

GENE FREQUENCIES IN WORLD CAT POPULATIONS AND THEIR RELEVANCE TO RESEARCH

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Introduction

There is a general but erroneous opinion that genetic control in cats cannot be a rigorous requirement in experimental designs utilizing this species. Certainly, there is no inbred cat supply comparable to the isogenic stocks of rats, mice, hamsters, and guinea pigs that are now available to the research community. Today, however, the formal and population genetics of the domestic cat are sufficiently well known that there can be no excuse for ignoring this potential for control. The following discussion will be limited to a consideration of the cats of northwest Europe and their derivatives. It will also be confined to three independent autosomal loci and a sex-linked factor, all of which affect coat colors and patterns. Neither of these limitations is particularly serious, since the majority of cats used for research are drawn from these populations and the four genetic markers have proven sufficient both to equate and to distinguish subunits of these populations.

History of the Domestic Cat

The domestic cat is indigenous only to the Old World. Its introduction into northeastern North America began in the seventeenth century, and it was not established in Oceania until 150 years later. The original populations brought to both continents came principally from England (and to a lesser extent from The Netherlands). While it is beyond the

scope of this paper to detail the dynamics of this introductory phase, the evidence available can best be summarized in the conclusion that the genetic character of these populations was fixed and stabilized as a very close approximation of a random sample of the parental populations.

Genetics of the Domestic Cat

For cats, the standard phenotype (wild type), to which comparisons are made, is that of the so-called striped tabby. This phenotype consists of hues of tan, brown, and black. The belly tends to be light tan, often having conspicuous darker spots, while the mid-dorsum is generally dark brown to black. The most distinctive feature is the alternating black (nonagouti) and tan (agouti) stripes arranged vertically on the sides. Each of the four mutants that will be noted below modifies this basic wild type in a particular way.

The first mutant to be considered is sex-linked orange (*O*). This allele transforms all black pigment to orange. The effect is to produce an orange and buff striped cat, called in the vernacular "ginger" or "marmalade." The two alternative alleles at this locus manifest lack of dominance toward one another so that the heterozygous female is an orange and black mixture known as tortoiseshell. The lack of dominance is apparently related to random deactivation of one X chromosome and has been taken as evidence for the single active X hypothesis.⁹ The occasional tortoiseshell male is frequently found to be XXY, corresponding to Klinefelter's syndrome in the human.¹⁴ Since the three female genotypes produced by this pair of alleles are phenotypically distinguishable, their distribution in the population is used in an analysis of randomness of breeding. The allele frequencies can be computed directly from a tally of individuals in a sample, and the observed and predicted phenotypic distributions based on the Hardy-Weinberg (binomial) distribution can be tested for concordance by a χ^2 test. All populations studied have proven to be random breeding according to these criteria, where the sample size has been adequate.

The second mutant to be considered is nonagouti (*a*), an autosomal recessive that results in the elimination of all agouti hairs and hence the striping characteristic of the wild type. The most common manifestation of this allele is the solid black cat. This allele is hypostatic to sex-linked orange so that an orange cat homozygous for nonagouti (*aa*) cannot be distinguished from the heterozygous (*a⁺a*) or homozygous (*a⁺a⁺*) alternatives. This is sometimes vividly demonstrated in tortoiseshell females that have solid black patches among striped areas of orange.

A third locus, usually referred to as tabby, affects the dispersal of agouti

hairs. In fact, at least three alleles are known that yield, in their order of dominance, Abyssinian "tabby" (t^A), striped tabby (t^+), and blotched tabby (t^b). Abyssinian is the total extension of agouti, striped is the wild type described above, and blotched is a variant of the striped pattern. The latter, in addition to being much darker than the wild type, is easily recognized by the replacement of vertical stripes on the sides by swatches and swirls of black and agouti. All three tabby alternatives are hypostatic to homozygous non-agouti (aa), and a black cat is black regardless of which alleles are present at the tabby locus. Abyssinian is basically irrelevant in the present context, for in northwest Europe and related populations it is rarely found. Except in a few areas where it has been recently introduced through carelessness or indifference on the part of breeders of show cats, it is not encountered. Blotched tabby, in contrast, is a common and almost characteristic mutant of European cats and their colonial relatives.

The final mutant to be considered is so-called blue or Maltese dilution (d), another autosomal recessive. This factor reduces black to gray and orange to cream (tortoiseshell to a mixture called "blue-cream") and is not usually difficult to identify.

A complete description of phenotypes, their genetic bases, and their interactions will be found in a useful synopsis by Robinson.¹⁰ A standard genetic nomenclature and symbolization for mutant factors in the cat has recently been promulgated by Dyte, *et al.*⁶

Discussion

EUROPEAN POPULATIONS

In Table 1 the results of several gene frequency surveys for European locations are summarized. All except Venice, which is included for comparison, represent samples from the northwest European gene pool. In order to clarify and characterize this population, it will be necessary to consider two determinants of gene frequency distributions in cats. The data from London, Mayenne, and Paris illustrate both phenomena well. Mayenne is a rural district in Brittany some 300 km west of Paris and approximately the same distance south of London. Although it is separated from the latter by the English Channel while at the same time quite accessible to Paris, there can be little doubt that the two urban populations are more similar to each other than either is to Mayenne. This demonstrates the first principal, *viz.*, that geographical barriers may be less important than other factors in influencing gene frequencies in cats. More important is the fact that for the two mutant alleles that result in darker phenotypes, *viz.*, nonagouti (a) and

TABLE 1 Mutant Allele Frequencies in European Cat Populations

	Phenotype				Approximate Sample Size	Reference
	<i>O</i>	<i>a</i>	<i>t^b</i>	<i>d</i>		
London	0.107	0.762	0.814	0.142	700	Searle (11)
Paris	0.066	0.74	0.76	0.33	1,000	Dreux (1)
Mayenne	0.140	0.66	0.58	0.26	300	Dreux (2)
Chamonix	0.12	0.70	0.76	0.31	94	Dreux (3,4)
Marseilles	0.07	0.69	0.70	0.30	272	Dreux (5)
Venice	0.058	0.579	0.483	0.348	210	Searle (12)

blotched tabby (t^b), the rural population of Brittany shows lower frequencies than either Paris or London. Similarly, for the darker wild type alternative of sex-linked orange (O^+) the frequency in London and Paris is higher than it is in Mayenne. Only in the frequency of dilution (d) is there a deviation from the pattern of darker urban and lighter rural phenotypes, with Paris higher than Mayenne. London in its extremely low frequency of dilution differs from all other northwest European and related populations. This may reflect severe conditions of selection in London, or it may be only a coincidental aberration. Unfortunately, no comparable data are yet available for Great Britain. Further clarification and characterization of the northwest European gene pool is provided by comparing the populations of Paris, Chamonix (at the western foot of Mt. Blanc), and Marseilles. Marseilles, which is the most distinct of this trio, and Chamonix are more similar to Paris than the rural population of Mayenne. The fact that both Marseilles and Venice are Mediterranean ports seems unimportant in determining cat gene frequencies, for these two cities differ considerably from each other.

A summary of the northwest European gene pool of the mid-twentieth century is, perhaps, best expressed by giving the outside ranges of mutant allele frequencies and noting that any geographic clines are less striking than internal urban-rural clines. The approximate values are, therefore: $O = 0.066 - 0.140$; $a = 0.66 - 0.76$; $t^b = 0.58 - 0.81$; $d = 0.14 - 0.33$. Finally, before leaving the consideration of this gene pool, it seems pertinent to note a special circumstance surrounding the survey of the population of Mayenne. The 300 cats tabulated in this study had all been transported from a collection point in Mayenne for use in neurophysiological experimentation in Paris. It does not take much imagination to visualize the confusion that might result when an effort is made to duplicate this research in Paris (or anywhere else) employing a sample from a different population.

NORTH AMERICAN POPULATIONS

Turning to the populations of the northeast United States, the data summarized in Table 2 immediately reveal great differences from European populations. On the average, frequencies of lighter mutants are much higher, and darker mutants are lower in this North American group than in Europe. For instance, *O* is 10 percent higher, and *d* is 12 percent higher, while *a* is 9 percent lower and *t^b* is 33 percent lower. In fact, the only noteworthy single exception to this is the high frequency (0.752) of nonagouti (*a*) in New York City, which falls high in the European range (0.66 - 0.762). New York is obviously exceptional in this regard since the four other cities, which virtually surround it, vary only between 0.637 and 0.68. On the whole, the five cities thus far studied in the northeast United States, encompassing an area of some one quarter million square miles, are quite homogeneous. Although no rural population has yet been studied adequately, internal differences correlate well with urban intensity, the highest frequencies of dark alleles being found in New York City and the lowest in Columbus, Ohio. The assumption that urban "pressure," as a function of both duration and intensity, is greater for New York than for Columbus is not difficult to support.

As an interesting aside, comparable gene frequency data for San Francisco are included in Table 2. These differ vastly from the northeast United States, but are otherwise inexplicable due to a lack of data for the cats of Mexico (from which this population is directly descended) or of Spain (which was the original source). Still, a cautionary note concerning the differences between the cats of the east and west coasts of the United States is in order. The results of experimentation performed in one place might be difficult to duplicate in another if any significant genetic variable were involved.

TABLE 2 Mutant Allele Frequencies in North American Cat Populations

	Phenotype				Approximate Sample Size	References
	<i>O</i>	<i>a</i>	<i>t^b</i>	<i>d</i>		
New York, N.Y.	0.145	0.752	0.473	0.443	250	Todd (17)
Boston, Mass.	0.193	0.642	0.443	0.426	300	Todd (16)
Rochester, N.Y.	0.196	0.643	0.444	0.421	150	Searle (13)
Philadelphia, Penna.	0.262	0.68	0.48	0.47	115	Tinney and Griesemer (15) Todd, unpublished
Columbus, Ohio	0.289	0.637	0.312	0.501	250	Tinney and Griesemer (15)
San Francisco, Calif.	0.32	0.70	0.50	0.13	120	Searle (13)

OCEANEAN POPULATIONS AND POPULATION CHANGES

Since cats of the northeast United States are derived from cats of northwest Europe, it is apparent that large shifts in the genetic structure of the two populations have occurred. The question is: Which populations have undergone what changes in the 350 years of separation? Remarkably, the answer is provided by the cats of Australia and New Zealand. One hundred fifty years after the arrival of domestic cats in the northeast United States, permanent cat populations were established from European sources in eastern Australia. This was followed half a century later by the introduction of cats (mostly directly from Great Britain) into New Zealand. Although the data from New Zealand are quite fragmentary and represent principally observations on the south island, they are consistent with other findings. In Table 3 the data available for the present populations of these areas have been compiled. It will be noted that frequencies for the alleles in question range between those found today in the northwest European and northeast North American populations: a is close to the former, and d (for Australia) is within the range of the latter, while O and t^b are intermediate.

TABLE 3 Mutant Allele Frequencies in Australian and New Zealand Cat Populations

	Phenotype				Approximate Sample Size	Reference
	O	a	t^b	d		
Brisbane, etc.	0.14	0.81	0.68	0.45	400	Moffatt (8)
New Zealand	?	0.81	?	0.33	170	Marples (7)

While cat gene frequencies are affected by the rural-urban cline, they appear otherwise stable for relatively long periods of time and over large areas. On this account it is reasonable to suggest that populations of the northeast United States approximate a sample of northwest European cats of the mid-seventeenth century while the cats of eastern Australia represent another sample made in the early nineteenth century. Thus it follows that the greatest changes in gene frequencies have occurred in Europe. These changes (Figure 1) presumably result from urbanization, which began at a much earlier time in Europe than in the colonial populations. Hence, removal of a sample from Europe emancipated it from the urban selection pressures and arrested the

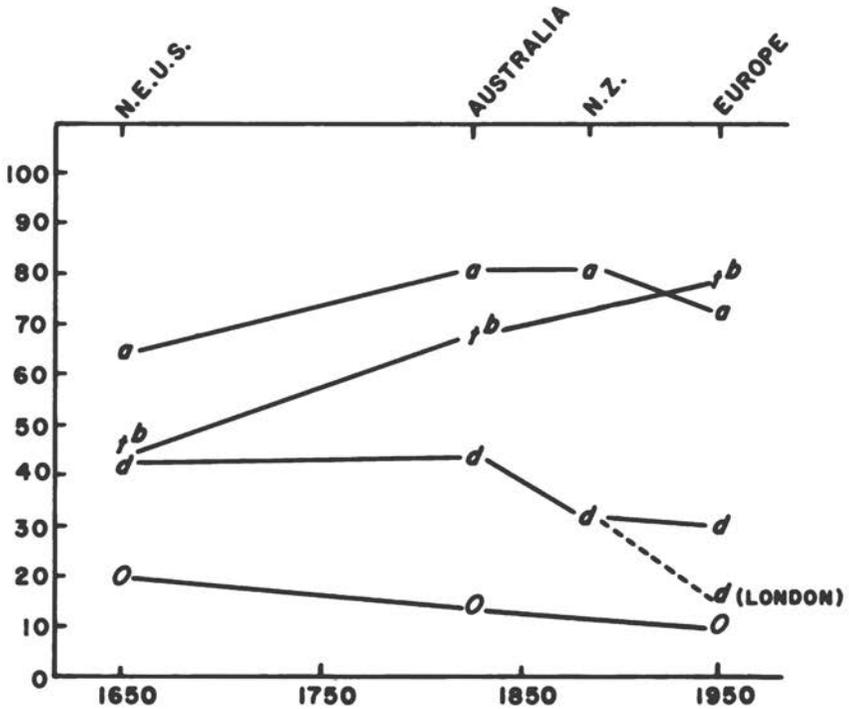


FIGURE 1 Gene frequency shifts in northwest European cat populations during the last three centuries.

change temporarily. Of course the same pressures must be assumed to be occurring now in the United States, as judged by comparative data for its populations, and also in Australia. However, in the absence of rural surveys, the extent of the changes that may have already taken place in these latter areas is undetermined. Therefore, the magnitude of the European changes cannot be fully appreciated, but they may well be greater than is readily apparent. A further complication lies in the nature of the selection pressures that appear to favor darker phenotypes, per se, rather than some pleiotropic effects of alleles that result in darker coats. Since there are several genetic alternatives that produce darker phenotypes, the selection pressures may shift over time from one locus to another, depending on a number of circumstances. Perhaps the best way to visualize the ultimate effect is to derive a "coefficient of darkness" that expresses the frequency, in a population, of the two darkest phenotypes possible for the four principal loci, viz., sex-linked black, orange (O^+ , O); agouti, nonagouti (a^+ , a); striped, blotched tabby (r^+ , r^b); and non-dilute, dilute (d^+ , d). For males, the predicted frequency of these two pheno-

types is given by inserting the appropriate phenotype frequencies in the formula $O^+d^+ (a + a^+t^b)$. This takes into account the epistatic relationships of the various alleles and gives the actual combined frequency of the two darkest phenotypes. The respective values for the northeastern United States, Australia, and northwestern Europe are 0.34, 0.57, and 0.65. Here, despite local aberrations in gene frequencies, the differences in total effect are clearly seen.

Conclusions

With regard to the utilization of domestic cats for research, at least two sources of error due to genetic variations are possible. The first is, of course, that which is due principally to the rural-urban cline. This can be controlled by taking appropriate measures to define, if not genetically, at least geographically, the animals employed. The second source of error is less obvious, although it is a further manifestation of the rural-urban cline. It is, in fact, the temporal shift caused by urbanization. While this may not be critical at the moment, the acceleration of urbanization portends the time when two samples drawn from successive generations may vary as much as those drawn from different areas at the same time. Although the complications implicit in both the present and future situations may seem discouraging, they are being steadily mitigated through the extension of information on cat populations around the world. If an effort is made to define and standardize samples as a preliminary step to other research, not only will the validity of that research be enhanced, but the task of validating further samples will be eased.

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DISCUSSION

DR. FESTING: Why are darker phenotypes favored in urban areas?

DR. TODD: There is nothing at this point except speculation and some interesting work that has been done by some behavioral scientists in Germany, particularly Paul Leyhausen at the Institut für Tiersi-kologie. He suggested that cats in their urban environment are subjected to crowding conditions, which disrupt their normal territorial establishment, and they are making all kinds of adjustments—some rather incredible adjustments—to living at these high densities with the innate behavioral patterns that have been evolved for millions of years.

Among these adjustments are moving to nocturnal patrol, because basically cats are diurnal—dusk, actually. Also the temporal dividing of territories must be dealt with. Finally, because they are saturated and overlapping, the old ol-factory cues no longer have too much significance, and they come to rely more and more on visual cues for territorial defense. So perhaps in the urban environment it behooves a cat to be less conspicuous. That means to be darker. This is one of the suggestions that has been made thus far.

In this regard, I might say there is no evidence that human selection is playing a role, that is, intentional human preference is playing a role. It tends to be self-defeating. If people like orange cats or black cats or blotched tabby

cats, they probably have them castrated or spayed in high numbers and the total biological effect is nil. For instance, in London at the moment something in the vicinity of 70 percent of the tom cats that one encounters in shelters and hospitals are castrated.

DR. WOLFF: Please explain more fully your suggestion that natural selection acts on coat color effect per se rather than on pleiotropic metabolic effects of the specific alleles.

DR. TODD: In the beginning I certainly would have been much happier if I could have said it is just coincidental. As I noted, in a total sampling we look at nine or ten different factors, and at least seven of these are coat-color mutants. There is absolutely no evidence that any of these are linked. That does not prove that they are not, but even if they are, they are at opposite ends of the chromosomes. Basically, the cat has a haploid chromosome set of 19. We have now got 24-25 markers. We have not found linkage yet, so what linkage there is must be very loose. All of these are independent, certainly. They have been pretty well tested, and the coat colors I am talking about are independent of one another. There are epistatic relationships and interactions, but it seems very hard to take all of these as they move, either to wild type or to mutant, but always in the direction of producing a darker phenotype in the urban areas, and say that there is an unknown pleiotropic effect associated with each one that by coincidence is producing a dark coat, when there really are four such effects. In the total sample seven or eight genetically independent factors are responsible for causing a dark coat.

DR. DIETERICH: What about the changes in rarer colors, like Burmese and Havana Browns?

DR. TODD: Burmese is an allele of the so-called albino series. It is also known as dominant Himalayan. It is dominant to Siamese. It is perpetrated and bred by cat fanciers in fair numbers, and thus far it has not been widely liberated into the population at large. These cats are fairly well controlled. Siamese on the other hand have been bred very extensively. For instance, the gene frequency in the cat population at large in Paris is 10 percent. That means phenotype frequency is 1 percent of that seen in stray cats. In Bangkok the gene frequency is only 29 percent, and that is where they came from originally.

Havana Brown is extremely rare, an extremely rare mutant in the cat. It is known basically in the chocolate point Siamese. That is where it came from originally, and it has been placed on a nonagouti-non-Siamese background by breeders. It is still quite rare and not often encountered. In fact, I have never encountered what was unequivocally chocolate brown or Havana Brown with its various names. I have never encountered that in the populations, other than in this chocolate point Siamese or in the lilac, which is simultaneously B and D dilution. But certainly Siamese is getting out, and it is having its effect.

DR. FOX: If cats are relying more on visual cues, why don't they have brighter contrasting colors, and if they are being forced to be nocturnal in urban areas, a bright coat visual signal might also be an advantage, or are there urban predators?

DR. TODD: No, there are no severe urban predators. The cat is his own worst enemy. Basically, to become inconspicuous is to reduce the chances of confrontation. This is the success that is involved. If the cat spends all his time scrapping with his neighbor, which they do when pressed, especially if their territories are liable to overlap, they don't derive too much from displaying and intimidating a neighbor if the neighbor thinks that is his land, too. So I think we could back up a minute and consider a rather curious thing about cats trying to be inconspicuous. There is only a certain group of felids that have the practice of burying feces and urine. These are the true lesser cats of the Old World, the bobcat, lynx, and puma. All other cats use these things to mark their territories. I think perhaps the same thing happened. If the puma wants to overlap the territory of a jaguar he wants to remain inconspicuous, so he buries his excrement and urine and does not use it to mark territories. In this way he remains inconspicuous. Cats fight very severely when crowded in residential neighborhoods, and the object is not the original one of intimidating a neighbor when you are on your own territory because he is easily intimidated when he is on your territory. This breaks down when there is a mutual sharing or an overlap.

DR. BOND: Are you aware of any statistical relationships between the gene data that you have presented and cat leukemias?

DR. TODD: The next step in this whole sequence is to take the pathology reports of Dr. T. C. Jones from Angel Memorial Hospital, on 6,000 cats that have also been tabulated according to genotype. A computer is trying to digest these data now, and there are other problems. I would not want to say anything specific. We did some very preliminary calculations. There were problems in the original data-gathering. We were unable to find any significant association between a genotype or a phenotype and some of the more well known cat diseases. We haven't even considered leukemias yet, although I am sure they are in the pathology material.

Interestingly, we found a very much higher incidence of infection, surgery, chewed ears, and whatnot among males and among the lighter phenotypes; for what it is worth, a higher incidence was detected among red cats, also a higher incidence of disorders associated with the bladder and urethra in red cats. Whether this will prove to be significant, I do not know, but we have this in mind, and hope we can work it up and get some answers. Obviously, the frequencies are quite different. San Francisco has been done, and now there is some very preliminary data in from Dallas. This is another population. This population obviously is not northwest European in origin. It is Mexican in

origin, and ultimately traces back to Spain. The gene frequencies are very different for San Francisco and apparently for Dallas. A little bit has come in from Wichita, but not enough to make much sense. If there are, however, relationships between these genotypes and certain kinds of diseases, disorders, and anomalies, veterinarians in one part of the country are going to encounter one kind of problem more frequently than they are in another part.

DR. SWEENEY: What is the expected sex ratio of the orange tiger phenotype?

DR. TODD: Where are you from?

DR. CLARKSON: White Eagle Farms.

DR. TODD: Where is White Eagle Farms?

DR. SWEENEY: Philadelphia.

DR. TODD: In Philadelphia? Just a minute. In males?

DR. SWEENEY: In orange tigers, how many in a random population do you expect to be males?

DR. TODD: I don't know whether I can get that slide out. It is about 25 percent for the gene frequency, and that is sex-linked, so 25 percent of the males in this case will be orange. I can't remember what the frequencies were for striped versus blotched alternatives. I think phenotypes 25-20—I can calculate it for you. I have got that information, and I do know that it happens to be one of the things that deviates.

Can I take one more minute for another point?

It did not come up logically, so I will bring it up illogically. One of the people who has done a great deal of this work is M. Phillippe Dreux from the University of Paris. He just came back from an incredible tour to the Kerguelen Islands. The nearest land is the Antarctic. It is 500 miles north of Antarctica in the middle of the Indian Ocean. Here he discovered the first founder effect in cat populations. This, of course, was an uninhabited island, even in the eighteenth century, and it still would be, except the French maintain an air force base there. The cat population there is uniformly black with white spotting. This is the first case of founder effect that has been established, and interestingly, it is in an insular population where one can imagine that the initial introduction was certainly not a nonrandom sample from the metropolitan area.

On his way back from Kerguelen, M. Dreux stopped at Réunion, where the cats look like the cats of Malaysia, a population that was established from Madagascar. We do not know what Madagascar is like yet, but there is a lot of speculation that the early settlement of Madagascar was, in fact, Asian. If it holds up, then the anthropologists can make some use of the fact that even if you can't trace the thing in the blood gene frequencies of the human population, because they have been fouled up subsequently, perhaps the cat gene

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frequencies will allow it, because they seem to be less susceptible to politics and other things. They will allow these trails to be followed.

Finally, on his odyssey he stopped in Bloemfontein in the Orange Free State, and I guess I should just say that the cats of the Orange Free State look like European cats, and they look like a population that we would project for some time in the early part of the nineteenth century. In fact, it was in the middle of the nineteenth century that Bloemfontein was founded.