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CHAPTER

43

The Feline Genome and Clinical Implications

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OUTLINE

Genomics is a field of genetic study focusing on the organization and formulation of the DNA sequence of a species' chromosomes and the order, distance, and structure of the genes within the chromosomes. Several early and prominent geneticists recognized that many visual, phenotypic, mammalian traits such as pelage colors and fur types, including those of the cat, had simple modes of inheritance and followed the same segregation rules noted by Gregor Mendel regarding pea traits. One of the first loci ever mapped in a species, the first genomics, was the *Orange* coat color of cats, which was recognized to be sex-linked to the X chromosome. Since that time the inheritance patterns of many phenotypic traits in the cat have been defined, the loci localized to chromosomes, and now the causative genes and mutations are under investigation. The feline karyotype and early gene mapping studies indicated that the cat has a genome organization more similar to that of humans than to that of the mouse or the domestic dog. Now that the limitations of the use of murine models in human studies have been realized and the cost of genomic and genetic resource development is within a feasible range, genomic studies in the cat have significantly advanced. The advances of the genetic tools and resources support the investigation of feline health, improving the direct health of the cat and facilitating the use of the cat as a model for human disease. This chapter presents an overview of the evolution of genetic tools for the domestic cat and highlights their use and value for improving feline health.

CYTOGENETICS

Early studies of mitotic chromosomes of the domestic cat revealed an easily distinguishable karyotype consisting of 18 autosomal chromosomes and the XY sex chromosome pair, resulting in a 2N complement of 38 chromosomes for the cat genome (Figure 43-1).[57-60] Cat chromosomes are fortuitously easily distinguishable, clearly defined by size, centromere position, distinctive giemsa banding patterns of the short *(p)* and long *(q)* arms of each chromosome, and the presence of only a few small acrocentric chromosomes, which have no *p* arms and are traditionally hard to distinguish. Various cytogenetic techniques, such as R-, RBG-banding and fragile site studies, have also helped distinguish and characterize the cat chromosomes.[47-49,52] For example, cats do not have a significant fragile X site on the X chromosome that is found in humans and is associated with mental retardation. Although a sequential numbering of the chromosomes has been suggested,[3] the historical classification of chromosomes into morphologic groups has been retained in the cat. Hence cats have three large metacentric chromosomes (A1 to A3), four large subtelomeric chromosomes (B1 to B4), two medium-size metacentrics (C1 and C2), four small subtelomerics (D1 to D4), three small metacentrics (E1 to E3), and two small acrocentrics (F1 and F2). The X chromosome is midsize and subtelomeric, similar to chromosome B4.

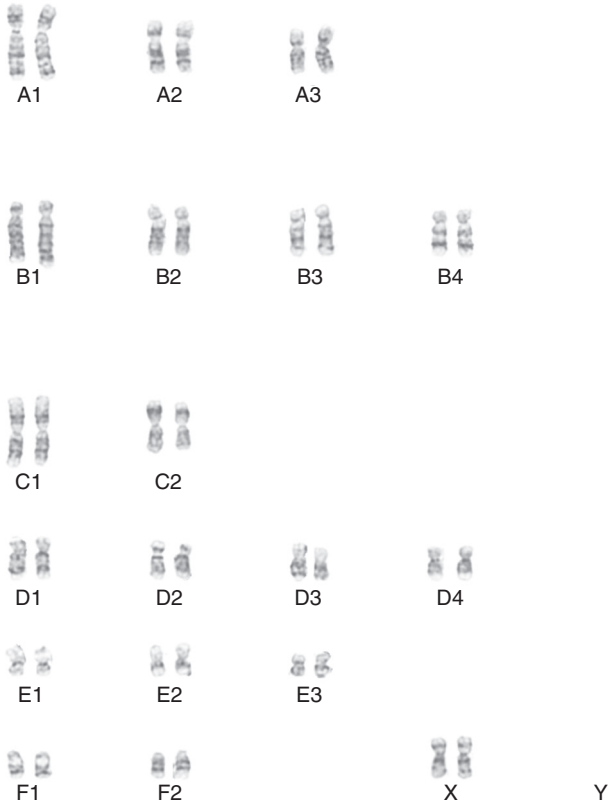

FIGURE 43-1 Karyotype of the domestic cat. Domestic cats have 38 chromosomes, including 18 autosomal pairs and the sex chromosomes, X and Y. This karyotype depicts a female cat and therefore has two X chromosomes. Cat chromosomes have retained the historical nomenclature of being grouped into alphabetical categories that reference the size and position of the centromere. *(Courtesy Roscoe Stanyon.)*

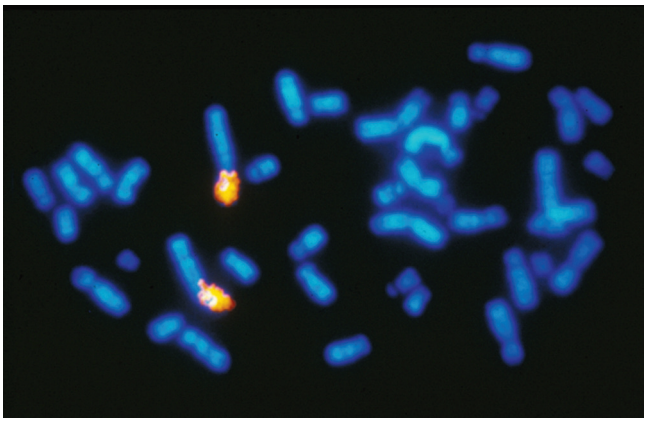

FIGURE 43-2 Chromosome painting of domestic cat chromosomes. DNA from flow-sorted human chromosome 13 was dye labeled and hybridized to a mitotic spread of cat chromosomes. The DNA for all of human chromosome 13 localizes to the short arm of cat chromosome A1, A1p. This comparative approach indicates that if a gene of interest is known to be on human chromosome 13, its location can be predicted to be on chromosome A1p of the cat. *(Courtesy Roscoe Stanyon.)*

Early chromosome staining recognized some major alterations in the felid genome, particularly the Robertsonian translocation of F1 and F2 to form chromosome C3 in the ocelot lineage of cats from South America (2N = 36).[59] Minor pericentric inversions, additions, or deletions of the small chromosomes cause variation in the felid karyotype. The pericentric inversion of chromosome F1 produces a small, more centromeric chromosome and represents as E4 in many cat species. Overall, domestic cats have a chromosomal architecture that is highly representative for all felids and ancestral for most carnivores.[34,44]

Historically, the first genetic consideration to explain reduced fertility or intersex cats is chromosomal differences, especially the loss of one of the sex chromosomes. Karyotypic and now gene-based assays are common methods to determine if a cat with ambiguous genitalia[50] or a poor reproductive history has a chromosomal abnormality. Karyotypic studies of male tortoiseshell cats have shown that they are often mosaics, or chimeras, being XX/XY in all or some tissues.* The minor chromosomal differences that are cytogenetically detectable between a domestic cat and an Asian leopard cat are likely the cause of fertility problems in the Bengal cat breed, which is a hybrid between these two species. Other significant chromosomal abnormalities causing common "syndromes" are not well documented in the cat.

The sufficient variation of cat chromosomal sizes also allowed for the easy flow sorting of cat chromosomes.[56] The DNA in the flow-sorted pools of each chromosome could be individually dye labeled. The dye-labeled DNA from each chromosome could then be hybridized to mitotic chromosomes of another species, such as humans, which provided a gross overall view of which chromosomes between the two species had the same DNA (Figure 43-2). For example, the *p* arm of human chromosome 1 (1p) is largely composed of the same genes that are on the cat chromosome defined as C1, whereas human chromosome 1q is composed of genes that are found on cat chromosome F1. The chromosome painting technique could also be performed reciprocally, implying painting cat chromosomes onto human mitotic chromosome spreads and human chromosomes onto cat mitotic chromosome spreads, revealing the high conservation of chromosomal arrangement of cat to humans,[56,61] specifically compared to mice.[53] Thus chromosome painting gave an excellent overview of cat genome organization,[38] which greatly facilitates candidate gene approaches because the location of particular genes could be anticipated in cats from comparison with the genetic map of humans.[55] This additional confirmation of conservation to human, with regard to genome organization, further supported additional genetic resource

*References 2, 4, 7, 10, 14, 19, 20, 42, 54.

development for the cat as a valuable animal model for human disease.

GENETIC MAPS

Somatic Cell Hybrid

The aesthetically pleasing karyotype supported the early somatic cell hybrid genetic maps of the cat.[35,37] A somatic cell hybrid is a fusion of the cell lines, generally fibroblasts, of two different species. The cell line of one species—usually a rodent, such as a mouse or Chinese hamster—is compromised in some way, such as by having an enzyme deficiency that causes growth incompatibility in non-supplemented media. The cell line from the species of interest, in this case the cat, is damaged by a different, chemical means. The fusion of the two compromised cell lines leads to the chromosomes of the cat integrating into the nucleus and sometimes the chromosomes of the rodent cell line, which then rescues the rodent cell line as a functional enzyme is now present to support the growth of fusion cells. Many different fusion lines are maintained and propagated; however, the entire complement of cat chromosomes is never completely retained in a given cell line. Thus a given cell line will have all the rodent chromosomes, which happen to be mainly acrocentric chromosomes, and only one or a few cat chromosomes. A proper somatic cell hybrid panel would have a representation of at least each of the cat chromosomes in the set of fusion cell lines. Analysis of the mitotic chromosomes of the cell lines can often show which specific cat chromosome may be present because the cat chromosomes are clearly distinguished from those of rodents by size and shape. These cell lines can then be assayed for the presence or absence of specific proteins, or DNA sequences, thereby indicating that the genes that create the proteins or are represented by the DNA segments must reside on the cat chromosome that is within the cell line. This mapping approach provided the first rudimentary genetic map of the cat with 105 different loci,[35] including the association for the genes for *hemoglobin beta (HBB)* and *tyrosinase (TYR)*.[36] The *HBB* polymorphism was shown to be associated with the Siamese coloration, also known as *points.* Recently, this coloration has been proved to be a mutation in *TYR.*[13,23,51]

The first cat map also provided the first indication that the cat genomic structure was very conserved to that of humans as many of the genes were clustering on the same chromosomes in a similar fashion to the human genetic map. This conservation to humans helped to promote the cat as a model for human diseases, insofar as finding genes in the cat would be drastically easier than in a species with a more rearranged genome.

Recombination Map

Interspecies Hybrids

During the late 1960s and early 1970s, the role of viruses in cancer etiologies was under intense investigation, and the cat figured largely in these studies. Feline leukemia had been shown to be caused by a virus (FeLV); hence the cat became an important model for viral carcinogenesis. Because leopard cats, a small and rather abundant type of wildcat from Asia, were shown to be resistant to FeLV infection,[43] genetic studies relating to viral carcinogenesis initiated with domestic and Asian leopard cats.[1] Although viral carcinogenesis did not play as significant a role in cancer etiology as was initially anticipated, the role of the leopard cat in cat genetics and genomics was crucial.

Genetic recombination–based maps of the cat are an improvement in resolution over somatic cell hybrid maps, with the added benefits of estimating gene order and distance between genes on a chromosome, not just presence or absence. The Bengal cat breed has been influential in the construction of the first genetic maps of the cat. Bengals are a hybrid between domestic cats, primarily Abyssinians and Egyptian or Indian Maus, and a different species of felid, the Asian leopard cat *(Felis [Prionailurus] bengalensis)*. The breed was developed in the late 1960s[15] and is now one of the most popular breeds in the world, although not all registries recognize it. The evolutionary distance between the parental type cats of the Bengal breed is significant.[16,17] The millions of years of evolution between a leopard cat and a domestic cat have made the DNA sequence of each gene more genetically diverse than the gene sequence found between any two domestic cats or any two leopard cats. Thus a pedigree consisting of the first-generation Bengals (F1) and a second-generation backcross to one of the parental-type cats was the basis of the first recombination map for the cat.[26] Genetic variation is required to build a genetic map based on recombination, and because these Bengal crosses would generate offspring with very high genetic polymorphism, the interspecies cross was efficient. The first version of feline interspecies hybrid-based linkage map contained approximately 250 microsatellite markers (also known as short tandem repeats [STRs]).[26] This map was effective for the initiation of pedigree studies for families segregating for particular phenotypic traits or diseases. Although rudimentary, the interspecies backcross map assisted targeted candidate gene approaches—in particular, the discovery of the mutation that causes feline polycystic kidney disease (PKD).[62] The genetic map also led to the discovery that a chromosomal rearrangement involving the gene *LIX1* causes spinal muscular atrophy in the Maine Coon cat.[8,12]

Intraspecies Families

Three different extended pedigrees have been developed from domestic cats to also produce recombination-based linkage maps of the cat. Although less efficient than interspecies hybrid maps, intraspecies families often segregate for more than one trait of interest, and they can more readily be produced or ascertained. An autosomal genetic linkage map based on a large (n=256) multigenerational intraspecies cat family, which was maintained by the Nestlé Purina PetCare company, contains 483 STRs.[28] Cat families from WALTHAM and the University of California, Davis have supported the pedigree studies for traits in the cat, such as *Tabby*,[22] *Spotting*,[5] and *Orange*.[9] Once these family studies help find a locus for a trait of interest, gene-scanning techniques are used to find the specific causative mutations. The causative mutations for the two different forms of progressive retinal atrophy in Abyssinian cats have been located in this manner.[27,29] These mutations are now assayed by commercial services to help identify cats that may develop blindness and help determine carriers so that affected cats will not be produced in breeding programs.

Radiation Hybrid

Another form of a gene map is termed a radiation hybrid (RH) map. RH panels are a variation of the somatic cell hybrid technique.[6] Radiation is used to fragment the DNA from the cat cell line, which is then rescued by the fusion process with the rodent cell line. Because the radiation fragments the DNA, smaller fragments get retained readily throughout the rodent chromosomes in the hybrid cells, not complete chromosomes. When the hybrid cells are tested for the presence or absence of a gene, genes must be in very close proximity to be found in the same cell line. Thus RH panels can map genes that are within 1 Mb or less on a chromosome. This level of resolution is a great improvement over a somatic cell hybrid panel and slightly better than a genetic map derived by recombination events in cat families. The current 5000_{Rad} radiation hybrid map of the cat has had several reiterations and currently has a 1.5 Mb resolution, consisting of 1793 markers.[24,25,30-33] The RH map has also proved useful for assisting with sequence assembly for the feline genome sequencing project.

FELINE GENOME PROJECT

The cat's importance in human health, comparative genomics, and evolutionary studies supported the decision of the National Institutes of Health—National Human Genomics Research Institute (NIH—NHGRI) to produce a low coverage (2×) sequence of the cat genome (http://www.genome.gov/Pages/Research/Sequencing/SeqProposals/CatSEQ.pdf). Led by the Broad Institute and AgenCourt, approximately 327,037 DNA variants termed single nucleotide polymorphisms (SNPs) were identified in the sequence from a solitary, highly inbred Abyssinian cat.[41] Because it was a small-scale sequencing effort, only approximately 65% of the euchromatin (gene-coding) sequence was identified. The sequence assembly suggested the identification of 20,285 feline genes that have counterparts (orthologs) in the human genome. This sequencing effort reiterated the conservation between human and cat chromosomal organization by identifying 133,499 regions of conservation and also identified additional introgression sites of endogenous retroviruses, such as FeLV.[45,46]

Recently, an additional approximate 10× genome coverage has been completed for the cat (http://www.genome.gov/19517271), and the work is in preparation for publication as of this writing. The more in-depth sequencing, which will provide a deeper coverage draft sequence of the cat, will improve the euchromatin coverage to approximately 90% to 95%. The better coverage implies that more cat-specific genetic sequence will be known for any gene of interest. Mutation screening methods will be more efficient, leading to the identification of causative mutations more rapidly and more efficiently. In addition to more genetic variation being identified in the Abyssinian cat used for the feline genome project, additional cats were partially sequenced as well. Four representatives from six breeds, including Birman, Maine Coon, Norwegian Forest Cat, Egyptian Mau, Japanese Bobtail, and Turkish Van, were sequenced. A pool of wildcats was also included, as well as four random-bred cats from Southeast Asia. In addition, Hill's Pet Nutrition, Inc. supported a private sequencing effort, which included Sanger-based sequencing of single cats from five different breeds (Persian, Siamese, Ragdoll, Cornish Rex, Burmese) and also a western random-bred cat and an African wildcat. These combined sequencing efforts helped identify the normal genetic variation that is found across cat breeds and populations, especially the SNPs.

CAT DNA ARRAY

An important by-product of the DNA sequencing effort is the identification of the normal genetic variation in the cat genome, SNPs. The SNPs can be verified to be specific to one breed or common across many breeds and populations. The genome assembly supports the proper positioning of the SNPs across the genome. A resource called a DNA array or DNA chip can then be produced that contains assays for the highly polymorphic and evenly dispersed SNPs; thus these arrays can assess the entire genome of the cat in one experiment. Hill's Pet

Nutrition, Inc. has also provided funding to support feline genome resource development[12a]; a cat SNP-based DNA array was commissioned and is due for release in early 2012. Each DNA chip, which is about the size of a microscope slide, has 12 regions; each region is used to test one cat. Each region has the assays for approximately 63,000 SNPs. The major benefit of the arrays is that they allow assessment of the entire genome; these are known as *genome-wide association studies (GWASs).* Because the SNPs are at such a high density, the cats used for a GWAS can be from a population, not direct relatives. Thus individual cases of diseases or traits can be examined from a population or across breeds and populations; cases (cats with the trait) and controls (cats without the trait) are required. In addition, because there is less concern for the mode of inheritance of the trait, a GWAS can be performed even with traits that may have complex inheritance but a high heritability or relative risk in a population. Fewer cases are required to investigate a recessive trait, more for a dominant trait, and even more for complex traits that cause an increased relative risk—the lower the relative risk, the more cases required.

A second factor, linkage disequilibrium (LD), is considered when determining the number of cases and controls required for a GWAS. LD is often different among breeds, as seen in dogs and horses, and generally nearly absent in large random-bred populations, such as humans and random-bred cats. The lower the LD, the lower the power of the SNPs to identify an association with a trait of interest. Thus either more SNPs are needed, *or* more cases and controls are required if LD is low, to have effective association studies. Because the chip will have a defined set of SNPs, the LD estimates will predict the number of cases and controls for a study. For a recessive trait, perhaps 30 cases and 30 controls will be required (typical for the dog),[18] but if the population under consideration has high LD, fewer samples will be required. If the population has lower LD, more samples will be required. A more extensive LD study is under evaluation for the domestic cat and its breeds to assist with the proper development of the feline SNP chip.

FUTURE OF CAT GENETICS

The deeper sequencing of the cat genome and the investigation of variation by resequencing in different cat breeds have allowed a great deal of progress in feline genetics, from the analysis of single gene traits to the investigation of more complex traits. However, many of the common diseases that plague humans and are also found in cats will likely be examined in the outbred populations of nonpedigreed housecats because only 10% to 15% of cats in the United States are representatives of a fancy breed, a proportion that is higher than most other nations.[21] Our random-bred/alley/moggy housecats are sharing our sedentary and indoor lifestyle as well as the associated health problems, such as diabetes, obesity, and asthma. Cats are obligate carnivores and require very high protein levels for normal nutrition. Increased fats and carbohydrates in pet foods lower the cost but can jeopardize the cat's health. Increases in the prevalence of feline inflammatory bowel disease and feline lower urinary tract disease are affected by commercial food qualities. Even though pet food companies do make enormous efforts to provide balanced nutrition for our companion animals, cats seem to be having complications with the transition from a wild-prey diet. Food allergies are of particular concern in cats, leading to the development of a wealth of alternative protein diets. Thus genes involved in complex dietary interactions will be important in future studies.

Disease resistances and susceptibilities are also important to the future of feline genetics. Susceptibility to feline immunodeficiency virus (FIV) and particularly to disease caused by feline coronavirus are likely to be of particular interest. Although FIV has low morbidity and mortality rates in the cat, the genes influencing the cat's tolerance of FIV could shed light on interactions in humans and other species with similar immune-compromising pathogens.[40] Feline enteric coronavirus is nearly ubiquitous in domestic cats.[39] As an enteric pathogen, the virus may cause some malaise and diarrhea, but it is otherwise innocuous. However, mutated viral forms cause feline infectious peritonitis (FIP), which has a nearly 100% mortality rate in domestic cats, regardless of race, color, or breed. Deciphering the genes involved with infection and disease progression for FIP would be a major advancement for feline health. The cat genome sequence and the DNA arrays will greatly facilitate these studies.

Once causative mutations for heritable conditions are identified in the cat, cats become a more important asset to human health. Gene therapy approaches are already being explored for several inborn errors of metabolism in cats.[11] Cats will become a more useful alternative and supportive animal model than rodent models for many heritable conditions for reasons such as the following:

- Cats provide a balance between cost and efficiency.
- Drug dosages are more easily translated between cats and humans.
- The longer life span of the cat allows repeated therapy trials and longer term studies.
- Cats have strong conservation of biology, anatomy, and physiology with humans.
- Cats provide a second animal for validation and efficacy.
- The larger size of the cat and its organs are more amenable to therapies.

Finally, cats are intermediate with regard to genetic variation, mimicking human populations and ethnic

groups more closely than inbred strains of mice. For example, many murine models exist for the study of cystogenesis, the hallmark of PKD; however, each rodent model has its shortcomings. PKD in cats is similar to human autosomal dominant PKD in several important aspects, including the following: (1) a causative mutation in *PKD1*; (2) a similar type of mutation that causes a similar protein disruption; (3) similar variability in disease progression; (4) cystogenesis in other organs, including the liver and pancreas; and (5) the fact that homozygosity for the mutation is lethal.

CONCLUSION

The available genetic resources for the cat are no longer a research bottleneck for feline studies; however, the acquisition of appropriate patients for sufficient cases and controls remains a rate limiting step. Hence the primary care veterinarian, veterinary specialists, and veterinary researchers need to join forces to properly characterize diseases and routinely collect research materials so that patients are not lost to important studies and health investigations. The development of the DNA tests for parentage and identification (http://www.isag.org.uk/), coat colors, and the prominent diseases (e.g., PKD and hypertrophic cardiomyopathy) has encouraged cat breeders to explore genetic research more openly and has encouraged their participation in research studies. For these reasons more cat breeders are banking DNA material from their animals and providing DNA to service and research laboratories. Many veterinary hospitals and large clinical conglomerates are developing electronic database systems that could facilitate the identification of proper patients, cases, and controls. Combined with DNA banking and specialty health care, the veterinary world stands to enhance the possibilities of complex disease research in the cat by leaps and bounds. Even though the origins of the cat remain a mystery and *domesticated* may not be the most appropriate term for the domestic cat, researchers are unlocking its genetic secrets to explain its form and function.

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