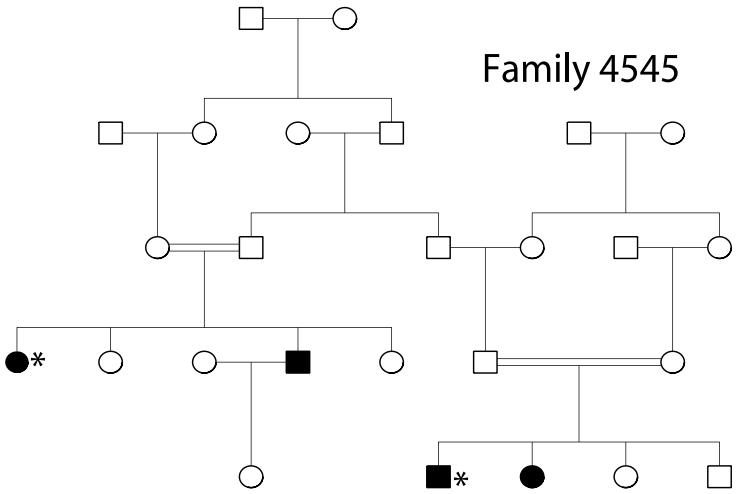
Mapping Homozygous Regions using HomozygosityMapper

Part 2 – Analyzing Sequence Data (VCF files) using HomozygosityMapper

In this exercise, we will use .vcf data from two hearing-impaired relatives from family 4545. To "**(re)analyse a project**", from the pull-down menu for **project**, select **HMexercise2.**



For **cases**, type in **4545A & 4545B** (shown with stars in the pedigree drawing). For unrelated **controls**, type in **C1, C2, C3 & C4**.

Check the tickbox for the field "**require genetic homogeneity**". To "**exclude homozygous stretches in controls**", put in 20 as value. For **allele frequencies** keep as **none**. Click **Submit.**

Question 4: In which chromosome(s) were regions of homozygosity detected at threshold ≥0.8?

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Question 5: The autosomal recessive nonsyndromic hearing impairment (ARNSHI) in family 4545 was previously mapped to a locus on chr11: 63591861-70933968. Using the .vcf genotypes do you see a homozygous region in the previously mapped locus? If yes, which positions on chr11 flank the homozygous region? *Hint: Open the genotypes table to see the full HM region.*

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Question 6: The advantage of submitting sequence data for homozygosity mapping is the possible inclusion of the actual disease-causal variant within the homozygous region. Variants that are homozygous in both hearing-impaired relatives from family 4545 occur at the following chr11 positions which fall within coding non-synonymous or canonical splice regions:

66033430
67287263

Which of the variants at these positions is likely causal of ARNSHI in family 4545?
Hint: Search the positions on the UCSC Genome Browser http://genome.ucsc.edu/ to know in which genes the variants lie and then check the gene information in OMIM.

References

Seelow D, Schuelke M, Hildebrandt F, Nürnberg P. HomozygosityMapper – an interactive approach to homozygosity mapping. Nucleic Acids Res 2009; 37(Web Server issue):W593-599.

Schrauwen I, Helfmann S, Inagaki A, Predoehl F, Tabatabaiefar MA, Picher MM, Sommen M, Seco CZ, Oostrik J, Kremer H, Dheedene A, Claes C, Fransen E, Chaleshtori MH, Coucke P, Lee A, Moser T, Van Camp G. A mutation in CABP2, expressed in cochlear hair cells, causes autosomal-recessive hearing impairment. Am J Hum Genet. 2012 Oct 5;91(4):636-45.

Answers

Part 2

Question 4: In which chromosome(s) were regions of homozygosity detected at threshold ≥0.8?

HM regions were detected on chromosomes 1, 9, 11 and 16.

Question 5: Using the .vcf genotypes do you see a homozygous region in the previously mapped locus? If yes, which positions on chr11 flank the homozygous region?

Yes, HM identified a homozygous region on chr11:65,810,239-67,128,712 which is smaller than the previously mapped locus.

Question 6: Which of the variants at these positions is likely causal of ARNSHI in family 4545?

The position at chr11: 67287263is the site of a *CABP2* splice variant c.637 +1 G>T that was identified to be causal of hearing impairment in family 4545 and is included in the HM region. However, by default, HM reassigns the variant alleles as 'A' or 'B', so the researcher would have to check the actual .vcf for the correct allele information and perform additional annotations.