mark the X (de) chromosome and 7 of 9 metacentric autosomes of the Novosibirsk race. Because the shrew chromosomes in the hybrid clones were derived from female shrews, we were not able to assign genes to the Y1 (s) and Y2 (dv) chromosomes. Surprisingly, 1 of the largest chromosomes, bc, remained unmarked. This cannot be ascribed to an error of mapping because bc is well discriminated by pairwise comparison from any other chromosomes (Figure 1).

It is important to discuss the reliability of the chromosomal localizations. Five genes (PGD, GSR, ENO1, ACP2, and PGM1) were localized using only shrew-Chinese hamster hybrid clones, because these markers did not display a difference in electrophoretic mobility between shrew and mouse. Nineteen genes demonstrated complete concordance with particular chromosomes: Almost all genes located on de (HPRT, G6PD, MDH1, IDH1, OTC, GLA, PKG1, ACP1); TK1 on hn; ACY1 on arm m of the chromosome mp; AK3, PGM1, and MPI on af; ADK, ACP2, LDHA, GSR, NP, and GPT on ik (Figure 2). Thirteen genes demonstrated a 95% level of concordance (only 1 discordant clone was found): PEPA on de; ADA, ENO1, PEPS, and PGD on jl; GUS2 and PP on ik; PGM2 and CLO1 on go; GH and NF1 on hn; GOT1 on q; and PEPR on arm m. Six genes (IDH2, AK1, GOT2, PEPE, SOD1, and ME1) displayed a lower degree of concordance (2 or even 3 discordant clones were found). In these cases another analysis was carried out using subsidiary hybrid clones in addition to the main panel.

An estimate of the quality of a panel for gene mapping is based on the level of discordance observed within that panel. In our case, 27 of 717 (3.8%) possible marker-chromosome combinations were discordant. The same level of discordance has been observed in a panel of mink-Chinese hamster hybrid clones used for gene mapping in the American mink (Serov and others 1987). In the present study, 2 clones made a substantial contribution in the discordance: SAS37 (8 cases of discordance) and C2-9 (5 cases).

The discordance may be due to unrecognizable chromosomal rearrangements that disrupt syntenic gene association or to differences in the resolving capacities of biochemical and cytogenetic methods. For example, the clone SAS37 was characterized by a visible deletion of the arm n of chromosome hn. This deletion might have been the reason for the discordant segregation of GH, GOT2, and PEPE and chromosome hn in this clone. In clone C2-9, the arm n of chromosome hn is present in only 17% of cells. This circumstance also may be a cause of discordant segregation between shrew PEPE and chromosome hn in this clone. We also suspect that these clones contained other chromosome rearrangements undetected by cytogenetic analysis. A deletion of a small part of chromosome go that contained genes for ME1, PGM2, and GLO1 presumably occurred in the clone C2-9. For this reason, this clone did not display these biochemical markers, whereas cytogenetic analysis indicated that it contained chromosome go.

The different sensitivity of electrophoretic and cytogenetic analyses might be the other cause of discordance. For example, it appears likely that the clones SAS3, SAS41, and C2-9 were negative for shrew GOT1 due to the low percentage of cells carrying chromosome qr (7, 10, and 13%, respectively), and the sensitivity of our electrophoretic method was insufficient to detect GOT1 in these shrew clones (Matyakhina and others 1997). Perhaps the same cause is responsible for a discordance between superoxide dismutase-1 (SOD1) and chromosome af in the clone C1-4 (Matyakhina and others 1997).

In summary, our results with the panel of shrew-mouse and shrew-Chinese hamster hybrid clones show that these can serve as a powerful tool for constructing a gene map of the common shrew at the level of the metacentric chromosomes of the Novosibirsk karyotypic race. As mentioned above, some hybrid clones of the panel contain the arms m and p of chromosome mp and q and r of chromosome qr as distinct entities. We viewed this as an opportunity to establish the position of the shrew genes at the level of the individual chromosome arms. Indeed, others have observed a high level of concordance in the segregation of shrew PEPR and ACY1 and the arm m of chromosomes mp (Matyakhina and others 1996), as well as in GOT1 and the arm q of chromosome qr (Matyakhina and others 1997) (Figure 2).

In the course of our mapping studies, we have observed the following phenomenon: Two shrew markers—glucose-phosphate isomerase and adenine phosphoribosyltransferase—were not detected in any shrew-Chinese hamster hybrid clones. We also did not detect the galactokinase of the shrew in any shrew-mouse clones. These markers were, however, easy to detect in shrew cell extracts, as well as in mixed shrew-mouse and shrew-Chinese hamster cell extracts.
FIGURE 2 Genetic map of the common shrew (Sorex araneus). In biarmed chromosomes, the first letter indicates the long arm. ACPI, acid phosphatase-1; ACP2, acid phosphatase-2; ACY1, aminoacylase; ADA, adenosine deaminase; ADK, adenosine kinase; AK1, adenylate kinase-1; AK3, adenylate kinase-3; ENO1, enolase-1; G6PD, glucose-6-phosphate dehydrogenase; GH, growth hormone; GLA, alpha-galactosidase; GLO1, glyoxalase-1; GOT1, glutamate-oxaloacetate transaminase-1; GOT2, glutamate-oxaloacetate transaminase-2; GPT, glutamate-pyruvate transaminase; GSR, glutathione reductase; GUS2, beta-glucuronidase-2; HPRT, hypoxanthine phosphoribosyl transferase; IDH1, isocitrate dehydrogenase-1; IDH2, isocitrate dehydrogenase-2; LDHA, lactate dehydrogenase A; MDH1, malate dehydrogenase-1 (NAD-dependent); ME1, malic enzyme-1; MPI, mannose phosphate isomerase; NF1, neurofibromatose-1; NP, purine nucleoside phosphorylase; OTC, ornithine carbamoyltransferase; PEPA, peptidase A; PEPB, peptidase B; PEPD, peptidase D; PEPS, peptidase S; PGD, 6-phosphogluconate dehydrogenase; PGM1, phosphoglucomutase-1; PGM2, phosphoglucomutase-2; PGK1, phosphoglycerate kinase-1; PP, inorganic pyrophosphatase; SOD1, superoxide dismutase-1; TK1, thymidine kinase-1.

COMPARATIVE MAPPING: COMMON SHREW AND OTHER EUTHERIAN MAMMALS

The genetic map of the common shrew currently contains 38 genes, providing enough information to compare it with those of other eutherian species. Comparative mapping data may reveal 2 types of gene association: conserved syntenies and conserved linkages (Eppig and Nadeau 1995). Here we discuss only the conserved syntenies because the mapping method we used allowed us to detect chromosome locations of the genes, but not their order within a chromosome. The "fluidity" of the karyotype of the common shrew produces a serious problem. Some syntenic groups may be race-specific rather than species-specific: Within the framework of our mapping method, we cannot distinguish synteny-within-arm from synteny-within-a-chromosome. The arms m, p, q, and r are fortunate exceptions for which we can establish
synteny-within-an-arm. To analyze conserved synteny between the common shrew and other eutherians, we used published comparative gene maps (Wakefield and Graves 1996; http://www.latrobe.edu.au/www/genetics/compmap.htm) for reference. In Table 1 are listed all of the shrew loci we studied, together with their chromosomal locations in shrews and other species.

Chromosome de (X)

The gene content of the X chromosome is well known to have been strongly conserved during the radiation of eutherians (Ohno 1967). Although rearrangements within the X have been found, synteny has been rigorously preserved, probably because of strong selection against reciprocal translocations between autosomes and the X chromosome. Given the status of the Insectivora as an early eutherian lineage, it is of particular interest that our results for the common shrew are consistent with Ohno’s law. In the common shrew (as well as in several other species of the genus Sorex), the “X” chromosome is actually a tandem fusion between the true eutherian X chromosome and an autosome—hence, the XX/XY,Y2 sex chromosome system (Pack and others 1993; Sharman 1956). HPRT, G6PD, PGK1, GLA, and OTC are X-linked in other eutherians and can therefore be presumed to be on the true X part of de in the common shrew. These genes belong to 1 of the most highly conserved syntenic.

### TABLE 1 Chromosomal localization of shrew biochemical loci compared with other eutherian mammals

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* X, localization.
groups known in eutherian mammals. PEPA, MDH1, ACP1, and IDH1 are presumably located on the autosomal part of de.

Three of these loci (ACP1, MDH1, and IDH1) are syntenic in both shrews and humans, although in humans they occupy different arms: ACP1 and MDH1 on 2p and IDH1 on 2q. ACP1 and MDH1 are syntenic in many species (chimpanzee, capuchin, marmoset, spider monkey, mouse lemur, cat, mink, and mouse), whereas MDH1 and IDH1 are syntenic in the common shrew and silver fox only. The shrew synteny for the PEPA and IDH1 genes has also been observed in the American mink. More data are needed to decide which loci of ACP1, MDH1, IDH1, and PEPA are ancestrally syntenic.

**Chromosome af**

AK1 and AK3 are syntenic in both shrews and humans; however, in humans they occupy different chromosome arms. More interesting is the synteny of AK3 and PGM1 shared between shrews and house mice. These genes are known to be very closely linked in the house mouse (2 cM apart).

**Chromosome go**

The shrew syntenic group of GLO1 and ME1 has been found in humans, many primates (although not all of those studied), and 2 carnivores (cat and mink).

**Chromosome hn**

The shrew syntenic group of NF1, GH, and TK1 is highly conserved in eutherian mammals. It has been found in humans and in owl monkey, mink, cattle, sheep, pig, mouse, and rat—that is, in primates, artiodactyls, rodents, and now insectivores. Remarkably, the gene order is the same in humans and mice. In humans, this group of genes covers the whole long arm of the chromosome 17, and in mice, the distal half of the chromosome 11; the distance between the flank markers is about 30 cM. The shrew synteny between GOT2 and GH has also been found in fox. Interestingly, the shrew syntenic genes for GOT2 and PEPD are also syntenic in fishes and frogs (Morizot 1994).

**Chromosome ik**

Three pairs of genes on the chromosome ik are linked in humans: LDHA-ACP2, ADK-PP, and GPT-GSR. The first pair is also linked in 5 other primates and in mink, cat, and rabbit, but not in dog, mouse, rat, or cattle. The second pair is syntenic in 4 of 5 species studied: marmoset, mink, and fox, in addition to humans. The third pair is specific to shrews and humans, whereas these genes are not syntenic in mink, fox, and mouse. It should be noted, however, that these genes are located rather distantly from each other on human chromosome 8 (GPT at 8q and GSR at 8p). A comparison between the shrew chromosome ik and the Chinese hamster chromosomes 1 and 3 reveals 2 other common associations of genes (NP-GSR-ADK on chromosome 1 and LDHA-IDH2 on chromosome 3). GSR and NP are also syntenic in dogs, and NP and ADK are closely linked in mouse; they are 10 cM apart and occupy the same chromosome band (14B).

**Chromosome jl**

ENO1 and PGD are located on the chromosome jl in the common shrew. They represent a synteny group that is conserved in many mammals: humans and all other primates studied, mink, dog, mouse (1 cM), Chinese hamster, rat, sheep, cattle, and pig. This group of genes has been shown to have been disrupted in the silver fox only. PGM1 is linked with the above-mentioned pair of genes in human, mink, mouse, Chinese hamster, rat, and sheep and with 1 of them in cat and fox. In the shrew, PGM1 is located on the af chromosome. The other 2 genes located on chromosome jl in the shrew (ADA and PEPS) have not previously been found to be linked.

**Chromosome m**

The synteny of PEPB and ACY1 appears to be unique to the common shrew.

**Conserved syntenic groups**

In total, we have identified 13 syntenic gene associations that also have been found to be linked in several species of eutherian mammals from different orders. Six of these syntenies were common to many species including primates, rodents, and carnivores. The minimal size of the conserved chromosomal segment varied from 1 cM (ENO1-PGD) to 30 cM (NF1-TK1-GH), based on the mouse genetic map. These 6 gene groups are among the most conservative elements of the ancestral eutherian genome. Some of the shrew syntenic groups are considered to be possible fragments of larger ancestral groups (such as ENO1-PGD-PGM1), which remain unbroken in many species but which have been disrupted in the shrew.

The other 8 syntenic associations were specific to the shrew and 1 other eutherian (PEPA-IDH1 and GPT-GSR: humans; GH-GOT2: fox; GSR-NP: dog; AK3-PGM1 and NP-ADK: mouse; NP-GSR-ADK and LDHA-IDH2: Chinese hamster). Some of these associations may represent convergence rather than common ancestry. For example, the gene pair GPT-GSR is syntenic in shrews and humans only; however, in humans, the 2 loci occupy different arms of chromosome 8.

Convergence may be a particularly likely explanation of common synteny in comparisons involving the shrew. As
mentioned above, no standard karyotype exists for the common shrew as a species; each race has its own karyotype. In the present study, the Novosibirsk race karyotype was used as a representative of the species. Therefore some of the syntenic groups we have identified may be race-specific rather than species-specific. The members of certain syntenic groups may be located on different chromosome arms. Their syntenic could therefore be the result of the fusion of these arms to form a metacentric chromosome.

This problem would be overcome by analysis of an all-acrocentric race of *S. araneus*, but such a race almost certainly does not exist (Searle and Wójcik 1998). There is, however, the sibling species *Sorex granarius*, which is almost identical to *S. araneus* in its complement of chromosome arms—except that all autosomes are acrocentric (Wójcik and Searle 1988). This species is also very similar genetically to *S. araneus* (Taberlet and others 1994). Analysis of a subsidiary panel of shrew-rodent hybrid clones involving *S. granarius* as the shrew partner appears to be a very productive approach for gene mapping at the level of the chromosome arm in shrews.

Other ways to extend the gene mapping study of shrews include chromosome painting by fluorescence in situ hybridization with chromosome-specific libraries. This method has become a valuable technique for comparative genomics (O’Brien and others 1997) and is currently used both to identify the location and approximate size of homologous chromosome segments and to estimate the number of rearrangements over the period of divergence of the species being compared (for example, Rettenberger and others 1995a,b; Scherthan and others 1994). A chromosome painting study of the Novosibirsk race shrew chromosomes by fluorescence in situ hybridization with human chromosome specific libraries will be reported shortly (Dixkens and others 1998).

**ACCESSIBILITY OF THE MAP**

Electronic databases of comparative mapping information are now available. The most comprehensive source of information is the Mouse Genome Database, which is accessible through the World Wide Web (http://www.informatics.jax.org). This database documents homologous genes and their chromosomal location in more than 50 mammalian species including the common shrew. The gene map of the common shrew and other information concerning the cytogenetics of *S. araneus* are available at the World Wide Web server of the International *Sorex araneus* Cytogenetics Committee (http://meiosis.bionet.nsc.ru/isacc/isacc.htm) or at its mirror site (http://bison.zbs.bialowieza.pl/isacc/isacc.htm).

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