Spring 2017 Genomics Exam #1
Genomic Sequences & Variations

There is no time limit on this test, though I don't want you to spend too much time on it. I have tried to design an exam that will take less time that exams in the past. You do not need to read any additional papers other than the ones I send to you. There are 4 pages, including this cover sheet, for this test. You are not allowed discuss the test with anyone until all exams are turned in at 2:30 pm on Wednesday February 15. **ELECTRONIC COPIES OF YOUR EXAM ANSWERS ARE DUE BY 2:30 pm ON WEDNESDAY FEBRUARY 10**. You may use a calculator, a ruler, your notes, the book, and the internet. You may work on this exam in as many blocks of time as you want. Submit your electronic version before 2:30 pm (eastern time zone).

The **answers to the questions must be typed in a Word file and emailed to me as an attachment**. Be sure to backup your test answers just in case (I suggest a thumb drive or other removable storage). You will need to capture screen images as a part of your answers which you may do without seeking permission since your test answers will not be in the public domain. Remember to explain your thoughts in *your* own words and use screen shots to support your answers. Screen shots without ***your*** words are worth very few points. Support your answers with data using screen shots liberally.

DO NOT READ or DOWNLOAD ANY NEW PAPERS FOR THIS EXAM. You may search and read abstracts. RELY ON YOUR EXPERIENCE, AND YOUR SKILLS. Spell out your logic for each answer.

-3 pts if you do not follow this direction.
Please do not write or type your name on any page other than this cover page.

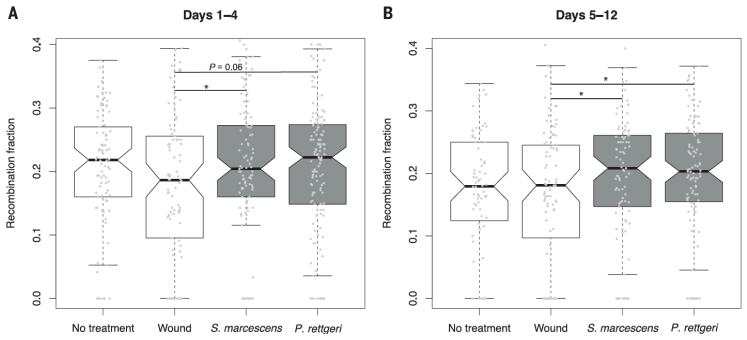
Name (please type):

Write out the full pledge and sign (electronic signature is ideal):

How long did this exam take you to complete?

10 pts

1) The offspring of some experimental fruit flies were measured for recombination frequency in their chromosomes under the four conditions shown here: no treatment; sterilely wounded by investigators; infected by two bacterial species as indicated. * = p < 0.05. Whiskers = most extreme data points, black line = median, boxes = second and third quartiles. Days indicate post manipulation time.



a) Interpret the experimental results in panels A and B based on the presented data.

A: within the first 4 days of manipulation, sterile wounding reduces chromosomal recombination in offspring, but not clear given * as shown

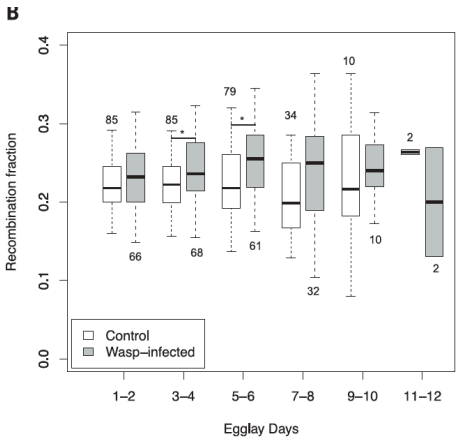
B: Between 5 – 12 days, it appears infection increases recombination compared to both control treatments.

b) What are the evolutionary implications of these data?

A fly that is infected produces more diverse chromosomes which might provide a selective advantage for self and/or offspring. The increased diversity may assist in resisting infection or fight it off.

10 pts

2) Continuing the fly research, here the recombination rates are grouped into 2 day bins post manipulation. * = p < 0.05 for paired data within a bin. Numbers above and below the whiskers represent the number of replicates for control or treatment.



a) Interpret these experimental results based on the presented data.

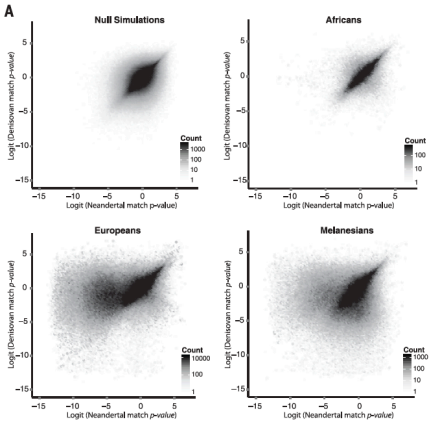
From days 3 – 6, the infected flies produced significantly more recombinant offspring than did the control flies. Before and after this time period showed no difference.

b) What molecular mechanistic implications can you speculate about using these data?

Infection triggers the production of new proteins that take a while to accumulate and affect recombination. After 6 days, the proteins are degraded to a point that they no longer increase recombination fraction.

10 pts

3) A group of genomicists wanted to find the origins of ancient hominid DNA present in modern human genomes. They sampled Esan people from Nigeria, northern Europeans, and people from Melanesia. Y-axis measures p-values for sequence matches



between modern and Denisovan DNA; X-axis measures p-values for sequence matches between modern and Neandertal DNA.

a) Interpret all four panels from this figure.

top left: null simulation shows the amount of variance in the data when there is no match between current humans and ancient hominids

top right: Africans do not show any admixture with either Denisovan or Neandertal DNA. Admixture did not take place within Africa, but only in those humans who migrated from Africa.

bottom left: Europeans show admixture with Neadertals as exhibited by the points moving to the left along the X-axis.

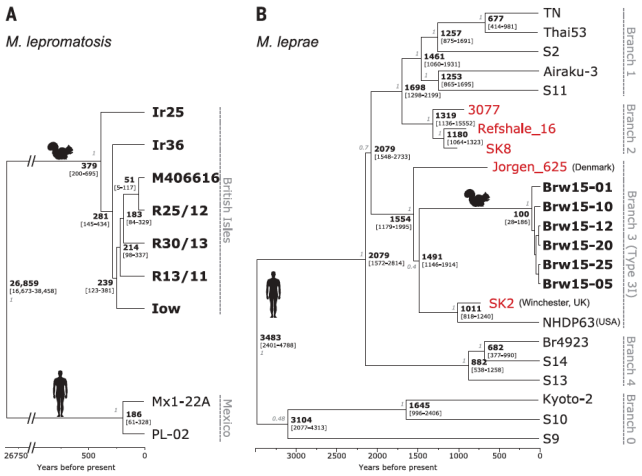
bottom right: Melanesians show admixture with both ancient hominids with points scattered in both X and Y directions.

b) Address the evolutionary significance of this finding given that the investigators compared ancient and modern DNA from about 160 geographically diverse modern populations.

Other non-human hominids co-existed with *Homo sapiens*. Neandertals interbred with the ancestors of Europeans and Melanesians. Denisovans interbred only with ancestors of Melanesians (of those shown here).

15 pts

4) Two species of leprosy-causing bacterial exist in the world. Panel A shows the evolutionary analysis of two populations, one from the UK and one from Mexico. The small black silhouettes show which host each strain came from (human or squirrel). Panel B shows a similar analysis for the other leprosy species. Red text indicates ancient samples, bold indicates squirrel samples.



a) Interpret the evolutionary relationships between the two different sources of bacterial genomes for panels A and B separately. Include a time scale in your answers.

A: Bacterial DNA sequences taken from squirrel and human are are not very similar, having separated 26,859 years ago.

B: Human and squirrel samples are more similar than in A, separated 3,483 years ago. However, squirrel sample is most similar to ancient samples taken from humans who lived about 1000 years ago.

b) Which human sample is the MRCA for the squirrel samples in panel B, based on the data?

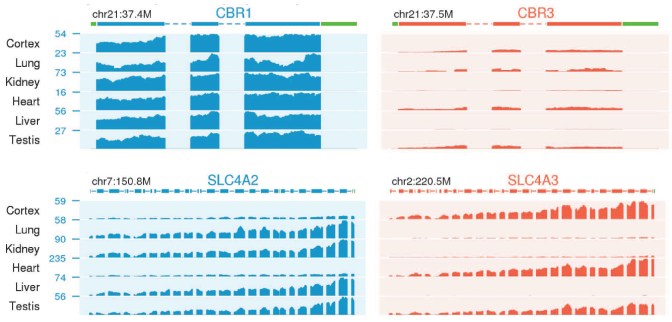
Branchpoint for SK2 ancient and NHDP63 (USA) modern, by 1491 date

c) What can you deduce about leprosy in British squirrels over the last 2,000 years given the investigators only sequenced squirrel samples from live animals?

All the squirrel samples diverged over the last 100 years, but they have probably been a non-human reservoir since about 1500 CE. It is only now that we are seeing the connection.

15 pts

5) The human genome contains many paralogs, as shown in these examples. Gene structures are shown above with histograms below showing transcriptome data.



a) Interpret the data for the top pair (CBR1 & 3).

CBR1 transcribed much more than CBR3, for these 6 tissues.

b) Interpret the data for the bottom pair (SLC4A2 & 3).

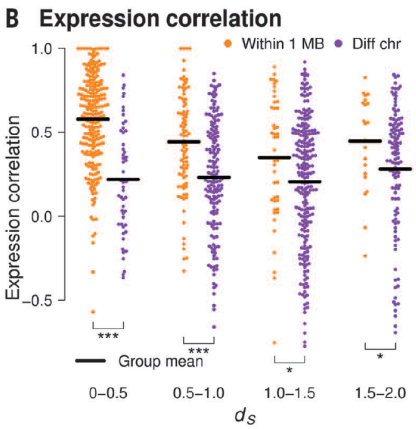
SLC4A2 transcribed where SLC4A3 is not, and vice versa. One exception is testis where both are transcribed.

c) Use these data to generate two hypotheses of what can happen to paralogs after gene duplication.

Some paralogs evolve to differ in tissue expression (SLC4A2/3). Some paralogs are not transcribed as much and may be non-functional (given limited tissue sampling here) as seen in CBR3.

15 pts

6) Continuing with human paralogs, here you can see investigators measured the correlation of transcription levels across many tissues for paralogs on the same chromosome or on different chromosomes, as indicated by orange and purple dots. * = $p < 0.05$; *** = $p < 0.001$. d_s is a proxy for time since the gene duplication event that produced paralogs. Bigger numbers means more years since duplication.



a) Interpret the figure for all four d_s categories.

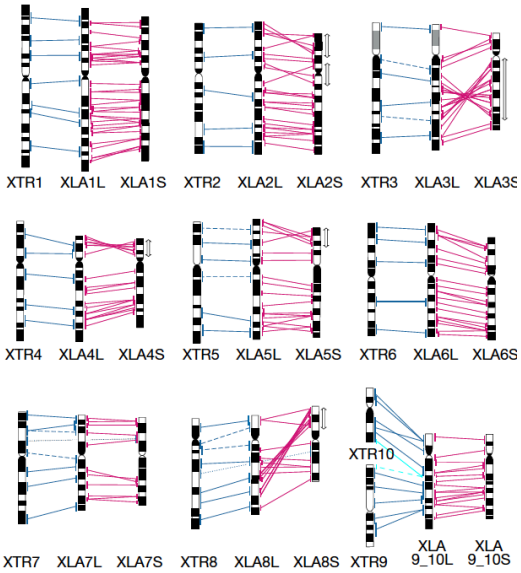
In all 4 time frames, paralogs on the same chromosome have higher correlation of transcription than do paralogs on different chromosomes. However, with overlapping distributions, this trend is not always true.

b) Which of the two scenarios in Question #5a and 5b best explains what is happening to paralogs on the same chromosomes? Support your answer using data from both questions 5 and 6.

Neither really. Correlation does not take magnitude into consideration, only directionality. Therefore 5a with with CBR1&2 might be correlated but their magnitudes differ substantially. But the better answer is that CBR1&2 represent one of the lowest orange dots for one of the d_s time ranges.

15 pts

7) *Xenopus laevis* (XLA) is a tetraploid frog whereas *X. tropicalis* (XTR) is a diploid; both frogs have had their genomes sequenced. The diagram shows 9 XTR chromosomes and how they map onto XLA chromosomes (L = large and S = small). Blue lines show positional relationships between conserved orthologs for both species (solid), only with XLAS (dotted) or only XLAL (dashed). Double headed arrows indicate inversions. Magenta lines show relationships between XLA paralogs.



a) For XTR chromosomes 1 – 9, indicate which XLA chromosome is more similar to XTR.

In all cases, XLA#L is more similar because it has more orthologs and syntenic DNA (fewer inversions or repositioned orthologs).

b) Integrate the data from Questions 5 – 7 to speculate what is happening to the XLA paralogs.

It seems that the XLA#S chromosomes are mutating away from original paralog/chromosome as shown in figure from 6 and 5b. One would predict that the correlation of paralogs from XLA would have low correlations, maybe developing tissue-specific transcription.

10 pts

8) Using the ExAC database, the figure to the right shows higher Z scores for SNPs that are selected against. Gray = synonymous SNPs, orange = missense SNPs, red/rust = nonsense SNPs.

a) Interpret the data based on this figure.

synonymous SNPs are not selected against, on average
missense SNPs are more selected against as shown by the rightward tail
nonsense SNPs are highly selected against as shown by the complete shift to the right.

b) ExAC found one SNP for every 8 bases. What is the evolutionary implication of the data in the figure given the assumption that all SNP mutations are equally likely to occur?

All mutations are possible during S phase, but selection weeds out SNPs that are deleterious during gestation or development, so that most remaining SNPs in living people are synonymous > missense > nonsense.