Using whole-exome sequencing for identification of disease-causing genetic variants in patients with impaired immune function
Do genetic defects play a prominent role in explaining phenotypes with increased susceptibility to infectious complications?

Individuals with increased susceptible to infections **not** caused by known factors (immunosuppresive therapy, HIV, etc)
De novo mutations: Mutations that are not inherited from the parents

Parent-offspring trio sequencing

Impaired immunity

Germline de novo mutations occur in egg or sperm cell before fertilization or immediately after fertilization
Homozygous rare recessive variants may be causative of disease

Parent-offspring trio sequencing

Impaired immunity

a: common allele
b: rare allele (<1% in population)
Overview of experimental steps for whole-exome sequencing

Exome contains 85% of disease-causing mutations in Mendelian disorders (Rabbani, *J Hum Genet*, 2014)
Mutations do not come with information about their interpretation: Various \textit{in silico} evidence can be used to assess potential pathogenicity

- Cohort mutation rate relative to background population
- Gene function
  - Known disease gene
  - Gene in disease-associated pathway
  - Gene expressed in relevant tissue
- Mutation impact
  - Mutation type
  - Evolutionary conservation
  - Protein domain prediction
- Mutations in patients
  - Multiple patients with mutations in same gene/pathway
Relationship between the size of the mutational target and the frequency of disorders caused by *de novo* mutations

**Frequency of disorder**
- Extremely rare
- Rare
- Common

**Size of mutational target**
- Locus specific
- Few genes
- Many genes

- Schinzel-Giedion syndrome
- Complex I deficiency
- Intellectual disability
Questions for discussion

Is this an illusion?

What is the throughput of the relevant patients at Rigshospitalet?

Is both patients and their parents available?

How similar are the patient phenotypes?

Are phenotypes likely caused by *de novo* mutations or rare homozygous recessive variant?

What is the heterogeneity of disease-causing genetic variants?

Is it possible to correlate specific genetic defects with susceptibility to infection from certain microbial pathogens?