**Questions and discussion items Freedman et al. (2011) 43: 513-518**

1. What is a major reason to perform a genetic study and identify strong risk genes?
2. What is the greatest challenge after a genome wide association study?

Despite these successes in identifying risk loci, the causal variant and/or the molecular basis of risk etiology has been determined for only a small associations fraction of these associations

1. Why is it important to identify the causal variant and/or the molecular basis of risk etiology

Biological insights can then be translated to clinical benefits, including reliable biomarkers

and effective strategies for screening and disease prevention.

**Mechanistic insight** will offer further the opportunity to identify and test potential evidence based treatment options with the ultimate goal to enhance clinical OA development.

1. What is the underlying hypothesis with respect to how SNPs exert their effect i.e. confer risk to complex diseases?

Our hypothesis is that the trait-associated alleles exert their effects by influencing transcriptional output (such as transcript levels and splicing) through multiple mechanisms.

1. What are 2 ways to assess the functionality / effect of a SNP?
2. What is different between these two methods.
3. What is a Tag SNP?
4. How could the SNP affect the epigenetically regulated gene expression?
5. What would be criteria for a strong candidate gene?
6. If a strong candidate gene is selected, likely to be affected by the genome wide association signal what would be next steps to proof causality to the disease.

