# Assignment 3

“Genome-wide association studies have greatly improved our understanding of the genetic basis of disease risk and genetic architecture. The fact that they tend not to identify more than a fraction of the specific causal loci has led to divergence of opinion over whether most of the variance is hidden as numerous rare variants of large effect or as common variants of very small effect.” (Rare and common variants – twenty arguments – Greg Gibson)

The content referred by Gibson in 2012 is the main topic of this paper discussion, where we confront the hypothesis ‘Common Disease, Common Variant’ (CDCV) by looking at 3 different articles and their following results. The CD/CV hypothesis was first introduced by Reich and Lander in the paper **‘On the allelic spectrum of common disease’** (2010). The two other papers **‘The genetic architecture of type 2 diabetes’** and **‘Large-scale genomics unveils the genetic architecture of psychiatric disorders’** are real data analysis that go in favor and against the CD/CV hypothesis.

To make this discussion more interesting please try to answer the following questions in groups and make sure you understand the main points and conclusions stated in each article. Have a good exercise! ☺

## Article 1: R ’On the allelic spectrum of common disease’

1. **What is the Common disease/ Common variant hypothesis?**
2. **What does the author mean when using the terms ‘simple allelic spectrum’ and ‘diverse allelic spectrum’?**
3. **What are the forces that balance the frequency of a disease allele? And what is the intensity of those forces in rare or common diseases?**
4. **Why does the spectrum of a disease loci shift from simple to complex after a bottleneck to a population expansion?**
5. **How population structure affects the disease allele frequency?**
6. **What would be the implications in the association studies if the CD /CV hypothesis is correct for human populations?**

## Article 2: The genetic architecture of type 2 diabetes

1. **Why did the authors hypothesized that lower frequency variants could explain the remainder heritability of type II diabetes (common disease)? How this hypothesis disagrees with the CD/CV hypothesis?**
2. **What were the strategies used by the authors to make sure they could detect causal rare variants of T2D?**
3. **What can affect the power of detection of causal rare variants? How did they improve their power of detection?**
4. **Why did the consortium collect individuals from five different ancestry groups? How does this relate to question 5?**
5. **What is the Goldstein (2010) hypothesis referred in the article?**
6. **How did the authors decide to investigate the genetic architecture of the trait? What are their final conclusions?**

## Article 3: Large-scale genomics unveils the genetic architecture of psychiatric disorders

1. **What is the genetic architecture of a trait and why is that so important in association studies?**
2. **What is the expected distribution of complex traits?**
3. **What was the possible reason for detection of 7 causal loci of schizophrenia (SCZ)?**
4. **Are there any other possible candidate variables than SNPs that could help us to understand the problem of ‘missing heritability’?**
5. **Why is still not possible to understand the overall contribution of rare variants to the heritability in the case of psychiatry disorders?**
6. **How do you think the psychiatric genomics consortium have contributed in the human genetics research?**