Genetic Diseases of the Eye

- Retinal & RPE Dystrophies
- Vitreoretinopathies
- Primary Glaucoma
- Optic Atrophies
- Ocular Cancer: Retinoblastoma, Uveal Melanoma
- Anterior Segment Malformations
- Corneal Dystrophies
- Cataract
- Ocular Mucle: Ptosis, Ophthalmoplegia
- Anophthalmos/ Microophthalmia
- Myopia/ Hyperopia

Pathology of the Eye: Genetics
Sensory Systems: Basics and Principles I
Epidemiology - Terminology

- **Prevalence**
  total number of cases of a certain disease in a defined population at a given time

- **Incidence**
  total number of new cases of a certain disease over a defined time period (typically one year) in a defined population

Epidemiology of Retinal Disorders

**Hereditary Retinal Disorders**

- **Prevalence:**
  1:1,490 *(Northern France)*
  (Puech et al., 1991, J Fr Ophthalmol 14: 153-164)

- **Prevalence in Children:**
  1:10,000 *(Denmark)*,

- **Incidence (Legal Blindness; VA<1/50):**
  1:192,300 *(Württemberg-Hohenzollern 1994)*
  (Krumpaszky et al., 1999, Ophthalmologica 213: 176-182)
Epidemiology of Retinal Disorders

Hereditary Retinal Disorders primarily affect Children and young Adults

Variability of Hereditary Retinal Disorders
# Variability of Hereditary Retinal Disorders

## Main Clinical Parameters for Categorization
- **Course:** Stationary <-> Progressive
- **Age of Onset:** congenital <-> late manifesting
- **Localization:** central <-> peripheral
- **Function:** Rod <-> Cone
  - Photoreceptor <-> Synapse
  - Neuroretina <-> Ret. Pigment Epithelium
- **Morphology:** Degeneration <-> Dysfunction
- **Symptomatic:** non-syndromic <-> syndromic

## Prevalence of Some Retinal Disorders

- **Retinitis pigmentosa**
  - Prevalence: 1:2,500 – 1:4,000

- **Stargardts Macular Dystrophy**
  - Prevalence: ~1:10,000
  - (Blacharski, 1988, in Newsome: Retinal dystrophies and degenerations, Raven Press, NY, p.135-159.)

- **Achromatopsia**
  - Prevalence: ~ 1:30,000 – 1:50,000
  - (Francois, 1961, Heredity in Ophthalmology. CV Mosby)
Patient L.M., 36 years old, Locksmith

Nightblind since late childhood, complaints about progressive Visual Problems, worries about his driving license

Visual Acuity: 0.5 / 0.4
Visual Field: concentric reduced Sensitivity
Color Vision: normal
Electroretinography:
- scotopic – severely reduced Responses
- photopic – in lower normal Range
Funduscopy: “bone-spicule”-like pigmentary Deposits in the Periphery, pale Optic Nerve Head, narrow retinal vessels
Light opaque Lense
Retinitis pigmentosa

- ~ 40-50% sporadic
- ~ 20-30% autosomal recessive
- ~ 10-25% autosomal dominant
- ~ 6-18% X-chromosomal recessive
- Very rare: maternal, digenic

Fishman 1978, Arch Ophthalmol 96: 822-826
Boughman et al., 1982, Am J Hum Genet 32: 223-235

Modes of Inheritance

- **Autosomal Dominant**
  One mutant Allel (a) is sufficient for the Expression of the Trait (e.g. disorder)
  - affects Males and Female with equal Frequency
  - an Affected is always Child of an Affected
  - 50% risk for each Child of an Affected

![Genetic Diagram](attachment:genetic_diagram.png)
Autosomal Recessive

- The Presence of two mutant Allels (a) are required for the Expression of the Trait (e.g. disorder)
- affects Males and Female with equal Frequency
- Parents are in typically unaffected (Heterozygote)
- 25% risk for each Child of a heterozygous Couple

X-chromosomal Recessive

- sole Presence of a mutant Allels (a) [in males; XY] or the Presence of two mutant Alleles [in Females, XX] is required for the Expression of the Trait (e.g. disorder).
- affects most exclusively Males
- no direct male-to-male Transmission
- 50% risk for each Son of a female Carrier
**Modes of Inheritance**

- **Digenic (co-dominant)**
  - The Presence of two mutant alleles (a, b) at independent loci is required for the expression of the trait (e.g., disorder).
  - affects Males and Females with equal Frequency
  - an Affected may be Child of an Affected
  - 25% risk for each Child of a double heterozygous Couple

- **Maternal (mitochondrial)**
  - A mutant allele (a) is required for the expression of the trait (e.g., disorder) and is exclusively transmitted via the mother.
  - affects Males and Females with equal Frequency
  - an Affected is always Child of an affected Mother
  - no male-to-offspring Transmission
  - 100% risk for each Child of an affected Mother
Heterogeneity in Mode of Inheritance

- Congenital Stationary Nightblindness
  X-L, AR, AD
- Cone Dystrophy
  X-L, AR, AD
- Stargardt Macular Dystrophy
  AR, AD
- Leber Congenital Amaurosis
  AR
- Usher Syndrome
  AR
- Best Vitelliforme Macular Dystrophy
  AD

Genetic Terminology

- **Locus**
  Physical or genetic Position of a Trait, Gene or DNA Sequence on a Chromosome.

- **Allele** (short for “allelomorph”)
  One of a series (two or more) of distinguishable Variants of a Locus on homologous chromosomes.

- **Genotype**
  (In a diploid Organism two copies of each Gene/DNA Element): Allelic Composition for a certain Gene or DNA Element on homologous chromosomes:
  - Homozygous/Homozygosity – Identity of Alleles
  - Heterozygous/Heterozygosity – different Alleles
  (Hemizygous/Hemizygosity – only one Allele present)
**Progress in Gene Mapping & Gene Identification**

**Locus Heterogeneity – AD Retinitis Pigmentosa**

<table>
<thead>
<tr>
<th>Locus</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Prevalence</th>
</tr>
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<tbody>
<tr>
<td>RP4</td>
<td>3q22</td>
<td>RHO</td>
<td>15-26%</td>
</tr>
<tr>
<td>RP7</td>
<td>6p21</td>
<td>RDS</td>
<td>3-9%</td>
</tr>
<tr>
<td>RP1</td>
<td>8q12</td>
<td>RP1</td>
<td>3-6%</td>
</tr>
<tr>
<td>RP13</td>
<td>17q13</td>
<td>PRPF8</td>
<td>3-6%</td>
</tr>
<tr>
<td>RP11</td>
<td>19q13</td>
<td>PRPF31</td>
<td>5-10% (21% in UK)</td>
</tr>
<tr>
<td>RP18</td>
<td>1q21</td>
<td>PRPF3</td>
<td>1-3%</td>
</tr>
<tr>
<td>RP10</td>
<td>7q32</td>
<td>IMPDH1</td>
<td>2-5%</td>
</tr>
<tr>
<td>RP27</td>
<td>14q11</td>
<td>NRL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19q13</td>
<td>CRX</td>
<td></td>
</tr>
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<td></td>
<td>17q25</td>
<td>FSCN2</td>
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<tr>
<td>RP17</td>
<td>17q23</td>
<td>CA4</td>
<td></td>
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<tr>
<td></td>
<td>1q22</td>
<td>SEMA4A</td>
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<tr>
<td>RP37</td>
<td>15q23</td>
<td>NR2E3</td>
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<tr>
<td>RP31</td>
<td>9q21</td>
<td>TOPORS</td>
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<td>RP42</td>
<td>7p15.3</td>
<td>KLHL7</td>
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<td>RP9</td>
<td>7p14</td>
<td>SNRNP2000</td>
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Source: Retinal Information Network (RETNET), [http://www.sph.uth.tmc.edu/Retnet/](http://www.sph.uth.tmc.edu/Retnet/)
### Locus Heterogeneity – AR Retinitis Pigmentosa

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
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<tbody>
<tr>
<td>RHO</td>
<td>3q22</td>
</tr>
<tr>
<td>PDE6A</td>
<td>5q33</td>
</tr>
<tr>
<td>PDE6B</td>
<td>4p16</td>
</tr>
<tr>
<td>SAG</td>
<td>2q37</td>
</tr>
<tr>
<td>CNGA1</td>
<td>4p12</td>
</tr>
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<td>CNGB1</td>
<td>16q13</td>
</tr>
<tr>
<td>RPE65</td>
<td>1p31(RP20)</td>
</tr>
<tr>
<td>RLBP1</td>
<td>15q26</td>
</tr>
<tr>
<td>ABCA4</td>
<td>1p22(RP19)</td>
</tr>
<tr>
<td>NRL</td>
<td>14q11</td>
</tr>
<tr>
<td>EYS</td>
<td>6q12</td>
</tr>
<tr>
<td>PROM1</td>
<td>4p15</td>
</tr>
<tr>
<td>SPATA7</td>
<td>14q31</td>
</tr>
</tbody>
</table>

+ 4 mapped Loci (RP22, RP28, RP29, RP32)

### Locus Heterogeneity – Usher Syndrome

**Usher Syndrome (AR):**

Typ 1: RP + congenital Deafness + Ataxia

Typ 2: RP + Deafness (HF)

Typ 3: RP + progressive Hearing Loss

<table>
<thead>
<tr>
<th>Locus</th>
<th>Chrom.</th>
<th>Gene</th>
<th>Locus</th>
<th>Chrom.</th>
<th>Gene</th>
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<td>?</td>
<td>USH2A</td>
<td>1q41</td>
<td>Usherin</td>
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<td>USH1B</td>
<td>11q13</td>
<td>MYO7A</td>
<td>USH2B</td>
<td>3p23</td>
<td>?</td>
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<tr>
<td>USH1C</td>
<td>11p15</td>
<td>Harmonin</td>
<td>USH2C</td>
<td>5q14</td>
<td>MASS1</td>
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<td>USH1D</td>
<td>10q22</td>
<td>CDH23</td>
<td>USH2D</td>
<td>9q32</td>
<td>Whirlin</td>
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<tr>
<td>USH1E</td>
<td>21q</td>
<td>?</td>
<td>USH3A</td>
<td>3q21</td>
<td>?</td>
</tr>
<tr>
<td>USH1F</td>
<td>10q11</td>
<td>PCDH15</td>
<td>USH3B</td>
<td>20q</td>
<td>?</td>
</tr>
<tr>
<td>USH1G</td>
<td>17q24</td>
<td>SANS</td>
<td>USH3B</td>
<td>20q</td>
<td>?</td>
</tr>
</tbody>
</table>
But also: Unique Disease Loci

- **Stargardt Macular Dystrophy**
  - AR  ABCA4  1p21-p22

- **Best Vitelliforme Macular Dystrophy**
  - AD  VMD2  11q13

- **Sorsby Fundus Dystrophy**
  - AD  TIMP3  22q12-q13

- **Cone Dystrophy with Supernormal Rod Response**
  - AR  KCNV2  9p24

---

How to identify a „Disease Gene“?

- **Candidate Gene Analyses**
  - Knowledge-based Approach, Hypothesis-driven
  - Reverse Genetics: From Gene to Function (Malfunction)

Mutation Screening in Genes which based on their specific Function and/or Expression in the affected Organ/Tissue/Cell are considered as potential Cause of a certain Disorder.

For Instance: Genes for Components of the Phototransduction Cascade (Rhodopsin, Transducin, Phosphodiesterase, CNG-Channel), Genes involved in the retinal Vitamine A Metabolism and ~ transport (ABCA4, LRAT, RDH5)
How to identify a „Disease Gene“?

- **Linkage Analyses & Positional Cloning**
  - Hypothesis-free Approach
  - Forward Genetics: From Phenotype to Gene

  Identification of a „Disease Gene“ based on its Location in the Genome.

  Hypothesis-free Approach overcomes the (still) limited Knowledge of Gene Function, Cellular Processes & Disease Mechanisms.

  „You can identify a Gene on which nothing is known or a Gene you never thought it might cause such a disorder“

  For Instance: Genes for ubiquitously expressed Splicing Factors in AD Retinitis Pigmentosa.

---

How to identify a „Disease Gene“?

**Steps in Linkage Analyses & Positional Cloning**

- **Linkage Analyses**
  - Mapping the Disease Locus to a specific Chromosome or chromosomal Region
  - Searching for a Marker that shows a valid Pattern of Co-Inheritance with the Trait in question.

- **Refined Mapping of the Disease Locus through meiotic Breakpoint Mapping**

- **Mutation Screening in Genes that localize to the mapped chromosomal Region**
Mendel’s Third Law (Principle of independent Assortment)

"Alleles for different traits are distributed to sex cells (offspring) independently of one another."

Recombination of traits will appear in the F2 generation in predictable ratios.

Trait 1: Flower Size
Trait 2: Flower Color

But: There are numerous examples in which the expected ratios of parental and recombinant phenotypes in F2 are not obtained.

>> The traits do not segregate independently.

Trait 1: Flower Size
Trait 2: Flower Color

Expected (n=160):
Obtained:
Chromosomes are the physical Units of Inheritance

- Genes (traits) localizing on different Chromosomes segregate independently.
- Genes (traits) localizing on the same chromosome segregate together (i.e. linkage)

Genes (traits) localizing on different Chromosomes segregate independently.
Genes (traits) localizing on the same chromosome segregate together (i.e. linkage)

Recombination events between homologous Chromosomes during Meiosis (Crossover) break this Linkage.

The Probability of a meiotic Recombination depends on the distance of the two Gene (Trait) Loci on the Chromosome.

The smaller the distance - the lower the frequency of recombination.

The frequency of recombination between two Loci is given in cM (centi-Morgan). 1 cM = 1% Recombination
Linkage Analysis relies on both
i) the co-segregation of Traits
ii) the Occurrence of Recombinations.

The Principle Question:
Am I able to establish a Linkage between a new, unknown Trait and a known test Trait?

If I now the chromosomal Localisation of the test Trait, then – in case of Linkage – I can conclude that the unknown Trait also localizes to the same Chromosome.

Autosomal Dominant inherited Disorder

Disorder is linked to ABO blood group, recombination frequency ~ 10%
Today DNA Sequence Variations are used as Marker: Microsatellites, Single Nucleotide Polymorphisms (SNP)

Microsatellite marker D2S2311 on Chromosome 2q11

```
CATGAGCATGGAGTGTCTTTGTTAGTGCCGGAAAGTACTCAAAA
AGCACAATGTGTTGGGGGCAAGTGGCGATAGGGCTTTCTACACAC
ACACACACACACACACACACACACACACACACACACACACACACACAC
GGAAAGAAAATTAGAGGGACATAGCAACCAACCTGGAAAGGGCTCC
CAATGGCCAAAACTGAAGCCATTTGGAAAACCAAATTTTTAAAT
TTAGTATTAGACTAT
```

The number of CA-repeats in this sequence varies in the population !!!!

---

### Linkage Analysis

**Microsatellite marker D2S2311 on Chromosome 2q11**

```
CATGAGCATGGAGTGTCTTTGTTAGTGCC
GGAAAGTACTCAAAAAGCACAATGTG
GGGGGCAAGTGGCGATAGGGCTTTCTA
ACACACACACACACACACACACACACACACACACACACACACACACAC
GGAAAGAAAATTAGAGGGACATAGCAACCAACCTGGAAAGGGCTCC
CAATGGCCAAAACTGAAGCCATTTGGAAAACCAAATTTTTAAAT
TTAGTATTAGACTAT
```

**PCR amplification**

```
Sizing of the DNA fragment on a gel
```

<table>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

---
Microsatellite Marker Segregation in a Disease Pedigree

No Recombination!!: $\phi = 0.0$ – but how reliable is that?

Genome scans

- STS: ~ 400 markers (ABI Prism)
- Mean genetic distance 8.9 cM
- Average heterozygosity 0.76

- SNP: ~ 10,000 markers
- Mean genetic distance 0.32 cM
- Average heterozygosity 0.37
  (Affymetrix 10K SNP array)
**Linkage Analysis**

**How to estimate \( \theta \)?**

- 18 non-recombinants
- 6 recombinants

Intuitively: \( \hat{\theta} = \frac{6}{24} = 0.25 \)

"maximum likelihood principle"

\[
P(\text{Data}(\theta)) = \left( \frac{23}{6} \right)^6 \theta^6 (1-\theta)^8
\]

**Pathology of the Eye: Genetics**

**Sensory Systems: Basics and Principles I**

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**Statistical Considerations of Segregation Data**

(Chance-)Probability: \( \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} = \frac{1}{8} \)
Linkage Analysis

Statistical Considerations of Segregation Data

A

B

A

B

A

B

A

B

A

B

A

B

A

(Chance-)Probability: $\frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} = \frac{1}{1024}$

Linkage Analysis

Statistical Calculations: LOD Scores

$\text{LOD score} = \log_{10} \left( \frac{\text{Likelihood at } \theta}{\text{Likelihood at } \theta = 0.5} \right)$

Rule-of-thumb: For a dominant trait you need 11 informative Meioses to reach a LOD score of $Z = 3.0$ (significance threshold).
**Linkage Analysis**

**Example of a Two Point LOD Score - Table**

<table>
<thead>
<tr>
<th>LOCUS</th>
<th>0.00</th>
<th>0.05</th>
<th>0.10</th>
<th>0.20</th>
<th>0.30</th>
<th>0.40</th>
<th>0.50</th>
<th>LOD</th>
<th>0.60</th>
<th>LOD</th>
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<td>D10S196</td>
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<td>-1.01</td>
<td>-0.01</td>
<td>0.68</td>
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<td>-0.00</td>
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<td>0.00</td>
<td>2.38</td>
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<td>7.60</td>
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<td>1.93</td>
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<tr>
<td>D10S599</td>
<td>1.76</td>
<td>1.61</td>
<td>1.45</td>
<td>1.16</td>
<td>0.74</td>
<td>0.37</td>
<td>0.00</td>
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<tr>
<td>D10S502</td>
<td>-5.42</td>
<td>-0.71</td>
<td>-1.19</td>
<td>-1.32</td>
<td>-0.98</td>
<td>-0.44</td>
<td>-0.17</td>
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<tr>
<td>D10S670</td>
<td>2.11</td>
<td>2.74</td>
<td>2.87</td>
<td>2.59</td>
<td>1.92</td>
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<td>-0.79</td>
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<td>1.59</td>
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<td>0.76</td>
<td>0.08</td>
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<tr>
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<td>3.42</td>
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<td>1.01</td>
<td>0.11</td>
<td>2.79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mapping of Meiotic Breakpoints**

- Reconstruction of the Phase of subsequent Marker Alleles
- Reconstruct Recombination Events
- Define Phase Segment that is shared by all Affecteds and absent in Unaffecteds

Pathology of the Eye: Genetics
Sensory Systems: Basics and Principles I
Problems using Linkage Analysis

- To obtain a significant LOD Score large Families are required:
  - e.g. 11 informative meiosis
  - = 6 Affecteds for an autosomal recessive Trait
  - = 4 Affecteds + 3 Unaffecteds
  - = 3 Affecteds + 5 Unaffecteds

- Combining unrelated Families for Linkage Analysis is possible (additive)

- Locus Heterogenity will blast your results
Homozygosity Mapping

- For autosomal recessive Traits
- Can be applied on small Families or even single Patients
- Requires known or suspected Consanguinity of Parents
- Hypothesis:
  Patient is homozygous for a Mutation due to IBD (identity-by-descent)
- In addition to the Mutation the Patient is also homozygous for the flanking chromosomal region

Identify Regions of Homozygosity on the Genome
- High resolution SNP chips (e.g. 250k)
- Typically several Regions (on different chromosomes) of several Megabases
Mutations

(Disease) Allele Heterogeneity
Presence of multiple Alleles of a Gene that give rise to the same (non-wildtype) phenotype.

In the Context of „disease Genes“:
Different Mutations in a certain Gene cause the same Disorder.

This is the rule in Retinal Disorders and also in most other inherited Disorders

Mutations: CNGA3

Protein Truncation
Substitution
### Frequency of Mutations: CNGA3

![Frequency of Mutations: CNGA3](image)

- **R283W**
- **R277C**
- **R436W**
- **F547L**

### Types of Mutations

- **Missense Mutation**
  - Amino Acid Substitution
  - \(-\text{GGA} \rightarrow -\text{AGA} = \text{Gly} \rightarrow \text{Arg}\)

- **Nonsense Mutation**
  - Change into a Stop Codon
  - \(-\text{GGA} \rightarrow -\text{GA} = \text{Gly} \rightarrow \text{Stop}\)

- **Deletion/Insertion**
  - Causes a Frameshift or the loss/gain of Amino Acid Residues
  - \(-\text{GGA AGA GGA C} \rightarrow -\text{GAA GAG GAC} \rightarrow\)
  - \(\text{Gly} \rightarrow \text{Arg} \rightarrow \text{Glu- Glu- Asp}\)

- **Transcript Processing Mutations**
  - Missplicing of primary Transcripts
  - Deletions/Insertions
Types of Mutations: Splicing Mutation

Example:
GNAT2 – Mutation in Achromatopsie

Activation of a cryptic Splice Site upon Mutation in the Intron (+24)

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Dominant Mutations

How to explain the dominant Effect of a Mutation

- Haploinsufficiency
  Single Gene Dose is not sufficient to maintain Function (whole Gene Deletions, early Stop Mutations)

- Gain-of-Function
  Mutant Protein with altered Function or Interaction:
  - permanent Activity, Mislocalization
Reduced Penetrance
The presence of a mutant allele does not always lead to expression of the trait/disease. In particular, in dominant diseases.

Retinitis pigmentosa (AD): PRPF31 (1115-1125del)

Expression level of the WT-allele
### Function of Genes implicated in HRDs

#### Phototransduction Cascade

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhodopsin</td>
<td>RHO</td>
<td>RP, CSNB</td>
</tr>
<tr>
<td>Cone Opsin</td>
<td>OPN1LW</td>
<td>Farbsehdefekte</td>
</tr>
<tr>
<td>Transducin</td>
<td>GNAT1</td>
<td>CSNB</td>
</tr>
<tr>
<td>C-Transducin</td>
<td>GNAT2</td>
<td>Achromatopsie</td>
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<tr>
<td>Phosphodiesterase</td>
<td>PDE6A</td>
<td>RP</td>
</tr>
<tr>
<td></td>
<td>PDE6B</td>
<td>RP, CSNB</td>
</tr>
<tr>
<td>CNG-Kanal</td>
<td>CNGB1/B1</td>
<td>RP</td>
</tr>
<tr>
<td>C-CNG-Kanal</td>
<td>CNGB3/B3</td>
<td>Achromatopsie</td>
</tr>
<tr>
<td>Arrestin</td>
<td>SAG</td>
<td>RP, M.Oguchi</td>
</tr>
<tr>
<td>Rhodopsin Kinase</td>
<td>GRK1</td>
<td>M.Oguchi</td>
</tr>
<tr>
<td>Guanylatcylase</td>
<td>GCY2B</td>
<td>LCA, Cone-Rod Dys.</td>
</tr>
<tr>
<td>GC-Aktivator</td>
<td>GCYATA</td>
<td>Cone Dystrophy</td>
</tr>
</tbody>
</table>

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**Function of Genes implicated in HRDs**

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**Function of Genes implicated in HRDs**

**Vitamine A – Metabolism and Transport**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Gene</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal metabolism</td>
<td>RPE65</td>
<td>LCA, RP</td>
</tr>
<tr>
<td>Retinal-binding protein (RLBP1)</td>
<td>RLBP1</td>
<td>Ret. punctata alb.</td>
</tr>
<tr>
<td>Retinol dehydrogenase (RDH5)</td>
<td>RDH5</td>
<td>Ret. punctata alb.</td>
</tr>
<tr>
<td>Retinol dehydrogenase (RDH12)</td>
<td>RDH12</td>
<td>LCA, RP</td>
</tr>
<tr>
<td>Activator of G-Protein (RGR)</td>
<td>RGR</td>
<td>RP</td>
</tr>
<tr>
<td>Lecithin-cholesterol acyltransferase (LRAT)</td>
<td>LRAT</td>
<td>LCA</td>
</tr>
<tr>
<td>Retinol-flipase (ABCA4)</td>
<td>ABCA4</td>
<td>Stargardt, CRD, RP</td>
</tr>
<tr>
<td>Retinal-binding protein (RBP4)</td>
<td>RBP4</td>
<td>PE-Pathie</td>
</tr>
</tbody>
</table>

**Diagram of the Retinoid Cycle and Phototransduction**

1. **Light** activates **rhodopsin**, which undergoes **phototransduction**.
2. **Rhodopsin** is converted to **all-trans retinal**.
3. **All-trans retinal** is converted to **11-cis retinal**.
4. **11-cis retinal** is converted back to **rhodopsin**.
5. **Rhodopsin** is converted to **all-trans retinal**.
6. **All-trans retinal** is converted to **11-cis retinal**.

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59, 60
The End