Indirect diagnostics of hereditary diseases by nucleic acid analysis

One of the two principles in DNA analysis. This approach combines information from family pedigree together with molecular examination of a polymorphism in tight genetic linkage (the closer the better) with the gene that is causative for the disease in question. We do not know the exact DNA mutation, but we see how the trait was inherited in a family because disease gene cosegregates with specific value of polymorphism.

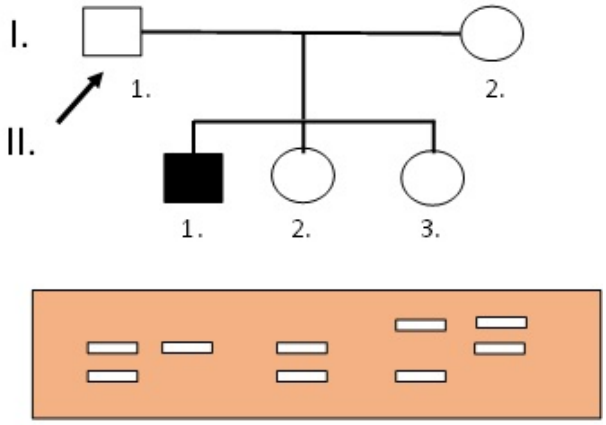
Polymorphic locus that is in linkage with a gene is called a **marker**. It is beneficial to use polymorphism (SNP, STR or small indels), because then there is a higher chance that examined person is a heterozygote. Each analyzed family must be re-examined, because polymorphism alleles are unique for every person and family.

Indirect DNA analysis can be performed in AD, AR, XD and XR diseases. Results of this technique may address the **recurrence risk of a disease in a family**. In situation where there are **more possible candidate genes** for one phenotype, like in Polycystic kidney disease (PKD), there are genes PKD1 and PKD2. The examiner will first perform indirect DNA analysis to ascertain which gene there should be directly examined afterwards. In time of panel NGS sequencing is this method is being overcome.

Many phenotypically distinct families provide valuable tool in candidate gene identification. In indirect DNA analysis a region of DNA that segregates with a disease in a family may serve as tool for further direct methods that search for new candidate genes associated with the disease. We use the term GWAS, that stands for whole genome association studies, that uses SNP data and affected/not affected family member comparisons.

We use the term **informative** for indirect DNA analysis, that provided information for evaluation of the risk or that assigned a gene to a phenotype. If the value of polymorphism did not provide such final statement, we use the term **non-informative**. Preferentially polymorphic intragenic markers are used to exclude the possibility of crossing over between disease gene and a marker.

Example: Family pedigree, AR metabolic disease, II/3 is a newborn, result of indirect DNA analysis, marker is an intragenic STR polymorphism



Evaluation: The question was: Is the girl II/3 in risk of developing metabolic disease as her older brother? We see that the affected boy II/1 is a homozygote for marker polymorphism. Both of these alleles must represent the a/a allele of the disease gene that he received from his parents. Girl II/3 received a different marker allele from her mother (linked with A allele of the gene) and a different marker allele from her father (linked with A allele of the gene), she is thus of AA genotype. The middle child is a heterozygote Aa receiving disease allele a from her mother. This analysis was informative.

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