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5. You have performed GWAS and found that nearly half of the genome appears to be significantly associated with your trait of interest. What is going on? Think of multiple possible explanations, indicate under which conditions they would be likely, and how we can test them. [25 points]

Many complex traits, such as height of an individual or immunity against diseases, are polygenetic, i.e., these traits are determined by the aggregate effect of many genes. This could be explained by Omnigenic model proposed by Boyle et al (2017). According to the models, a few genes have large effect (core genes) but a large number of peripheral genes have small effect due to highly interconnectedness (small world property) of gene regulatory network. But because the peripheral genes are large in number, collectively they might explain a considerably more variation in trait than core genes. Because of this GWAS study may show half of the genome might be significantly associated with trait of interest.

Another possibility is that the core genes might be linked to many other neighboring sites via linkage disequilibrium, which may lead to significant association between genes and traits. LD can be tested by doing rolling window analysis.