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Hands-On Eight Genomic Variations

Human Genomic Variation

Objectives:

- 1) Understand human single nucleotide polymorphisms and mine SNP databases.
- 2) Discover how SNPs can cause diseases.
- 3) Examine how SNPs can affect medical therapies.

Problem 1 The ApoE Gene

In parts A and B, we study a few SNPs that are present on the apolipoprotein E gene also known as ApoE.

A) Go to NCBI <http://www.ncbi.nlm.nih.gov>

- Choose “SNP” from the dropdown window on the same row as “Search”.
- Type “rs11542040” in the search window.
- Click on the blue button “Search”.
- From the new page, click on “GeneView” (in purple).
- Note that we get a page with many SNPs associated with ApoE.

1) On which exon of ApoE is the SNP rs11542040 located?

Hint: You will have to check the position of the SNP in the mRNA ([NM_000041.2](#))

- 2) How many SNPs that cause nonsynonymous mutations are there?
- 3) Will any of the SNPs alter the protein’s primary structure?
- 4) Quite a few SNPs are described in the table. Name 4 SNPs that will alter the protein’s primary structure.
- 5) Explain how the rs11542040 was validated.

B) Click on “SEARCH” in the blue, left-hand margin of the rs11542040 SNP report

- From the dropdown menu, click on “Population Detail”
- From the new page, choose the radio button “Submitter population id” next to “Search by:”
- Enter the population name “MDECODE-3” in the window under “starts with:” Note that MDECODE stands for “Molecular Diversity and Epidemiology of Common Disease”
- Click on “Search (case insensitive)”

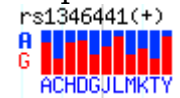
- 6) What population was sampled to find this SNP?
 - Click on the “[MDECODE-3](#)” link that appeared with your search
 - Click on “[MDECODE-APOE-SNPS](#)” under “submitter batch id”
- 7) Determine the human source of MDECODE-4.
- 8) Once you have determined the identity of MDECODE-4, go back to the page that has all four MDECODE populations listed with the link “[detail](#)” under “View Frequency”.

Compare the genotype diversity among the four populations. Do you detect any ethnic differences? Which one appears to have more SNPs? For example: compare the African American population with the 3 others in terms of bi-allelic SNPs.

Problem 2 The SCN5A Gene

- Go to the HapMap web page at <http://hapmap.ncbi.nlm.nih.gov>
 - Click on “HapMap Genome Browser release #3 (Phase 3 - genotypes, frequencies)” under “Project Data”
 - In the new page, type “Chr5:134530001..134570000”, in the “Landmark or Region:” window
 - Click on “Search”
- a) What is the name of the SNP for which there is an obvious difference between the residents (and descendants) of African nations and the rest of the other ethnic groups?

Hint: Note the population code above the ideogram, next to “Population rs1346441(+)”
descriptors”. These correspond to the letters “ACH..” in figures, eg.



See the lecture notes for the one-character explanations.

- b) What is the exact location of that SNP on chromosome 5?
- c) What can we conclude about the differences between the genotypes of residents (and descendants) of African nations and the other ethnic groups?
Hint: Compare the genotype frequencies.

Problem 3 The Two Isoforms of SCN5A

We are going to study the two isoforms of SCN5A. It has 2 alternative splicings leading to 2 proteins that differ by one amino acid.

- Go to the HapMap web page at <http://hapmap.ncbi.nlm.nih.gov/>

- Click on “HapMap Genome Browser release # 3 (Phase 3 - genotypes, frequencies)” under “Project Data”
- In the new page, type “SCN5A”, in the “Landmark or Region:” window
- Click on “Search”

If you scroll down you will see under “Details” two alternative splicing cartoons illustrating the two slight variants of this protein (that differ by only one amino acid) and you will also see the name of the gene.

- a) What does this gene encode?
- b) What is the amino acid that differs between them? In what position is it? To be able to answer this question we will need to get the two proteins and align them.

We are going to learn more about this gene.

- Scroll down and click on (or simply enter at NCBI) “NM_000335”.
 - Scroll down and click on “GeneView in dbSNP” from under “All links for this record” on the right-hand side of the webpage.
 - Scroll down to amino acid position 524.
- c) What is the reference number (rs) of the SNP?
 - Click on the rs link to be taken to the SNP page with details on that particular SNP.
 - Scroll down to “Population Diversity” which contains information about the allele and genotype distributions of five populations.
 - d) Which populations have the largest diversity wrt this particular SNP?

Problem 4 The Ensembl Genome Browser and SCN5A

In this problem, we continue exploring the SCN5A gene.

- Go to the “Ensembl Human Genome Browser” at <http://www.ensembl.org>
 - Choose “Human” from the dropdown window next to “Search:”
 - Type “SCN5A” in the window to the right of “for”
 - Click on “Go”
 - From the new page, click on “Gene” to expand that window
 - Click on “Human (1)”
 - From the new page, click on “**SCN5A** [Ensembl/Havana merge: ENSG00000183873] ”
 - Click on “Variation Image” under “Genetic Variation” on the left-hand side of the page
- a) Do you find this display more or less helpful than NCBI’s?
 - b) By clicking on “Comparison Table” under “Genetic Variation” we get the known SNPs for that gene. Can you find the SNP of the previous problem?

Problem 5 The Nos2A Gene

We are going to get some information on Nos2A.

- Go to NCBI and choose “OMIM” from the dropdown menu (upper left corner of the page)
- Type “Nos2” in the search window and click on the blue “Search”
- From the OMIM page, click on “[*163730](#)” link which is on NOS2A for humans

- a) Read the first paragraph and identify two cell types that utilize Nos2A.
- b) In which article did the authors claim that NO levels may help save children from malarial death?

Problem 6 The Mc1R Gene

We are going to get some information on the Mc1R gene.

- Go to NCBI and choose “Gene” from the dropdown menu
- Type “Mc1R AND human” in the search window and click on “Search”
- Click on “[MC1R](#)” (with MIM: 155555)

- a) According to the summary, what feature is unusual about the gene structure?
- b) According to the summary what is a second phenotype that correlates with accumulation of pheomelanin?
 - Go to “Links” at the right-hand side of the page, and click on “[SNP: GeneView](#)” to view all the known SNPs.
- c) What surprising trend do you find in the types of SNPs present in this gene?
- d) Search PubMed Central for “SLC24A5”. What role does it play in human skin color? Hint: Find the article published by Jiali Han et al. in 2008.