Genetik – Klausurvorbereitung

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1 Genetic disorders

Genetic disorders, that make up for a bout 30% of newborn-diseases and probably even more for elder people, can be ordered into groups according to the location and dominance

1.1 single gene disorders

Single gene defects can be mapped to one specific gene or sometimes even further to one defined genetical location or basepair. They usually follow simple mendelian laws. In man, about 5000 such defects have been characterised and can be looked up in the *"Online Mendelian Inheritance in Man"* Database.
The frequency (percentage of affected in a population) can be calculated using the *Hardy-Weinberg* distribution:

$$p^2 + 2pq + q^2 = 1$$

where p is the frequency of the more common allele and q is the frequency of the les common one.

1.1.1 Autosomal recessive

So called *"Loss of function"* diseases. Can be common in populations. Haemochromatosis is as frequent as 1 in 500 in some parts of Europe. This especially means that the heterozygote form is very spread, e.g. 1 in 22 people is a carrier for cystic fibrosis in western Europe. Some heterozygote phenotypes can be an advantage in a given environment, like some anaemia's in Africa.

1.1.2 Autosomal dominant

"Gain of function" disorder. reproduction of a carrier means that the chance a child is affected to is 50%. Example: Huntington's disease.

1.1.3 Gonosomal diseases

Located on the X-Chromosome. Normally, women are not or just very mildly affected, e.g. the mutation is recessive. Some rare diseases are dominant, so they are passed from a father to all his daughters but to none of his sons. Due to X-inactivation in early development of women, they sometimes show mosaic-phenotype of the diease.

1.1.4 Complexity of single-gene disorders

Investigating on single-gene disorders is not as straightforward as it seems. Some fact make it difficult to locate the source of a disease from a given pedigree:

1.1.4.1 *genetic heterogeneity*

completely different mutations can have similar phenotypes (*Non-Allelic*) and vice versa, diverging phenotypes can have closely related sources(*Allelic*).

1.1.4.2 *Penetrance*

The frequency, with which the disease will occur in people inheriting the allele. Some disorders do not inevitably cause a phenotype. They are said to have *incomplete penetrance*.

1.1.4.3 *Expressivity*

The severity of the disease can vary, e.g. in sickle-cell anaemia.

1.1.4.4 *mosaicism*

see above.

1.1.4.5 *Phenocopy*

Environmental effects can sometimes show the same phenotype as genetical ones, e.g. deafness of a child can be hereditary or due to *rubella virus* infection of the mother

1.1.4.6 *Anticipation*

Some diseases show an increase in severity over generations, e.g. the mother is just very slightly affected with *muscle dystrophy, but children are handicapped.*

1.1.4.7 Genomic imprinting

genomic imprinting is said to occur when the expression of an allele is dependant on the parent from which it was inherited. The mechanism is not absolutely clear but is thought to be related to DNA-methylation.

1.2 multifactorial disorders

Most diseases that are genetically influenced are also being affected by environmental effects. To measure the extent of the genetical influence, you can compare monozygotic twins to dizygotic ones to the population concerning the phenotype frequency. Out of this emerges a value called *heritability*. It gives information on how important genetic factors are for a disease. Interesting enough, the heritability for TBC is higher then the one for general breast cancer!

1.3 Chromosomal imbalance

1.3.1 non-disjunctions

Segregation-failures in chromosomes either lead to trisomias or monosomias.

1.3.2 translocation

A form of chromosome rearrangement, i.e. an exchange of segments between non-homologous chromosomes. If the evolving chromosomes are inherited together, chances are good that it is viable, as no information was lost, just the place of the gene changed.

1.4 Mitochondrial diseases

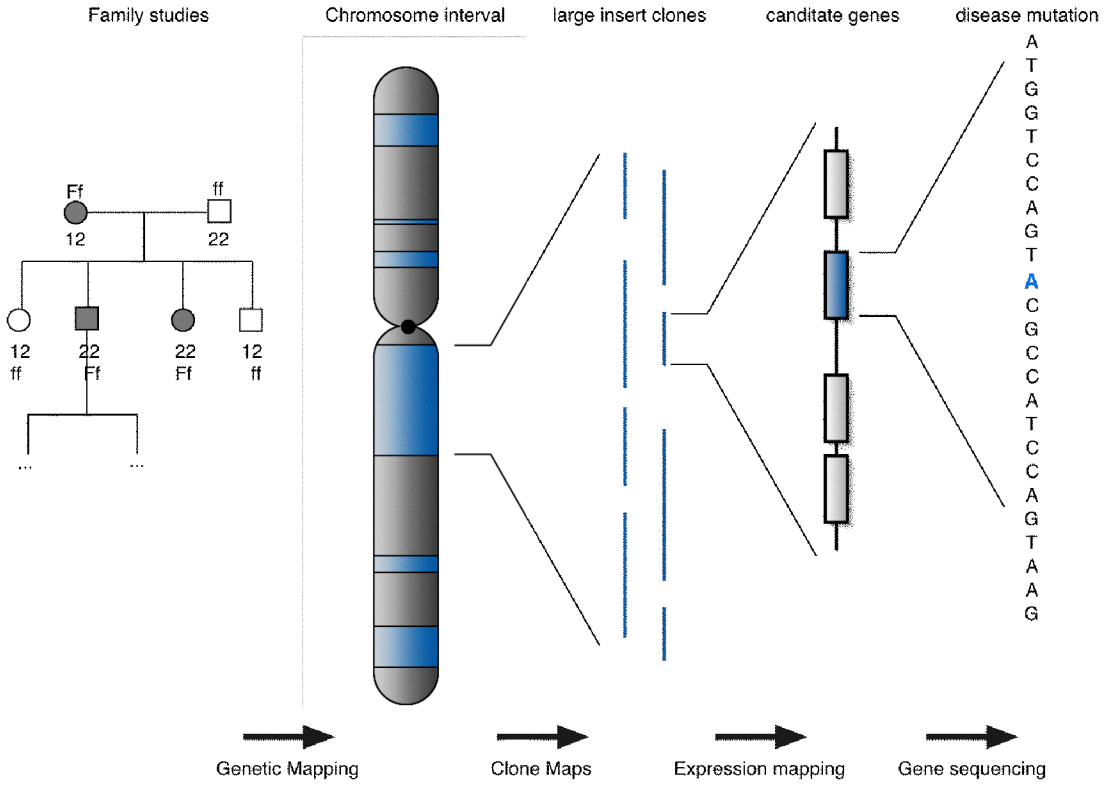
Mitochondria have 37 genes, of which 22 code for tRNA, 2 for rRNA. The remaining 13 genes mostly code for proteins of the oxidative phosphorilation. Mutations and disorders in Mitochondria are much more likely than in the nuclear DNA, because they lack proof reading and introns. Also, the oxidation taking place in them releases O^-radicals that can affect the DNA. Mutations in mitochondrial DNA is thought to progress the aging-process. Naturally, mutations in Mitochondria mainly affect the energy-metabolism of the cell. They thus affect muscle-function as well a nerve-activity (which needs a lot of ATP), but can also have effects on glands and digestion.

A normal cell hosts about 10000 mitochondria. They needn't have the same DNA, in which case they'd be called homoplasmic, but if a mutation takes place in parts of the Mitochondria-population, a cell can be heteroplasmic. Tendency is that cells return to homoplasmicity after a few generations, though.

Each Mitochondrium can have multiple copies of its own DNA-set, to. All this means that the mosaic-patterning of an individual with mitochondrial disorders can be widespread.

2 Mapping

There is a great need in science and medicine to be able to determine the gene(s) responsible for a phenotype, locate them on the DNA, get their sequence and thus being able to investigate on the proteins involved. To do so, you need maps that describe the Genome in a way that you can assign locations for an unknown target. These locations need not be physical, i.e. a defined basepair on a chromosome, but can also be of a genetic type, e.g.: recombined twice as often together with marker 1 as with marker 2. In that way, you can easily go from one map to another focusing on more details.



2.1 STS as the link between genetic and physical maps

STS stands for *Sequence tagged site*. Originally, STS where invented to help sequencing chromosomes by connecting YAC's to shotgun-clones. An STS is generated by shotgun-cutting a Chromosome into small pieces and then expressing these in a clone which can later be sequenced. Then you take a clone, design primers for a part of the inserted sequence of about 400bp and amplify it using PCR. Finally, you can take your primers and use them on the YAC-Chromosome. If you get a result, it is very likely the YAC-Chromosome-piece contains you STS, so you can assign the sequenced clone-piece to that chromosome part, or vice versa. If 2 YAC's react to the STS, their sequence is likely to overlap.

Sof far STS are only useful for physical mapping, because the piece of DNA they tag to is probably not heterozygote. To use STS as markers for genetic mapping, as described below, you need a piece of chromosomal DNA that is very likely to be *different* between individuals, but still hereditary. The most common sequence-type that matches these needs are *microsatellites* (parts of DNA that cosist of *Tandem repeats*, i.e. short sequences that are repeated over and over).

2.2 Genetic maps

Genetic maps make a statement about the frequency of a marker and a target being expressed together. This is only significant if they lie on the same Chromosome at locations neither too far away nor too closely related. Then the statistical frequency of recombination gives you a genetic distance measured in *cM* (centiMorgan). If marker and target are not linked, you get a recombination frequency of 50%, which means it is equally probable to have the marker or not, as it resides on a different chromosome and is inherited independently.

This concept demands a marker that is *polymorphic*, i.e. phenotypically distinguishable. Owners of the target-gene need to differ in the marker-gene somehow to make a statement about the linkage of the genes. When using STS, which are so called *neutral molecular polymorphisms* (which means that you don't see a phenotype expressed, but still have a polymorphism), you calculate the linkage between the target-gene and some microsatellites. Their size is a characteristic and can be used as a marker when analysing pedigrees.

2.2.1 Map unit

The unit of genetic maps is a *centiMorgan*. One cM is defined as a recombination-fraction of 0.01 (which means 1 out of 100 gametes is recombinant).