Study Guide for Exam 1
Anth 4234: Genes, Health, and Human History

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1 Introduction

This study guide covers lectures only—not readings. The paragraphs are written as essay questions, but the exam itself will be a mixture of multiple-choice and short-answer questions.

Each section heading below corresponds to one lecture topic.

2 DNA

The lecture is organized around 5 properties that any sensible substance of heredity ought to possess. What are these properties, and how does DNA satisfy them? What do A, T, G, and C stand for? Which nucleotides pair with which?

What is a protein? What is a codon? How does DNA code for protein?

Use the genetic code in table 1 to translate the following DNA sequence into a sequence of amino acids:

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DNA template: 3' ccc.cgt.gtc.caa 5'
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Don't memorize the code. Just be prepared to use it.

What evidence supports the view that human chromosome 2 was formed when two ancestral chromosomes fused?

3 Transposable elements

What is a *transposable element*?

Fairbanks discusses two types of transposable elements: *transposons* and *retro-elements*. What are they? How do they differ? Which is more common in the genome?

Which type most useful for phylogenetic analysis, and why is it useful?

Be prepared to infer a phylogeny from data on transposable elements.

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What do transposable elements imply about the phylogeny of whales and land mammals?

What do transposable elements imply about the phylogeny of humans and apes?

4 Pseudo-genes

What is a gene? What is a pseudogene?

List three types of mutation that can turn a gene into a pseudogene. (See Fairbanks and/or lectures.)

Why do humans need vitamin C in their diets? What happens if they don't get enough?

Summarize the evidence relating the GULO pseudogene to the phylogeny of humans and apes.

Why do humans have high blood levels of uric acid? What happens if this level gets too high?

Summarize the evidence relating the urate oxidase pseudogene to the phylogeny of humans and apes.

What does the Glucocerebrosidase (GBA) gene tell us about primate phylogeny?

What do the β-globins tell us about primate phylogeny?

5 Molecular evolution

The neutral theory explains the following facts:

1. A typically linear relationship between the genetic difference between species and their separation time.
2. Different proteins evolve at different rates.
3. Intron evolve faster than exons.
4. In coding regions, the 3rd codon position evolves faster than positions 1 and 2.
5. Synonymous nucleotide sites evolve faster than nonsynonymous ones.
6. Within species, there is more variation in introns than in exons, at the 3rd codon position than at positions 1 and 2, and at synonymous sites than at nonsynonymous ones.

How does the neutral theory explain each of these facts?

Table 1: The universal genetic code (DNA version)

First Position	Second Position				Third Position	
	A	G	T	C		
A	Phe	Ser	Tyr	Cys	A	(adenine)
	Phe	Ser	Tyr	Cys	G	(guanine)
	Leu	Ser	Stop	Stop	T	(thymine)
	Leu	Ser	Stop	Trp	C	(cytosine)
G	Leu	Pro	His	Arg	A	
	Leu	Pro	His	Arg	G	
	Leu	Pro	Gln	Arg	T	
	Leu	Pro	Gln	Arg	C	
T	Ile	Thr	Asn	Ser	A	
	Ile	Thr	Asn	Ser	G	
	Ile	Thr	Lys	Arg	T	
	Met	Thr	Lys	Arg	C	
C	Val	Ala	Asp	Gly	A	
	Val	Ala	Asp	Gly	G	
	Val	Ala	Glu	Gly	T	
	Val	Ala	Glu	Gly	C	

Some modern species, such as frogs, opossums, and horseshoe crabs, look a lot like their ancestors many millions of years ago. Morphological evolution has been slow in these species. Has molecular evolution been correspondingly slow? Why does this make sense?

6 Human and chimpanzee genomes

What functional categories of gene have evolved rapidly in the line leading to humans and chimps?

What functional categories of gene have evolved rapidly in the line leading to humans?

What is the K_a/K_s ratio, and why does it tell us about selection? (Prof. Knapp used an alternate notation. Her d_N is my K_a; her d_S is my K_s.)

Human-accelerated regions (HARs) are those regions evolved most rapidly in the hominin lineage. Where in the genome are these regions located, and what does this suggest about human evolution?

7 Genetics and population size

In lecture, I presented data on mitochondrial diversity within populations of humans and of chimpanzees. Are humans more or less variable than chimpanzees? Within humans, are Eurasians more or less variable than Africans? What do these facts suggest about the history of population size among chimpanzees, African humans, and Eurasian humans?

Why do large populations tend to have more genetic variation than small ones?

What is a gene genealogy? A mismatch distribution?

Why does population growth generate a comb-shaped (or star-shaped) gene genealogy?

Why does this generate a wave in the mismatch distribution?

Fig. 1 shows two gene genealogies, one from a population that has expanded in size and the other from one whose size has been constant. You should be able to tell an expanded population from a constant one either from the gene genealogies or from the mismatch distributions.

What does the PSMC method tell us about the history of human population sizes? Over what time interval do all populations share the same history? When did the ancestral population grow? When did it shrink? Which populations suffered most during the lean times?

8 Archaeology, history, genetics & linguistics

Which of the following are Indo-European languages: Arabic, Celtic, Turkish, Hebrew, Korean, Sanskrit?

Manco lays out an important timeline for the course. Try to have it all approximately straight. A

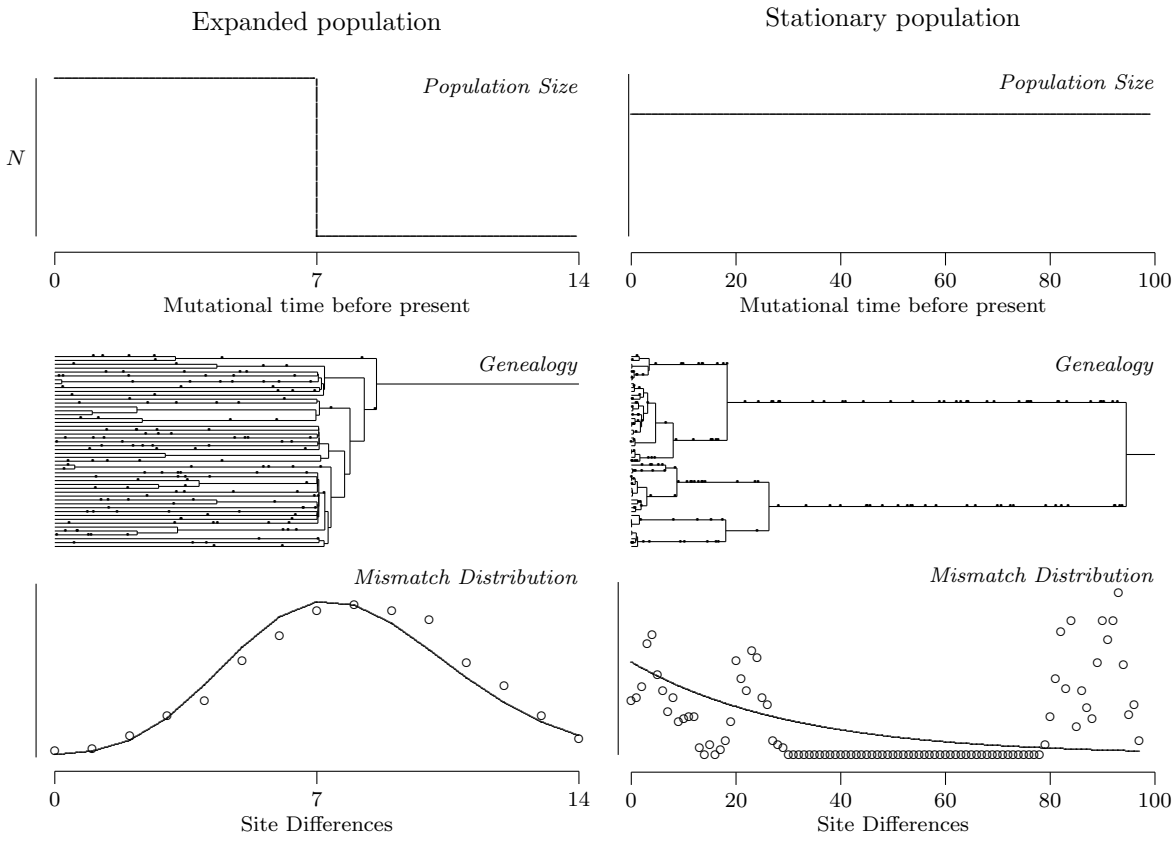

Figure 1: Population histories, gene genealogies, and mismatch distributions of two populations

few questions: "When Caesar invaded Gaul, how long had iron been worked?" and "When did the Vikings start causing trouble?" When did modern humans reach Europe? Australia? The New World?

How did Childe define a culture? What does "pots not people" mean?

What and when was the Bantu expansion?

9 Adaptive evolution

A *selective sweep* occurs when a favorable allele arises (either by mutation or by introgression from another population) and increases in frequency under the influence of natural selection.

Compare and contrast the various methods for detecting natural selection. How does each method work? Over what time scale is each relevant?

What is the site frequency spectrum? Why do we expect an excess of singleton sites at which a favorable allele has recently swept through the population? (The slides refer to an excess of "rare derived alleles," which means the same thing.)

What are crossing over, recombination, and linkage disequilibrium (LD)? Why do we expect LD in the chromosomal region surrounding a recent selective sweep?

We infer selection when we find a common derived allele within a large block of LD. Why is selection *not* implied by

1. a common allele within a small LD block, or
2. a rare allele within a large LD block?

10 Early modern humans

How does the archaeology of modern humans differ from that of archaics, such as Neanderthals?

Where and when did Neanderthals live?

Where and when do anatomically-modern humans first appear?

Summarize the findings of Xing et al (2010) about the expansion of modern humans out of Africa.

Why is it puzzling that the 45-ky-old Ust'-Ishim specimen from Siberia is equally related to northern and to southern populations of modern humans—i.e., equally related to Europeans and Australians?

Discuss the evidence of Neanderthal admixture into the Ust'-Ishim specimen. How is it similar to admixture into modern Eurasians? How is it different? Why the difference?

Discuss evidence of Neanderthal admixture into Oase 1, a 40-ky-old man from Romania. Which modern populations are most closely related?

Discuss evidence of Neanderthal admixture into the 36-ky-old Kostenki specimen from Russia. Which modern populations are most closely related?

Which modern populations are most closely related to the 24-ky-old specimen from Mal'ta, in Siberia? Why is this surprising?

Discuss evidence of Neanderthal admixture into the 7-ky-old La Braña specimen from Spain. How similar is this genome to modern Europeans? What do we know about the color of skin and eyes? About lactose tolerance? About dietary adaptations? About immune alleles?

Be familiar with Posth et al (2016), who used ancient DNA to study variation in European mtDNA at different points in time. They recognized two points at which the amount of variation changed dramatically. Did it increase or decrease? What climatic events coincide with these changes?

What did the study of Lazaridis et al (2014) imply about the history of population size among Mesolithic foragers?

11 Archaic admixture

Summarize the logic that allows us to infer archaic admixture into modern populations from data such as the following:

	Nucleotide Site Pattern		
	ea	*en*	*an*
European	1	1	0
African	1	0	1
Neanderthal	0	1	1
Chimpanzee	0	0	0
#	303,340	103,612	95,347

In these data, "0" represents the ancestral allele, and "1" the derived allele. The bottom line shows the count of each site pattern.

What fraction of modern genomes derives from Neanderthal admixture in Eurasia?

In which modern populations do we find evidence of admixture from Denisovans?

Summarize the logic that allows us to infer archaic admixture into modern populations from long haplotypes that differ at many nucleotide sites—from the combination of deep separation and extensive LD.

Using this technique, several studies have shown that archaic segments are unevenly distributed within the human genome. Discuss this unevenness. What are the possible causes? What evidence bears on this issue?

What evidence suggests that archaic alleles have been opposed by selection in modern populations?

Modern Asians have more Neanderthal DNA than modern Europeans. What hypotheses have been proposed to explain this fact. What evidence bears on these hypotheses?

Archaic populations (both Neanderthal and Denisovan) had very small population sizes. What consequences did this have for adaptive evolution in these species? Discuss the evidence.

Harris and Nielsen (2016) did a simulation study to find out how the long history of small population size should have affected fitnesses of archaic populations. They found a substantial reduction in fitness. What category of deleterious mutations made the largest contribution to this reduction in fitness?

(The answer is simplest in terms of the parameter $N_A s$, where N_A is Neanderthal population size and s is the fitness cost of the deleterious allele.)

12 How archaics shaped the modern immune system

Humans have an *innate immune system* and an *adaptive immune system*. The latter is found only in vertebrates; the former is found in plants, animals, fungi—just about any multicellular organism you can name. The innate immune system has no memory. It uses "rules of thumb" to recognize pathogens, and attacks them in a variety of ways. Inflammation is part of the innate immune system. The adaptive immune system memorizes the proteins in your body and attacks cells that exhibit foreign proteins. It "remembers" pathogens it has seen before, which is why vaccines are useful.

The Major Histocompatibility Complex (MHC) is part of the adaptive immune system. In humans, the MHC is called Human Leucocyte Antigen (HLA) system. The human MHC consists of over 200 loci, all on chromosome 6. These include some of the most polymorphic loci known. HLA-A has 1000 known alleles; HLA-B has 1600.

Why does selection favor rare alleles at MHC (also known as HLA) loci?

What does this do to genetic variation at these loci and to the depth of MHC gene genealogies? Why?

Eurasians have many HLA alleles acquired by introgression from Neanderthals and other archaics. According to one estimate, >50% of Eurasian HLA alleles came from archaics. It appears that HLA alleles are more likely to introgress than alleles at other loci. Why should this be?

What evidence supports the view that the HLA-B*73.01 allele entered the modern population via Neanderthal admixture?

What fraction of Eurasian HLA alleles seem to derive from archaic admixture?

The OAS1 locus codes a protein that is part of the innate immune system. At this locus, one allele (the P allele) is restricted to Melanesia, and the other is worldwide. What evidence supports the view that the Melanesian allele derives from archaic admixture?

Also at the OAS1 locus, the R allele seems to derive from Neanderthal admixture. Where is it found today?

The STAT2 locus is involved in viral defense. What evidence supports the view that the N allele derives from Neanderthal admixture?

13 Mesolithic

The first anatomically modern humans in Europe are called *Upper Paleolithic*, arriving about 40 kya. They lived well, it seems, with cave art, sculpture, beadwork, elaborate tool types, and projectile weapons. They exploited large animals at first, and gradually broadened their diet to include smaller prey such as tortoises. As the environment decayed, the elaboration of the Upper Paleolithic withered, art and fancy tools went away, small stone tools like arrowheads and scythe inserts became more common. This is then the *Mesolithic*.

13.1 Kalahari foragers

In the Kalahari desert of southern African, there is a population of foragers who are called in the literature by a variety of names: Bushmen, !Kung, San, or Žu/wasi. They are in many ways like Mesolithic people: no fancy decoration, simple technology, lots of plant foods. They exhibit a suite of unusual biomedical characteristics:

1. Adults are glucose intolerant.
2. Blood pressure declines with age.
3. Edge-to-edge bites. Agricultural populations such as ours have overbites because we eat soft food. When children eat a soft diet, their jaws don't grow, and they end up with an overbite.
4. No cavities; no toothache.
5. No hookworm, because they're moving all the time.
6. Children are active, bright-eyed, and look healthy.
7. Very little body fat, especially in nursing women.

8. When children get sick, they are likely to die. Harpending suggests that you need body fat to sustain illness.

Times got hard for the !Kung when farmers moved into the area: the cattle outcompeted game animals and trampled on wild foods. The farmers also hunted game animals. All this impoverished the foragers. Some responded to the crisis by adopting aspects of the farming economy. They became sedentary farmers rather than mobile foragers.

How do sedentary and mobile !Kung differ in (a) sharing and reciprocity, (b) access to privacy, (c) sex roles, and (d) health? Harpending claims that being tethered to production, either to gardens or to goat herds, leads inevitably to a large array of consequences.

13.2 Mesolithic Scandinavians

In the archaeological record, when do we begin to see evidence that humans lived in Scandinavia?

Günther et al (2018) study the genetics of Scandinavian hunter-gatherers (SHG) of the mesolithic. They show the SHG were a mixture of two earlier populations: eastern hunter-gatherers (EHG) and western hunter-gathers (WHG). In what part of Scandinavia was the genetic contribution of EHG largest? Ditto for WHG?

According to Günther et al, what route did EHG take into Scandinavia? Ditto for WHG?

What is known about the history of population size among the ancestors of SHG? Did there ancestors experience a bottleneck during the Pleistocene? How much did these populations grow after the bottleneck?

Although modern Scandinavians inherit only a small fraction of DNA from mesolithic Scandinavians, some mesolithic alleles are still common in Scandinavia. Several of these are in the TMEM131 gene, which has been associated with physical performance. Günther et al suggest that this may reflect adaptation to cold.

What does the genetic data suggest about the color of skin and eyes among mesolithic Scandinavians?