Topics

- What is developmental genetics?
- Functional classes of alleles
- Nature of allelic forms
- Genotype/phenotype relationships
- Maternal versus zygotic genetics
- Genetic screens
- Reverse genetics
- Human developmental genetics
“Forward” genetic screens in *Drosophila*

- Whole-animal recessive lethal or mutant
- Enhancer/suppressor
- GAL4/UAS overexpression
- FLP/FRT mosaic (clonal)
- Whole-genome RNAi in cultured cells
An F₁ screen for dominant phenotypic enhancers in a “sensitized” genetic background
Mutations identified by $F_3$ recessive or enhancer/suppressor screens

- wingless
- staufen (maternal)

WT

roundabout

commissure-less

GMR-argos/+,
sprouty
Control of commissural axon projection by **Comm** and **Robo** in the fly embryo

**Comm**: Attractive cue
**Slit**: Repulsive cue
**Robo**: Slit receptor

Robo protein distribution
Commissural axons cross
Non-commissural axons do not cross

Robo downregulated
No down-regulation of Robo

Slit: Repulsive cue
Robo upregulated

Midline
The GAL4/UAS system can be used for targeted mis- or over-expression screens
The FLP/FRT system for generating mitotic clones can be used for $F_1$ recessive loss-of-function screens.
Use of the FLP/FRT system for mosaic (clonal) screens in a specific tissue
Mutations identified by FLP/FRT mosaic screens

“pinhead” screen
A FLP/FRT mosaic (clonal) screen in the female germline
“Reverse” developmental genetics in *Drosophila*

- “Local hopping” of P element transposon
- “Imprecise excision” of P element transposon
- Homologous recombination
- RNAi (whole embryo or tissue-specific)
Homologous recombination ("gene replacement") in *Drosophila*
RNAi in *Drosophila*

[Diagram showing the process of RNA interference (RNAi) in *Drosophila*.]

- dsRNA is injected into the fly, leading to the expression of UAS genes.
- Processing of dsRNA into 21-25 nt sRNA results in target locus degradation, leading to gene silencing.
Only a minority of human fertilization events result in term pregnancies.

<table>
<thead>
<tr>
<th>Event</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>Eggs in contact with sperm</td>
<td>20.0</td>
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<tr>
<td>Successful fertilization</td>
<td>16.8</td>
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<tr>
<td>Successful implantation</td>
<td>13.8</td>
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<tr>
<td>Successful development, fourth week</td>
<td>8.4</td>
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<tr>
<td>Successful development, eighth week</td>
<td>7.0</td>
</tr>
<tr>
<td>Fetuses coming to term</td>
<td>6.2</td>
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Numbers surviving of original 20.
Down syndrome results from trisomy for chromosome 21

Down syndrome is the most frequent genetic disorder in humans
Genes Included in the Down Syndrome Critical Region (DSCR)

- **DSCR1**: overexpressed in Down syndrome; encodes a protein that inhibits calcineurin (major calcium regulatory protein)
- **DSCAM**: alternatively spliced transcript encodes a cell adhesion protein involved in axon guidance
A Challenge to the DSCR Hypothesis

Fragile X syndrome results from expansion and hypermethylation of CGG repeats in the *FMR1* gene

*FMR1* encodes an RNA-binding protein involved in targeting and translation of mRNAs with roles in synapse formation.
Mutations in genes encoding transcription factors are responsible for many human genetic diseases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation phenotype</th>
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<tbody>
<tr>
<td>Androgen receptor</td>
<td>Androgen insensitivity syndrome (Ch. 20)</td>
<td>PAX2</td>
<td>Renal-coloboma syndrome (Ch. 15)</td>
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<td>AZF1</td>
<td>Azoospermia</td>
<td>PAX3</td>
<td>Waardenburg syndrome type 1 (Ch. 13)</td>
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<td>CBFA1</td>
<td>Cleidocranial dysplasia (Ch. 15)</td>
<td>PAX6</td>
<td>Aniridia (Chs. 5, 21)</td>
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<td>CSX</td>
<td>Heart defects</td>
<td>PTX2</td>
<td>Reiger syndrome (Ch. 11)</td>
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<td>EMX2</td>
<td>Schizencephaly (Ch. 23)</td>
<td>PITX3</td>
<td>Congenital cataracts</td>
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<tr>
<td>Estrogen receptor</td>
<td>Growth regulation problems, sterility (Ch. 15)</td>
<td>POU3F4</td>
<td>Deafness and dystonia</td>
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<tr>
<td><strong>Forkhead-like 15</strong></td>
<td>Thyroid agenesis, cleft palate</td>
<td>SOX9</td>
<td>Campomelic dysplasia, male sex reversal (Chs. 15, 20)</td>
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<tr>
<td>GLI3</td>
<td>Grieg syndrome (Ch. 16)</td>
<td>SRY</td>
<td>Male sex reversal (Ch. 20)</td>
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<tr>
<td>HOXA-13</td>
<td>Hand-foot-genital syndrome (Ch. 16)</td>
<td>TBX3</td>
<td>Schinzel syndrome (ulna-mammary syndrome)</td>
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<tr>
<td>HOXD-13</td>
<td>Polysyndactyly (Ch. 16)</td>
<td>TBX5</td>
<td>Holt-Oram syndrome (Ch. 16)</td>
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<td>LMX1B</td>
<td>Nail-patella syndrome (Ch. 16)</td>
<td>TCOF</td>
<td>Treacher-Collins syndrome</td>
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<td><strong>MITF</strong></td>
<td>Waardenburg syndrome type 2 (Chs. 5, 21)</td>
<td>TWIST</td>
<td>Seathre-Chotzen syndrome</td>
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<td></td>
<td></td>
<td>WT1</td>
<td>Urogenital anomalies (Ch. 15)</td>
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</tbody>
</table>
Positional cloning of *PAX6*, the gene associated with *aniridia* in humans
A **candidate gene** approach to identifying the locus associated with **Waardenburg syndrome type 2**

**Waardenburg syndrome type 2:**
deafness, heterochromatic irises, white forelock
Mutations in developmental pathway genes often have pleiotropic effects (multiple defects)