UNIVERSITY OF Cincinnati

Department of Environmental Health College of Medicine

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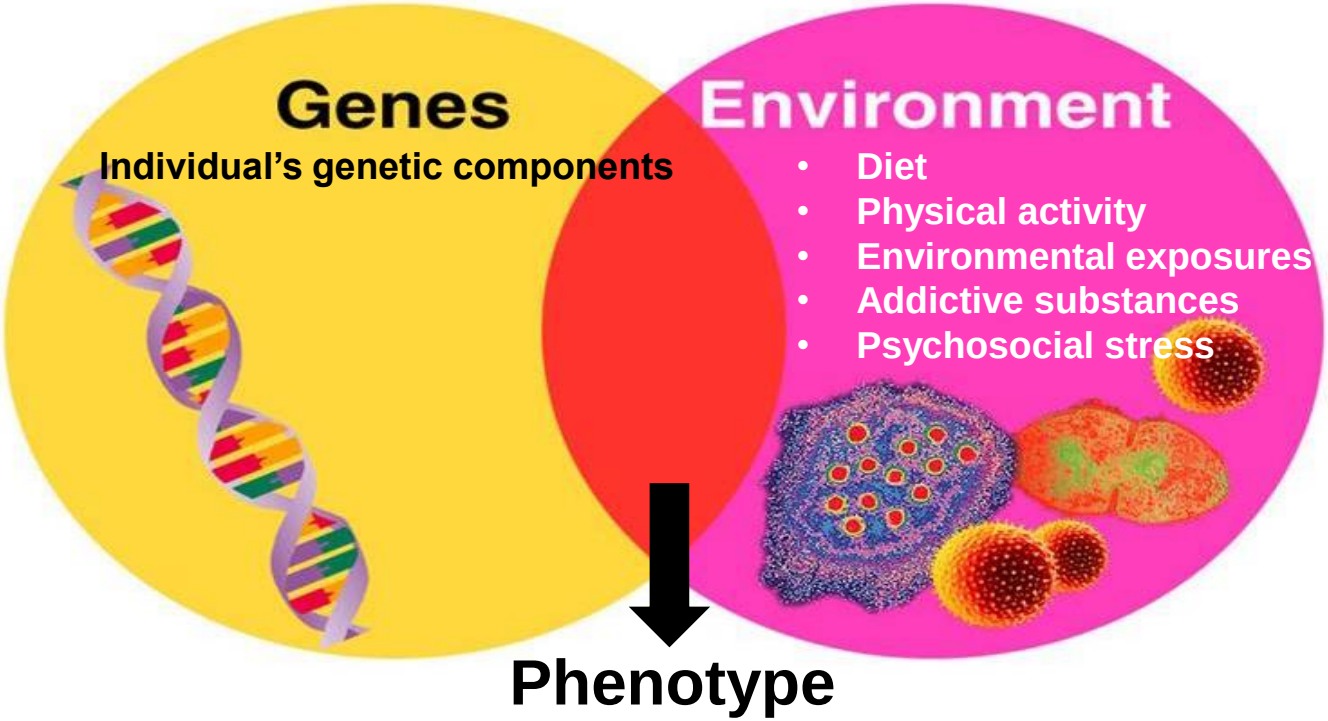
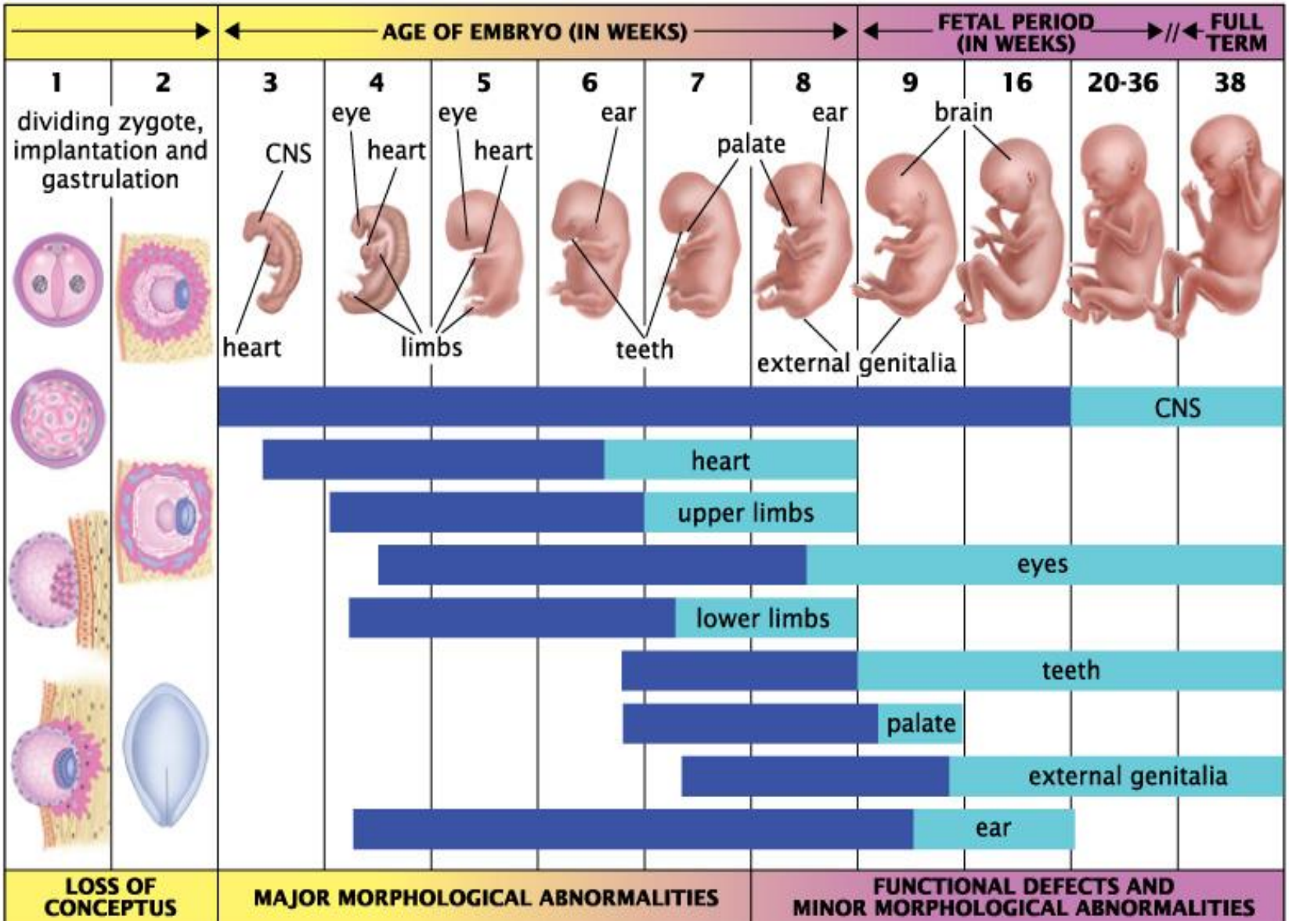
Environmental Genetic and Molecular Toxicology (EGMT)

https://med.uc.edu/eh/divisions/egmt

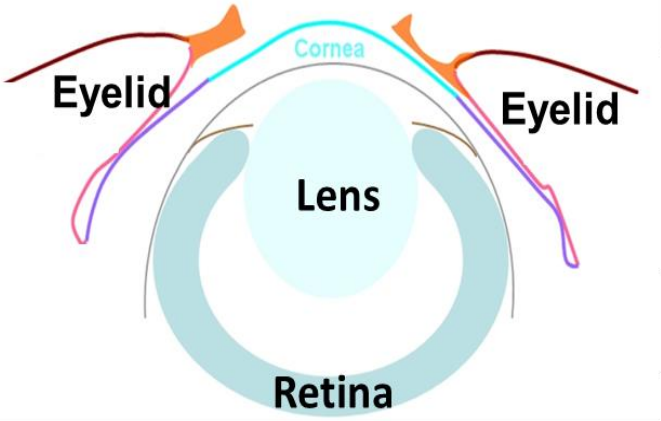


Stages of Mammalian Development



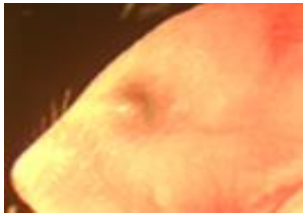
http://www.environment.ucla.edu

Transient Eyelid Closure in Mammals

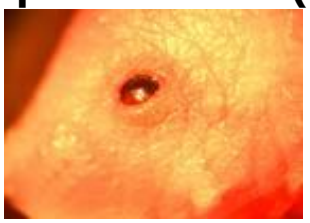


Huang, et. al. Development. 2009 May 15

normal



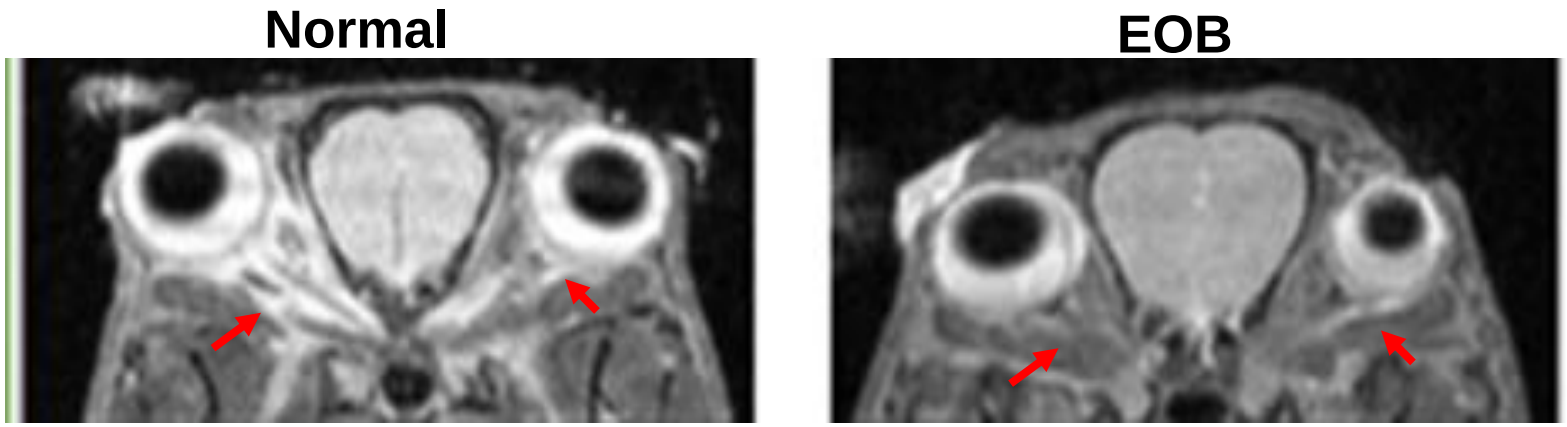
Eye open at birth (EOB)



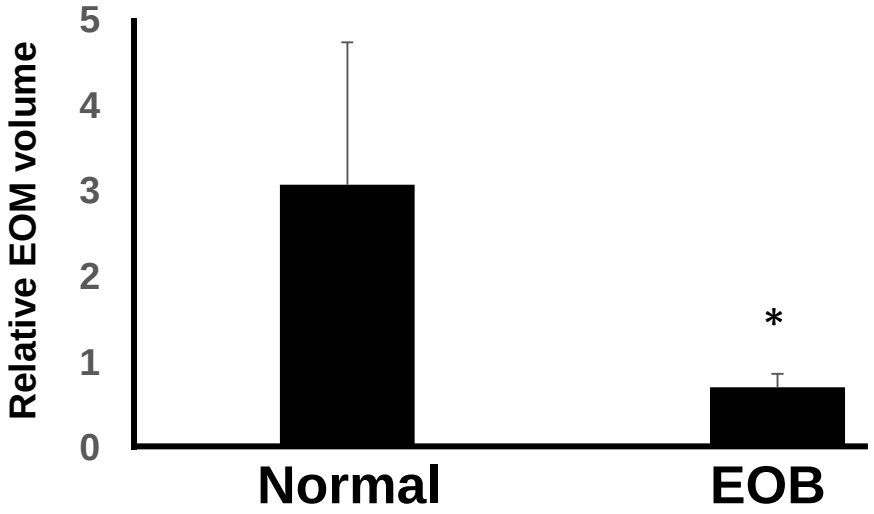
in > 150 genetic mutants

Mouse		Human
E11.5		6-8 weeks
E15		
E15.5		
E16		2-3 months
E18.5		
Birth		
Postnatal day 12-14		4-7 months

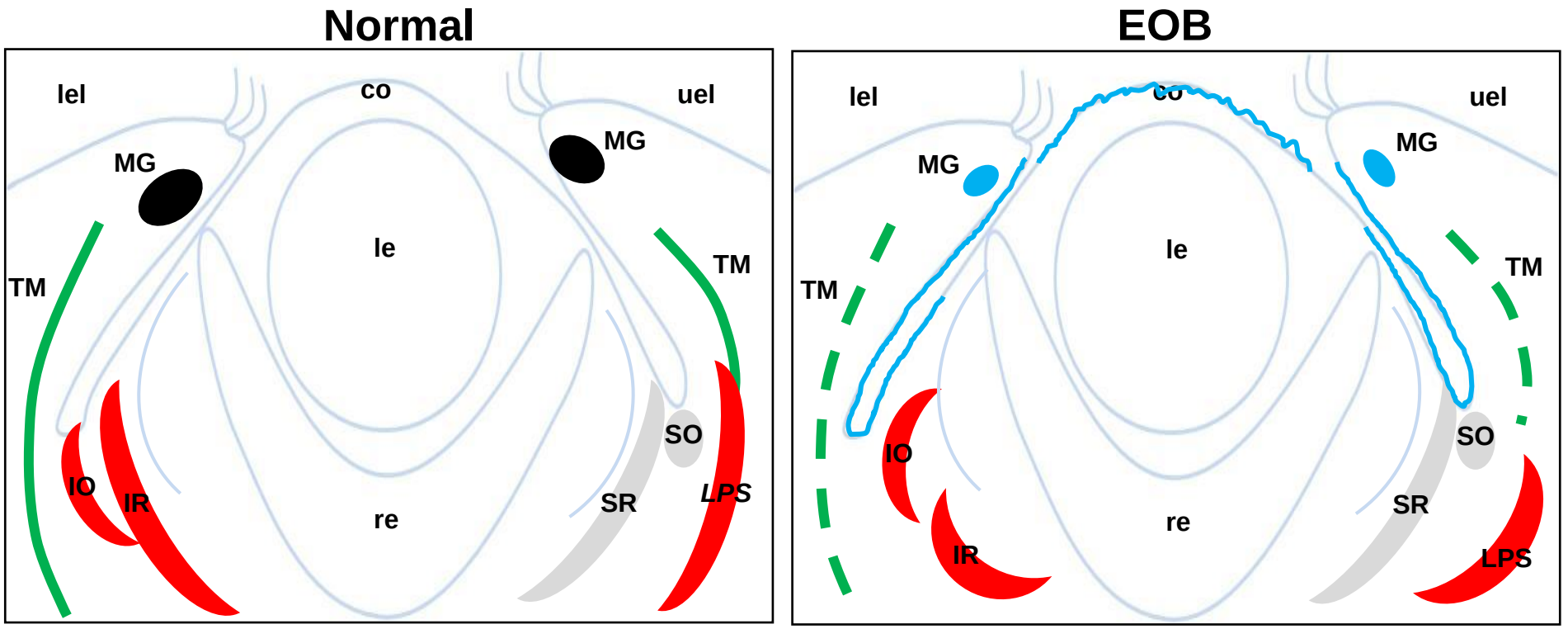
Extraocular Muscle Atrophy in Mice with Defective Eyelid Closure



MRI Imaging



Congenital Eye Abnormalities in Mice with Defective Eyelid Closure



- **Protection of ocular surface**
- **Structural support for ocular adnexal development**

Potential Birth Defects

Strabismus (4%)

- Can be inherited as the results of genetic insults: *PHOX2A*, *KIF21A*, *SALL4, ROBO3,* and *HOXA1*
- Environmental Risk Factors
  i.g. cigarette smoking during pregnancy

floridalionsfoundation.org

Blepharoptosis (<0.01%)

- congenital cases may result from genetic or chromosomal defects, and neurologic dysfunction
- Genetic etiology: *FOXL2,*
  Noonan Syndrome: *PTPN11*, *RAF1*, *BRAF*, *MAP2K1*
  Marfan syndrome: *Fibrillin-1 (FBN1)*

eyewiki.aao.org

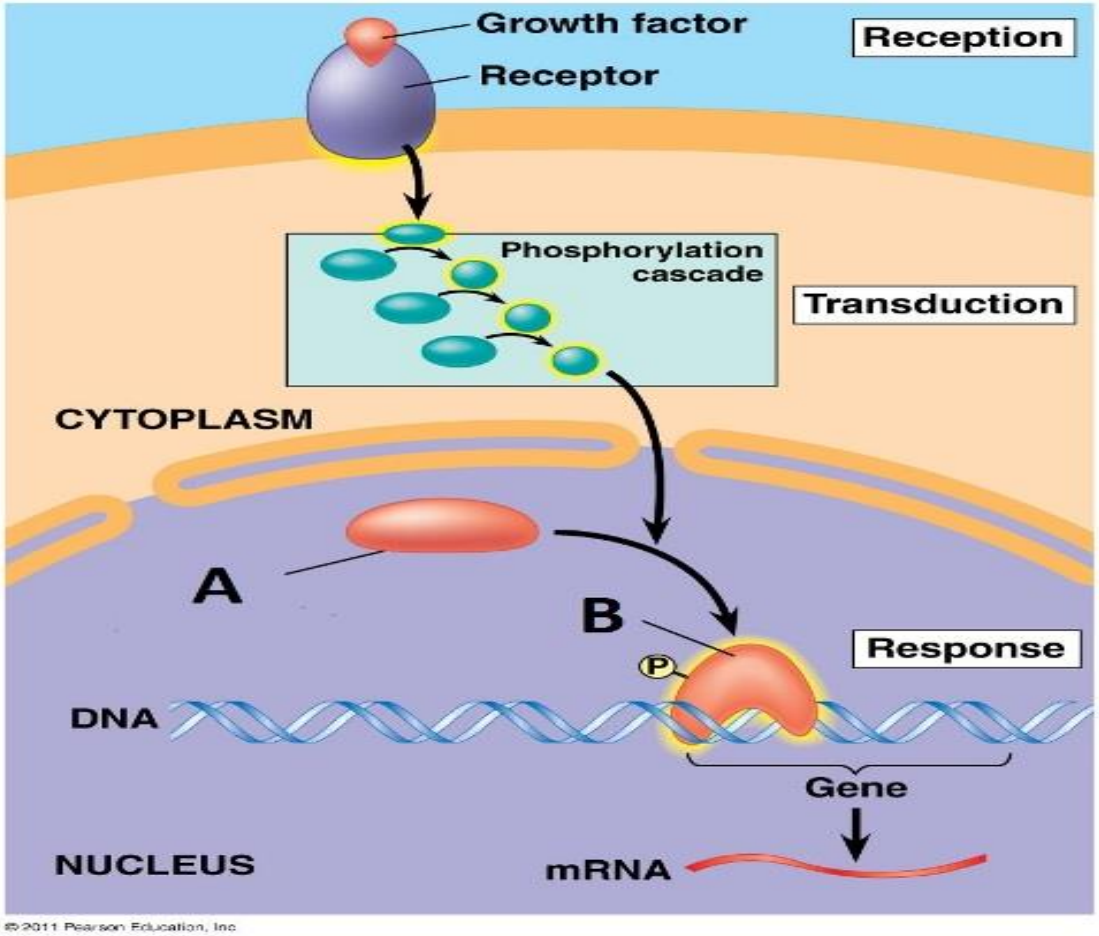
The etiology is diverse, complex and poorly understood for most cases

Outline

1. To investigate the genetic and signaling mechanisms of morphogenesis

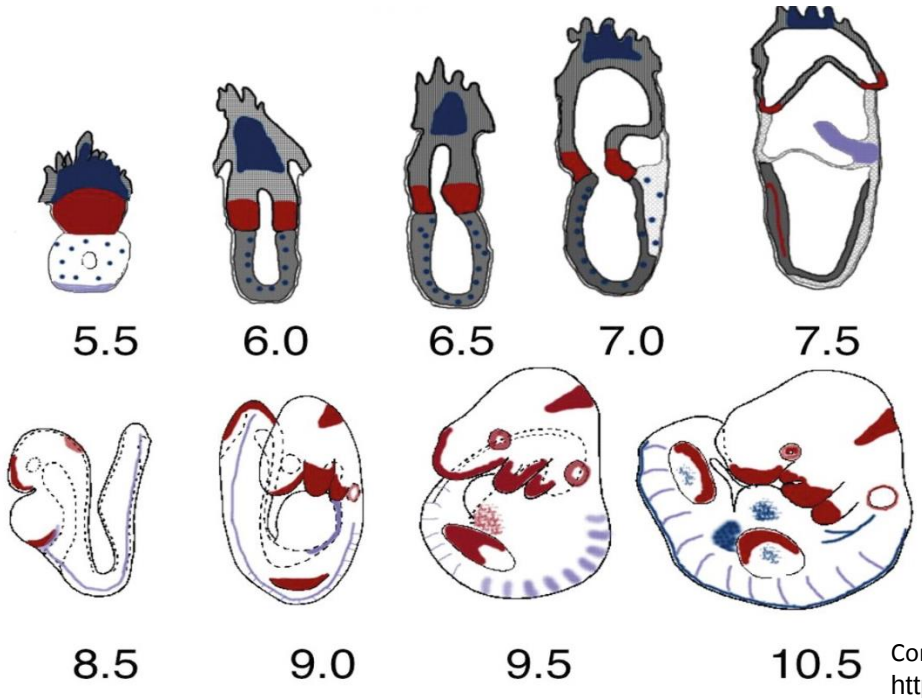
2. To understand genetic risks of environmental chemical exposure and the mechanisms of GxE interactions

Signal Transduction Pathways



Spatial and Temporal Signaling Events in Morphogenesis

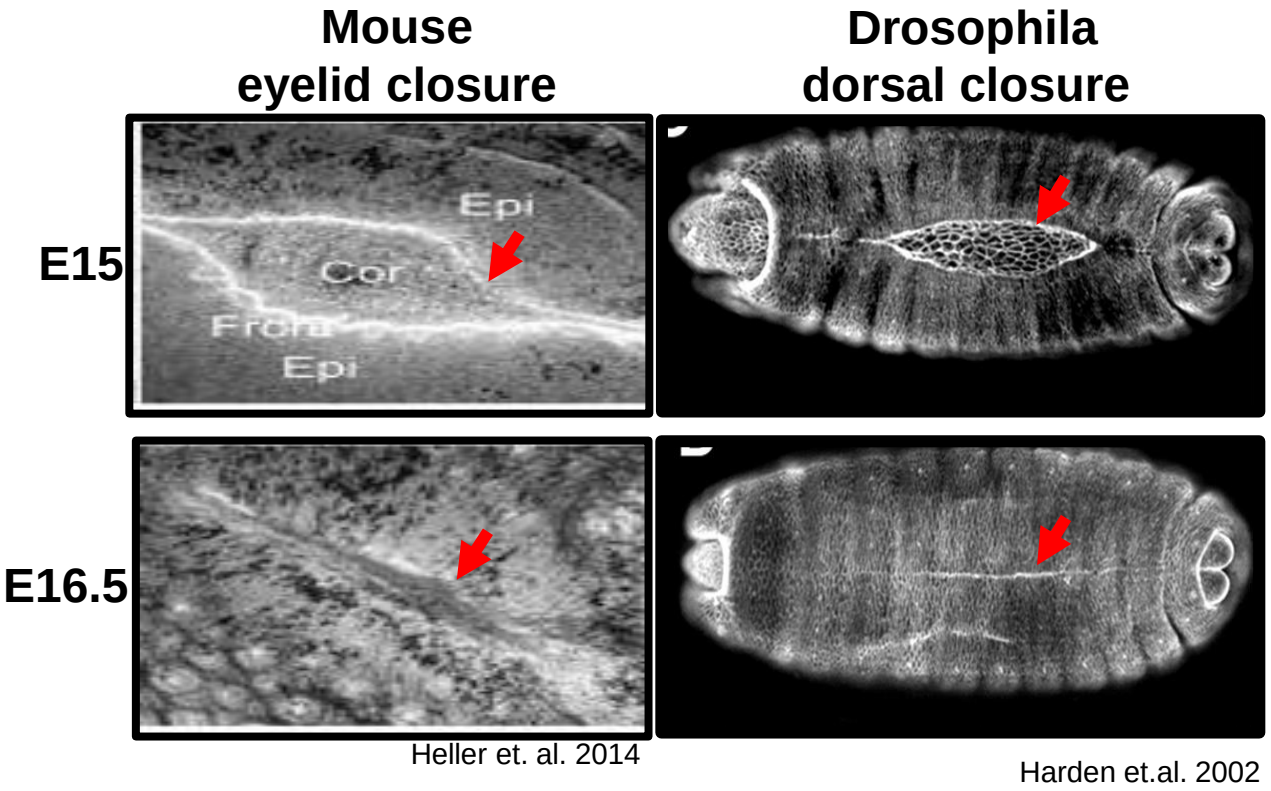
ERK activation



Corson et. al, 2003, Development
http://genex.hgu.mrc.ac.uk

- **Discrete with well-defined boundaries of ERK activation, indicating specific regulation of signaling**
- **Transient activation was seen in neural crest, peripheral nervous system, nascent blood vessels, and anlagen of the eye, ear and heart**

Eyelid Closure v.s. Dorsal Closure

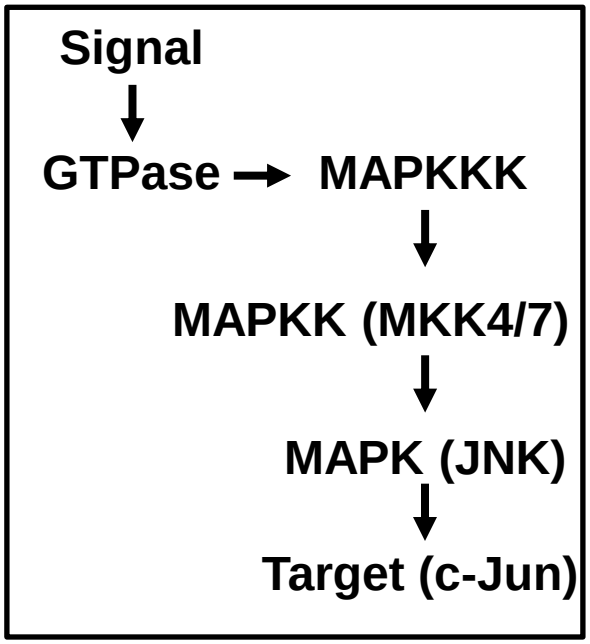


Heller et. al. 2014

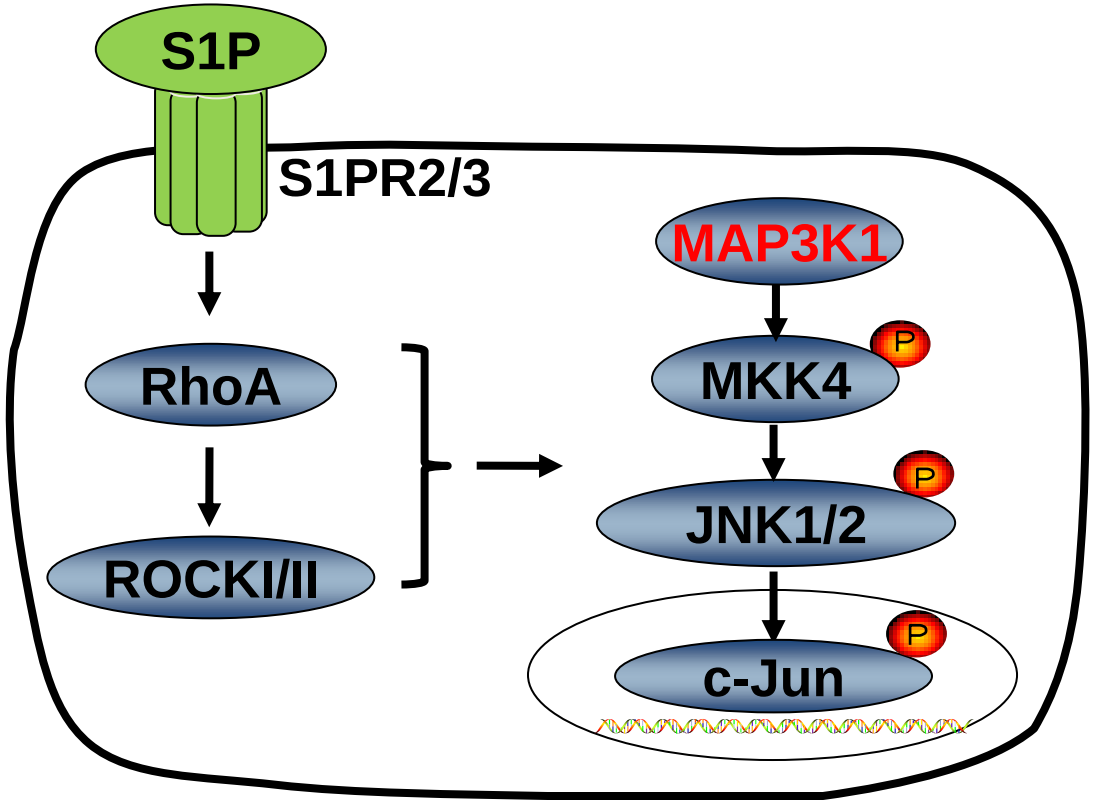
Harden et.al. 2002

Evolutionarily Conserved Signaling Mechanisms in Tissue Closure

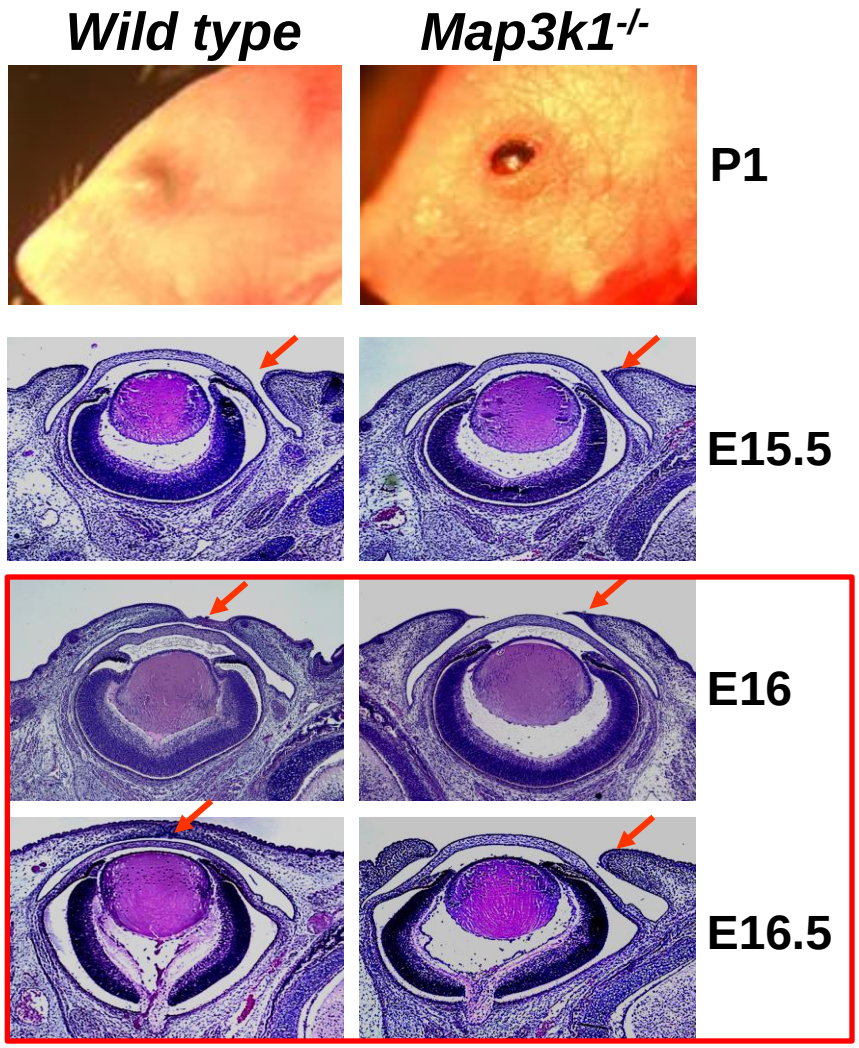
Drosophila dorsal closure



Mammalian eyelid closure

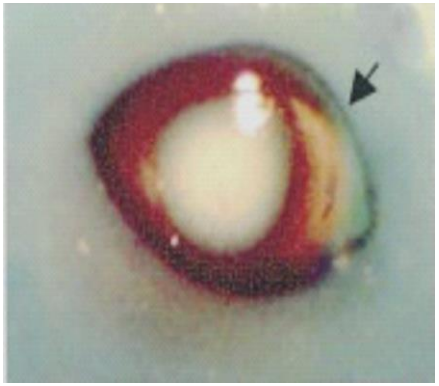


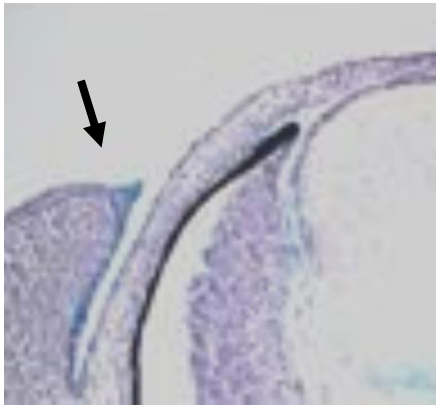
MAP3K1 Required for Embryonic Eyelid Closure



MAP3K1-Dependent Activation of the MKK4-JNK-c-Jun Cascades

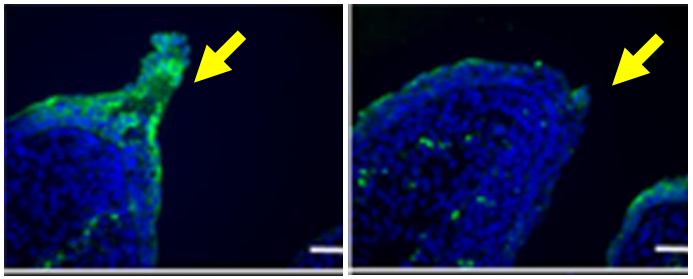
MAP3K1 Expression



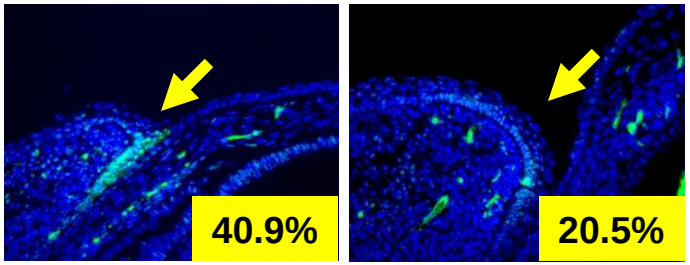


E15.5

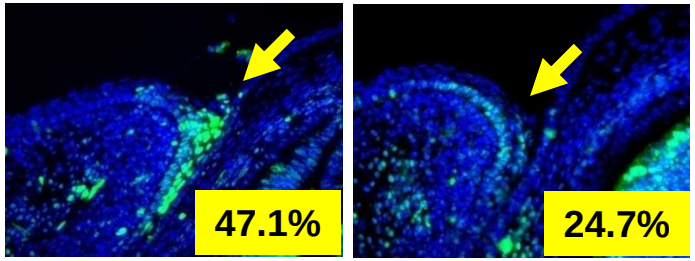
Wild type ***Map3k1$^{-/-}$***



p-MAP2K4



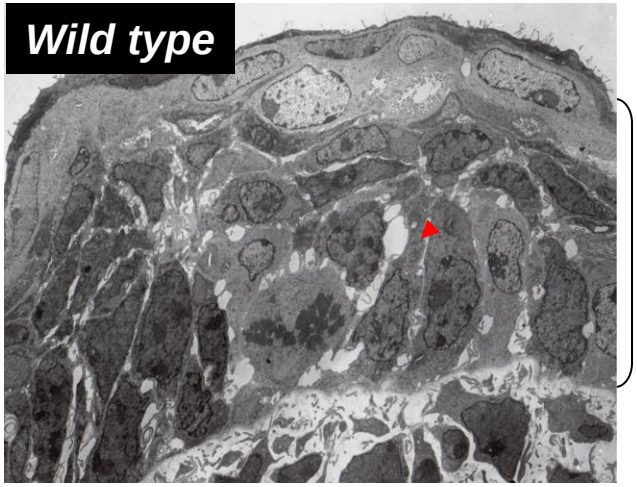
p-JNK

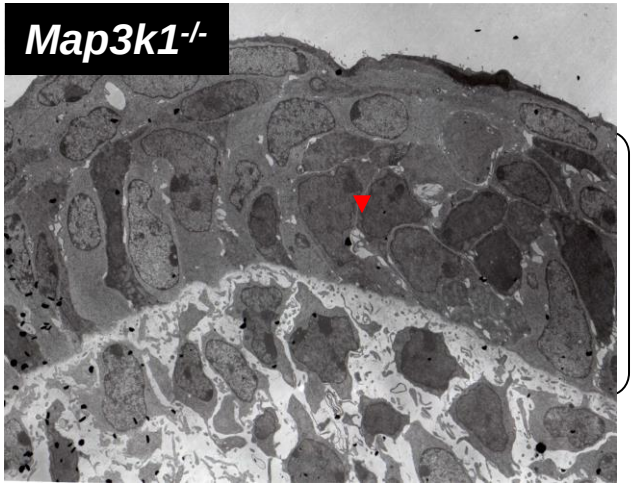


p-c-Jun

MAP3K1 Dependent Eyelid Epithelial Morphogenesis and Actin Polymerization

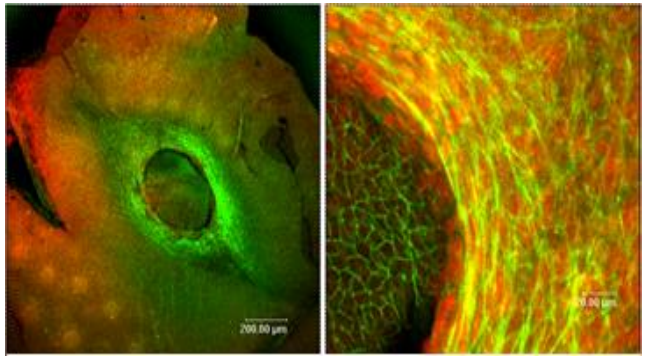
Epithelium of Eyelid Tip



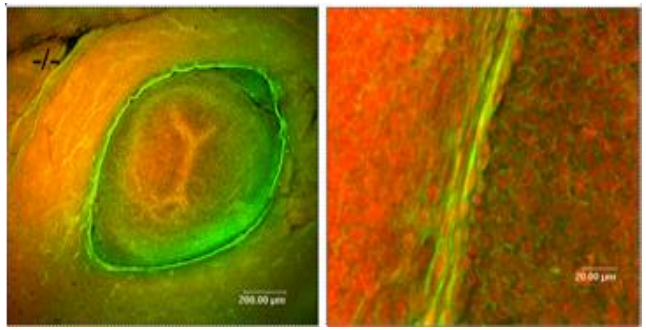


Actin Polymerization

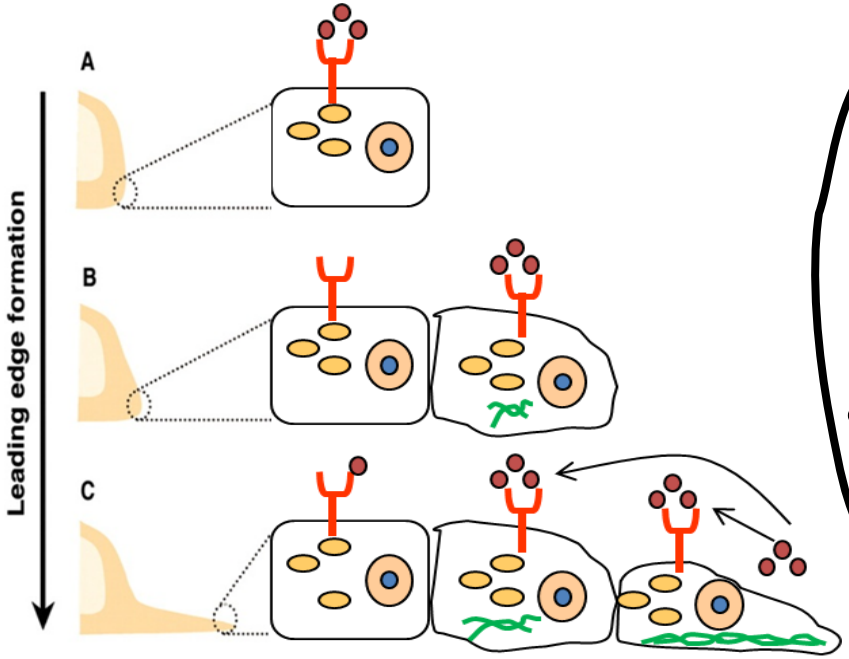
Wild type

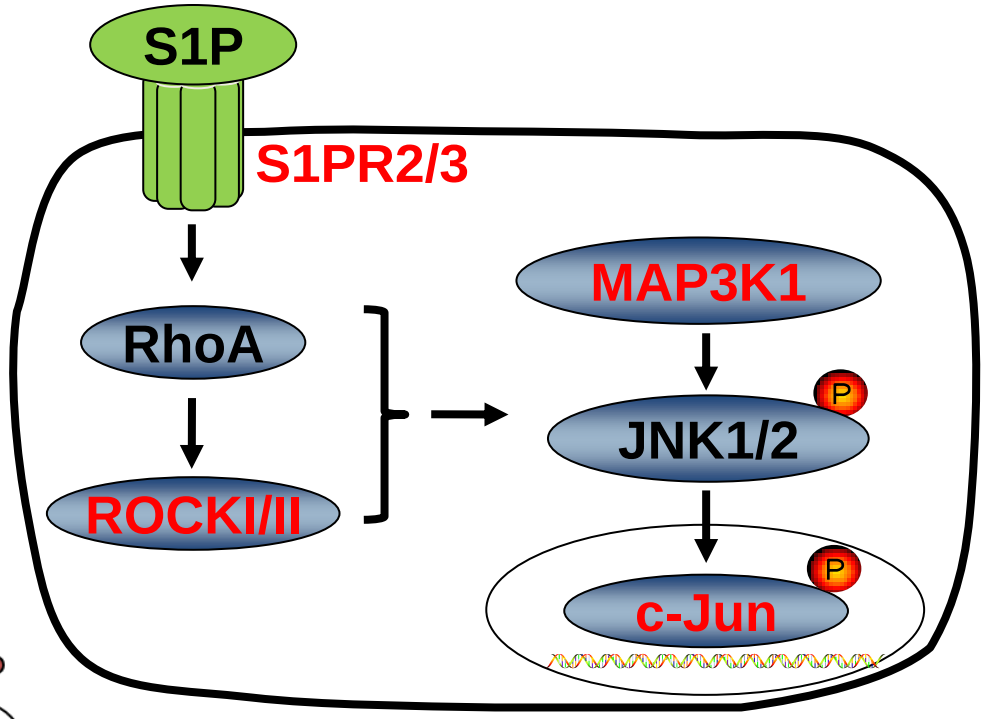


Map3k1$^{-/-}$



Genetic Evidence for the Signaling Network in Eyelid Closure

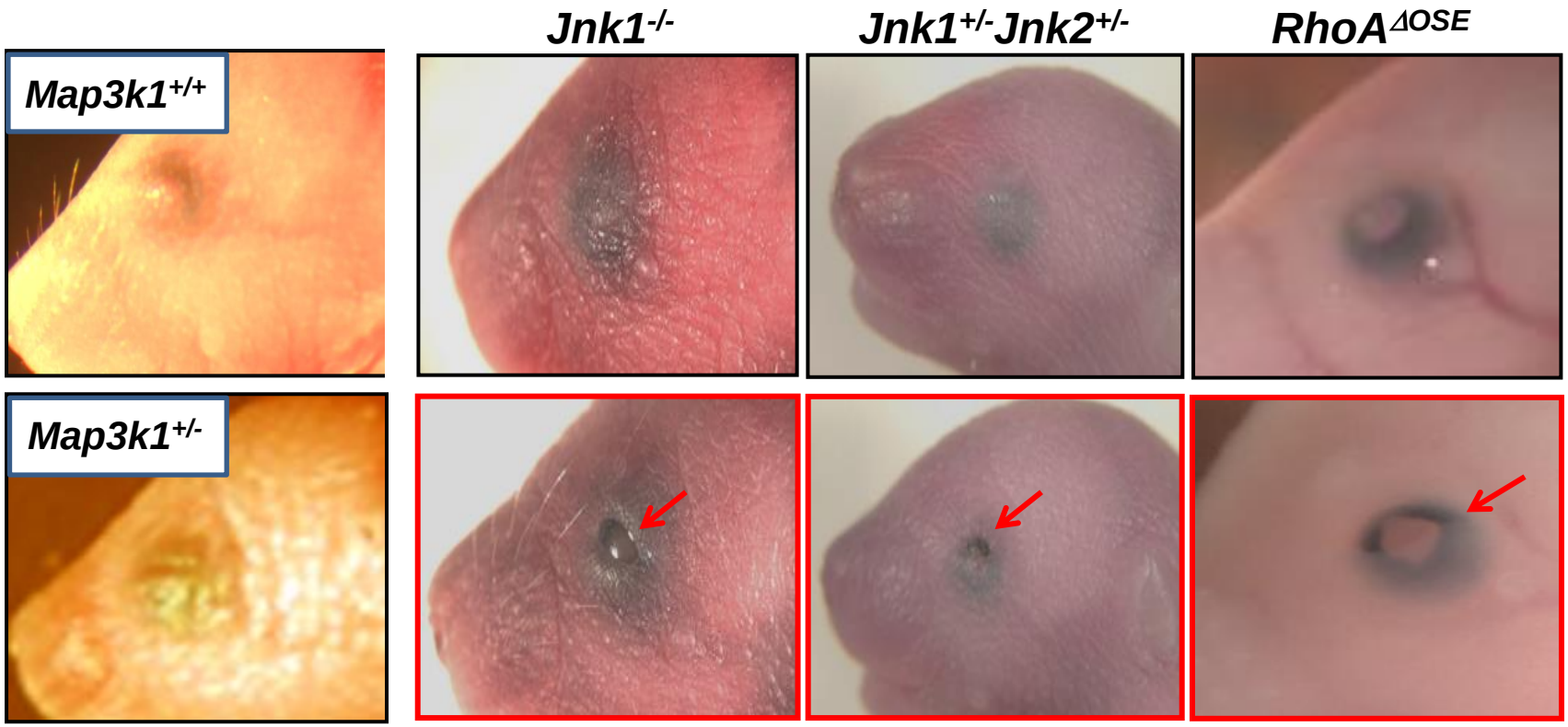




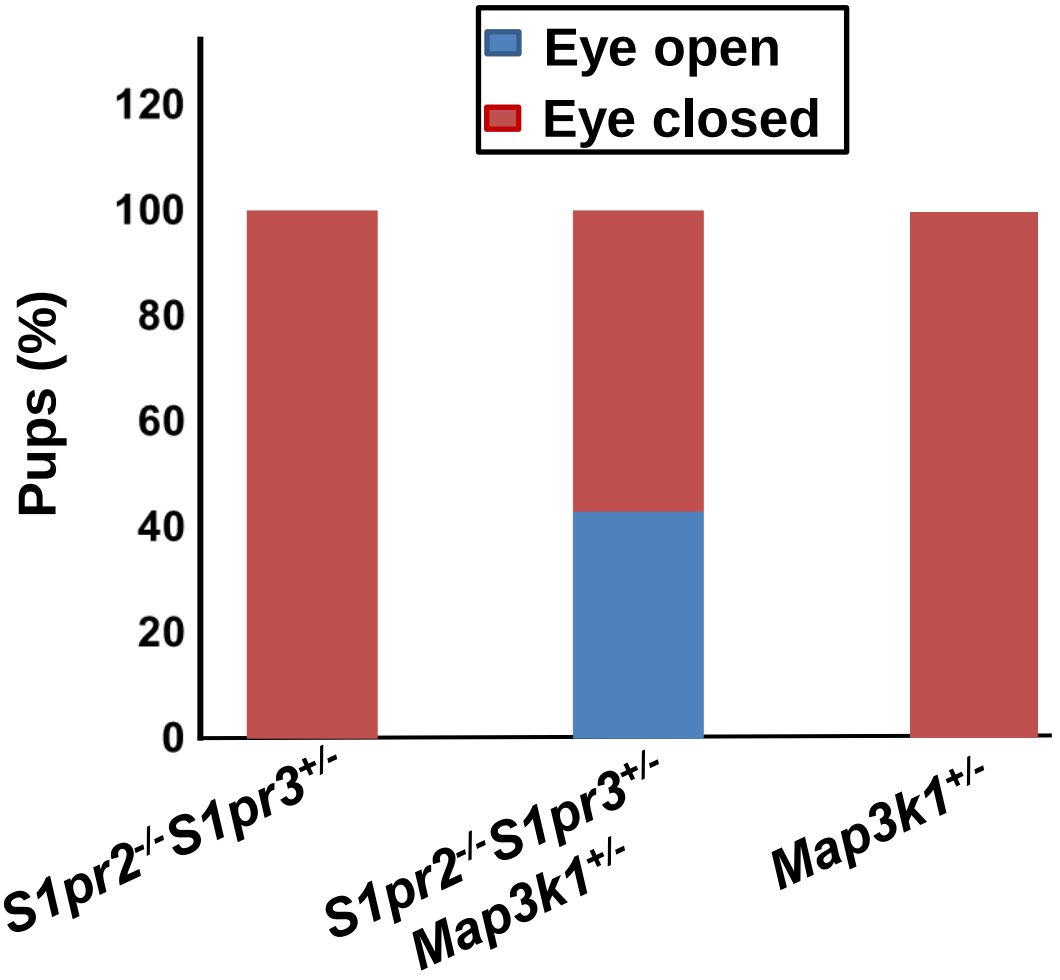
Cytoskeleton re-organization
Epithelial cell migration

Inactivation of network factors causes eyelid closure defects

Multiple Genetic Lesions Have Additive Effects



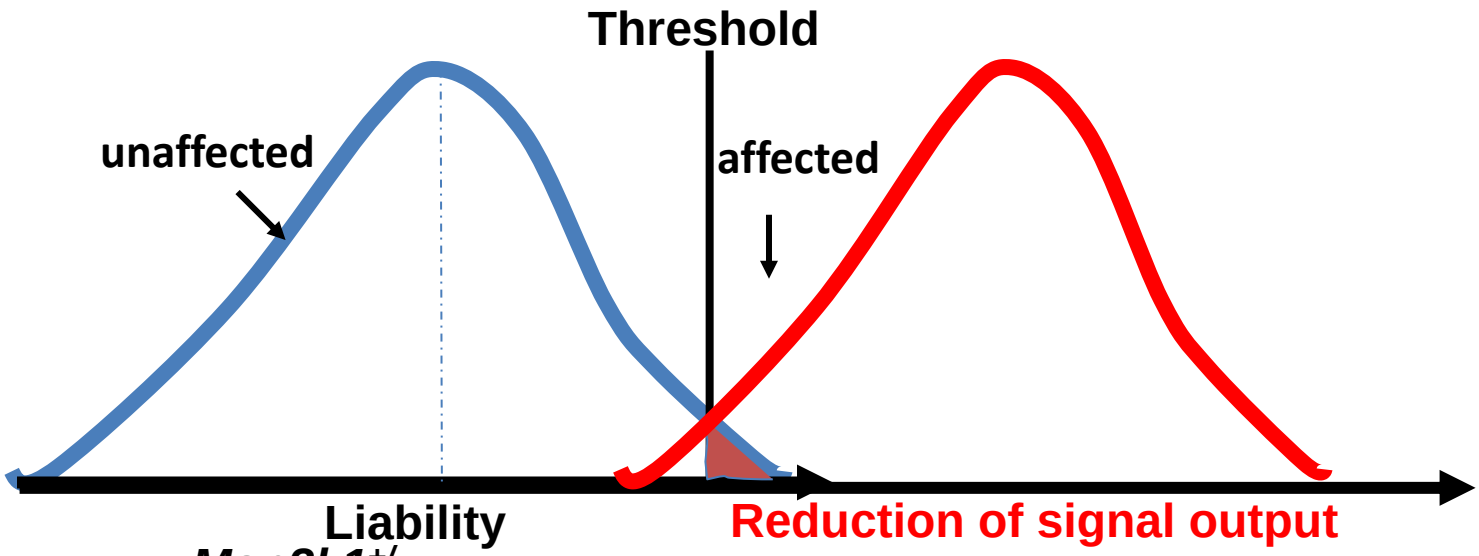
Gene-Gene Interactions in Eyelid Closure Defects



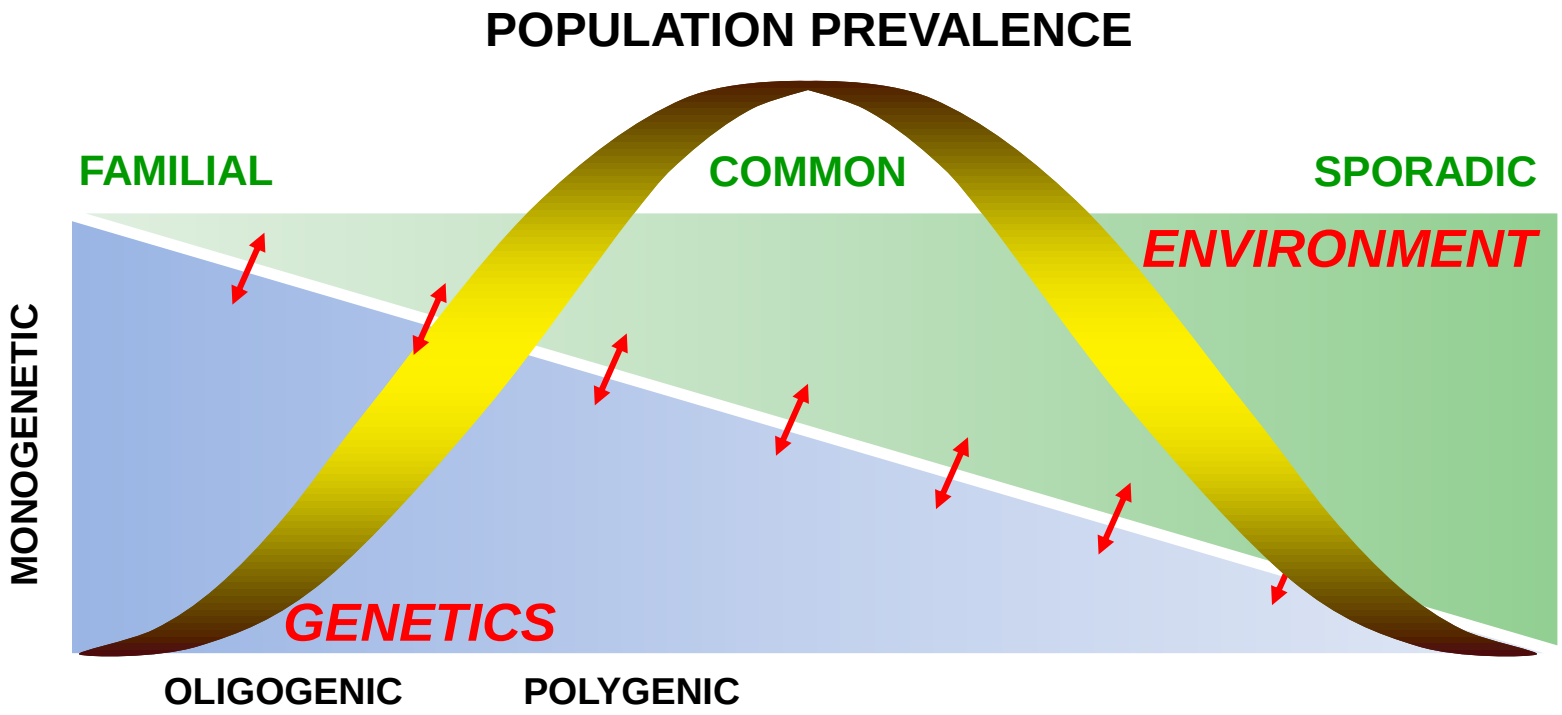
Developmental Threshold

- **Multiple factors (genetic and environmental) make continuous contributions to the liability**

- **When the culmulative liability reaches beyond a threshold value, the individuals will be affected**



Gene, Environment and Human Diseases



Dioxin Like Compounds (DLCs)

- ***De novo* sources**
  - **Pesticides**
  - **Unintended synthesis as a byproduct of industrial process**
  - **Combustion of waste, smelting**
  - **Natural fires, volcanoes**

- **Property**
  - **Resistant to environmental degradation, biopersist and bioaccumulate**
  - **Highly lipophilic (build up in adipose tissue)**

Dioxin-like Compounds and Birth Defects

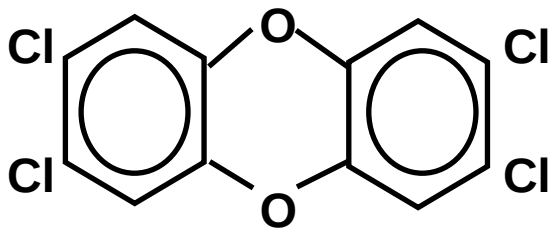
- **Developmental toxicity is well established in animals**
- **Gestation in areas with high industrial, natural, or accidental release of dioxin like compounds**

  Seveso, Vietnam, Yucheng,
  Fukuoka and Nagasaki
- **Fetal PCB syndrome**

  Pigmentation (100%)
  Hearing difficulties (18%)
  Exophthalmos (13%)
  Precocious dentition (13%)
  Anemia (4%)

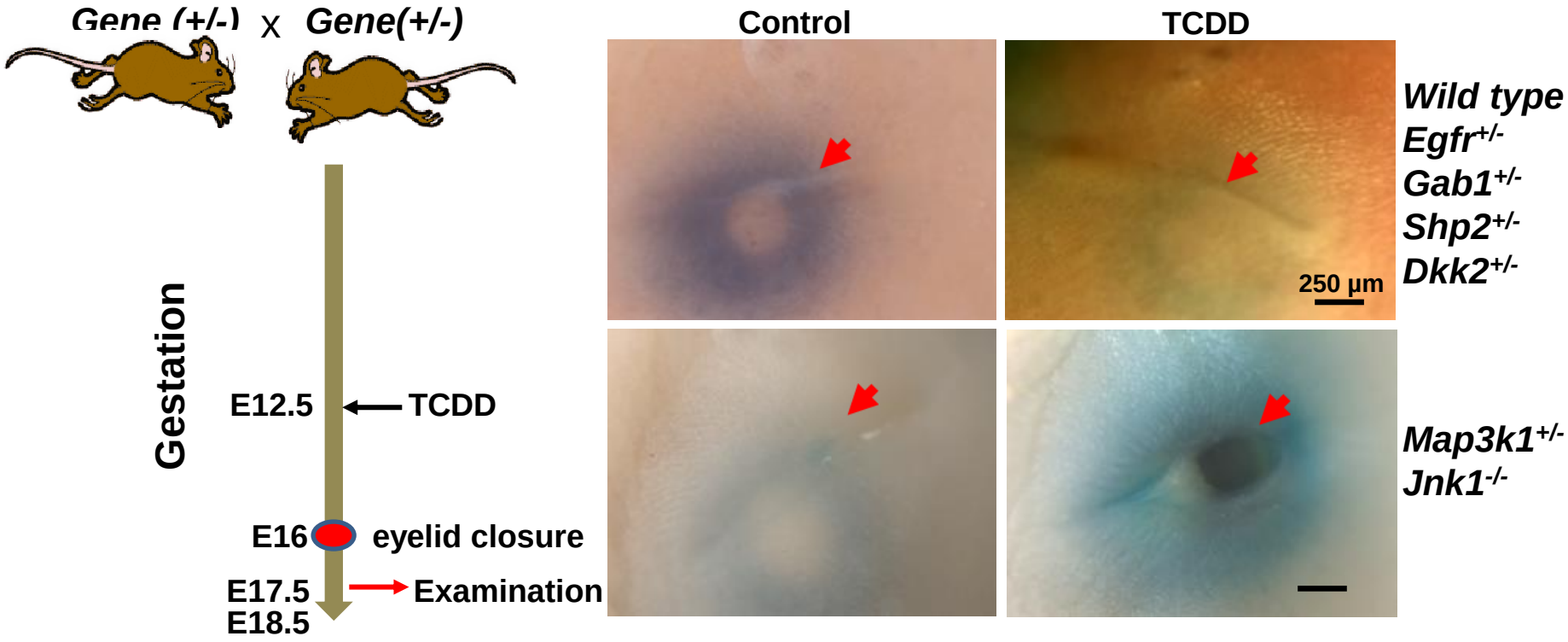
  (Yamashita and Hayashi; Reggiani and Bruppacher)

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)



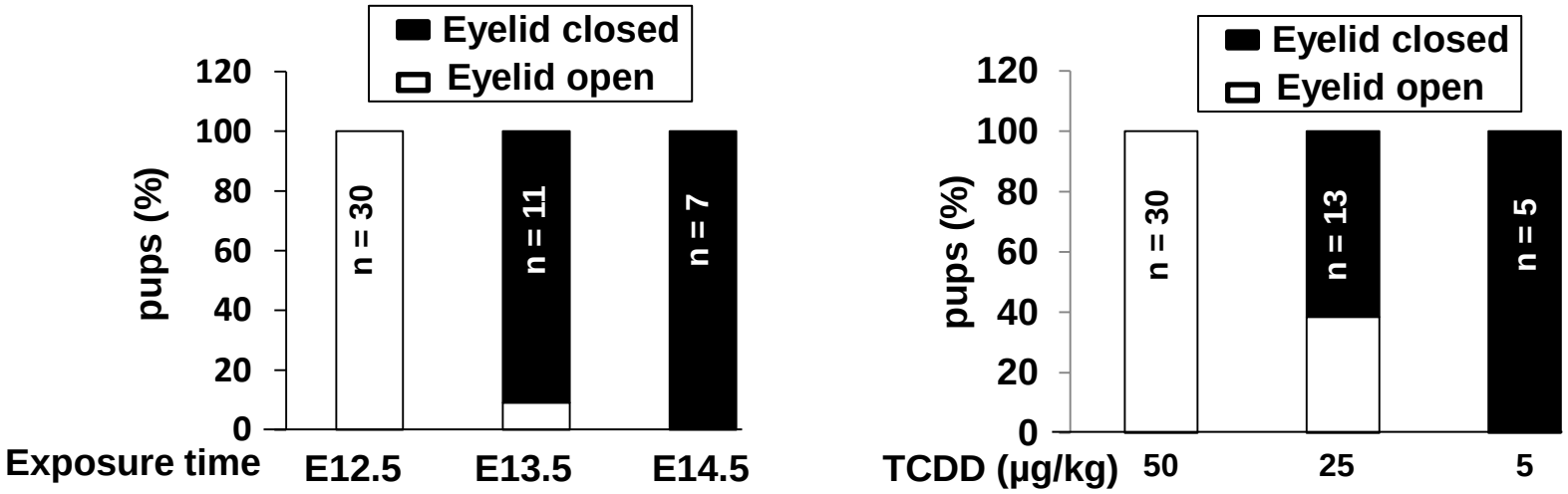
Effects in humans or primates	Effects in rodents, amphibians or fish
Chloracne	Cleft palate and hydronephrosis
Porphyria	Tumor promotion
Endometriosis	Liver hyperplasia
Carcinogenesis	Antiestrogenic
Heart disease	Testicular atrophy
	Splenic atrophy
	Immunosuppression
	Thymic involution
	Wasting syndrome
	Death

Genetic Risk of TCDD Exposure?

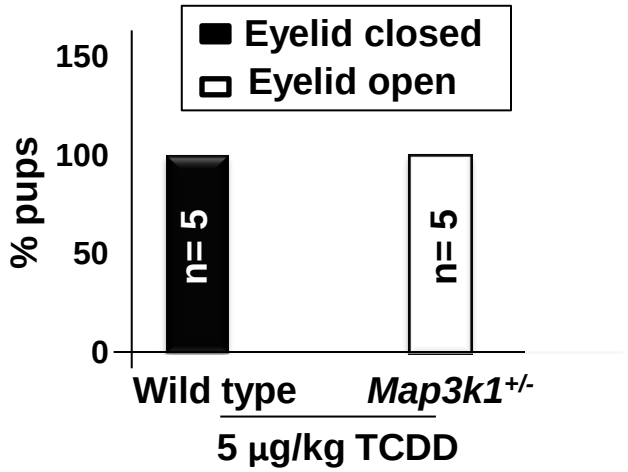


Exposure Dose and Developmental Window

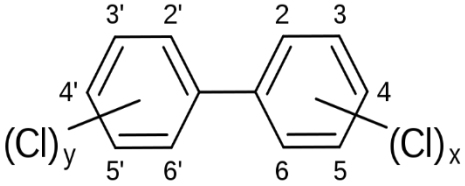
Single Exposure



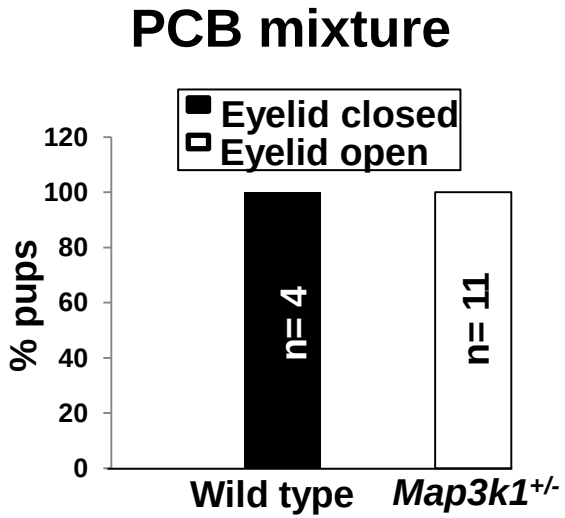
Multiple Exposure



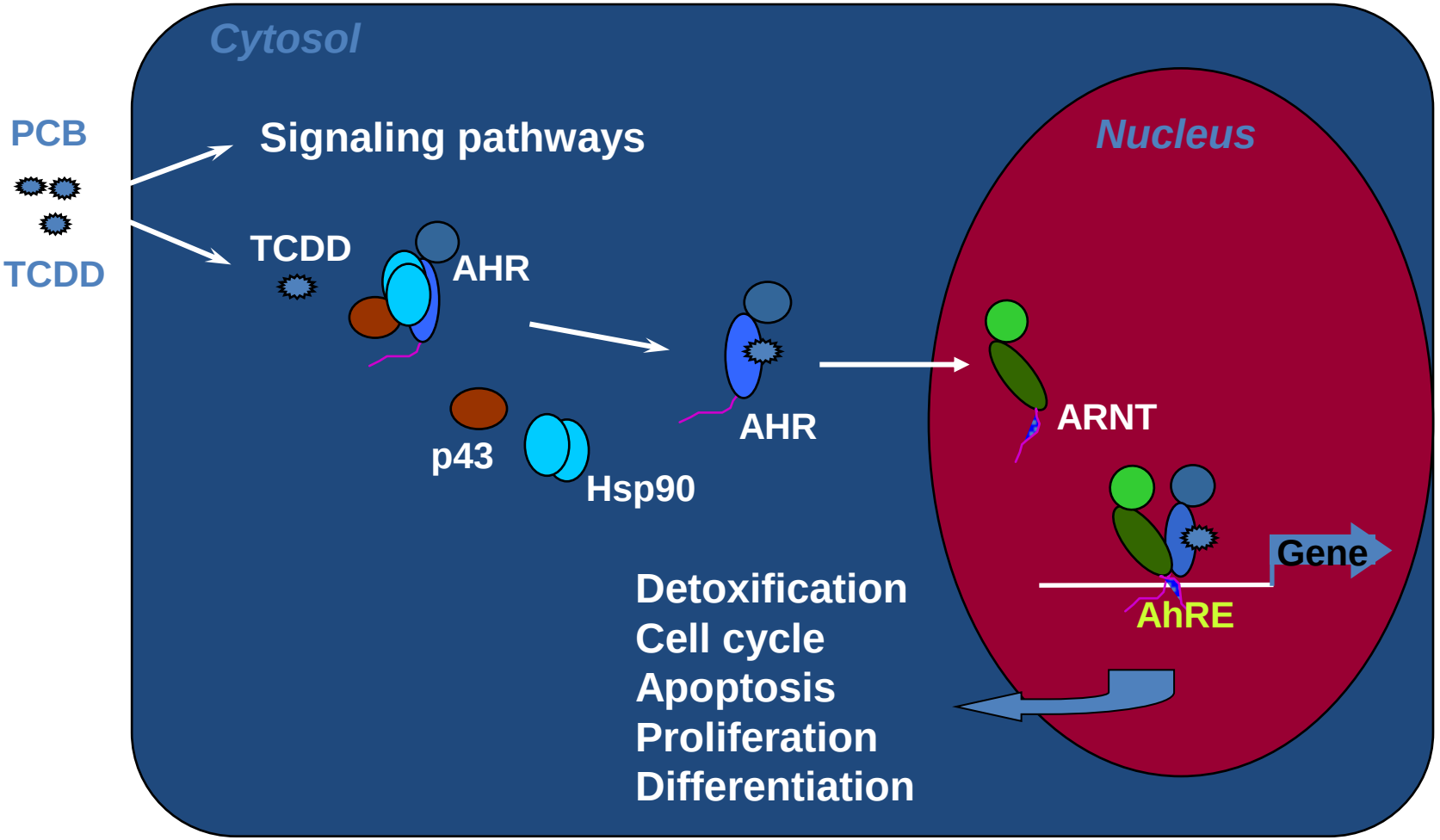
Polychlorinated Biphenyls (PCBs)



- **A group of manufactured organic chemicals that contain 209 individual chlorinated chemicals (known as congeners)**
- **Used widely as coolants and lubricants in transformers, capacitors, and other electrical equipment**
- **People who are regularly exposed to PCBs are at greater risk for a variety of health problems, including neurological, reproductive and cancer**
- **No longer manufactured since 1977, but because they do not break down easily, PCBs are now found widely distributed in our environment; the chemical properties of PCBs cause them to be concentrated up the food chain**

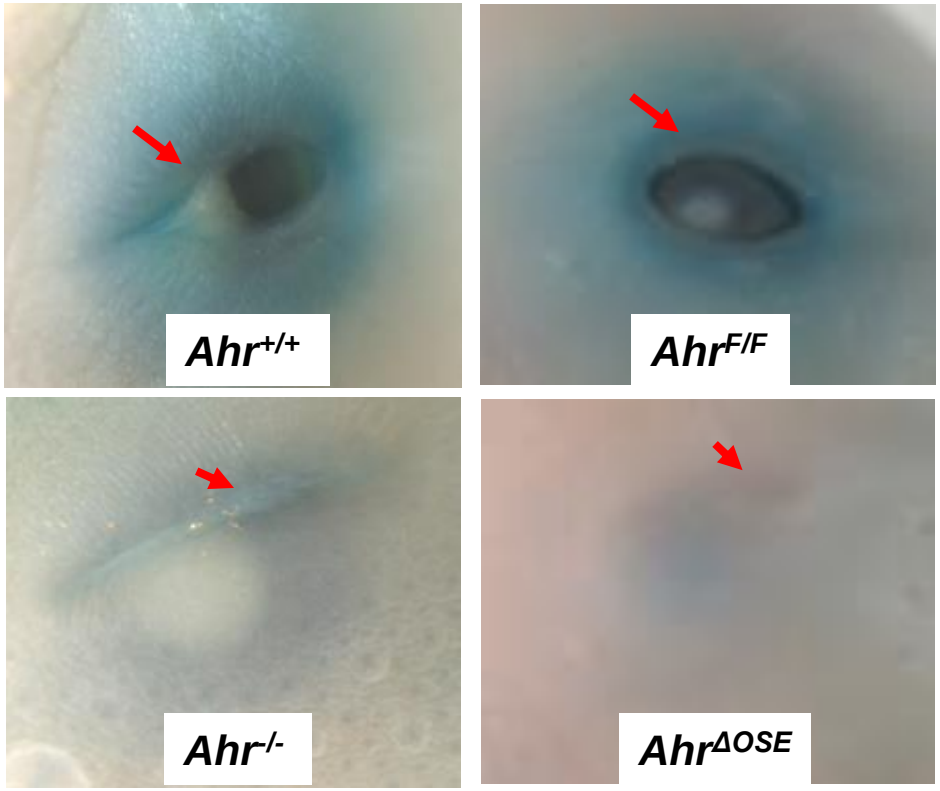


Aryl Hydrocarbon Receptor (AHR) Signaling



Is Ah Receptor Involved in TCDD Toxicity?

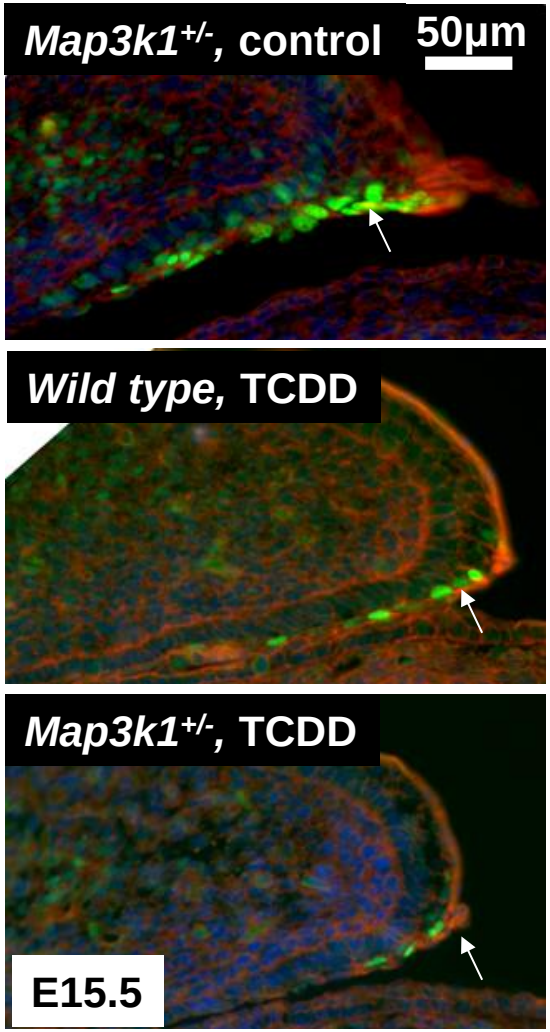
***Map3k1*$^{+/-}$**

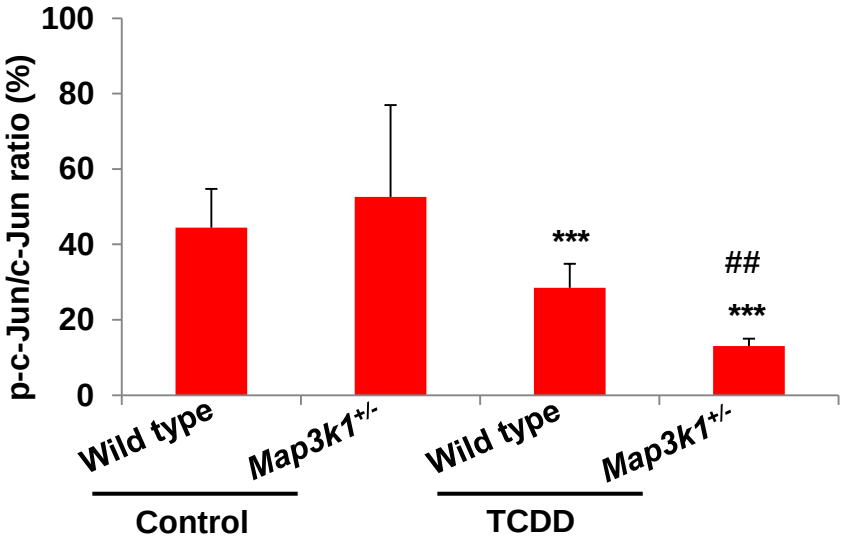


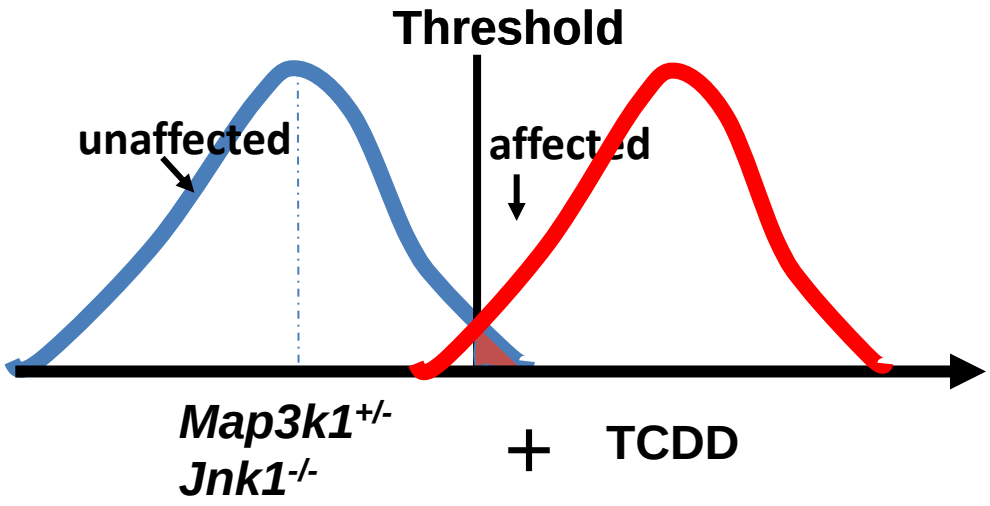
E17.5

The TCDD-AHR axis crosstalks with the MAP3K1-JNK pathway

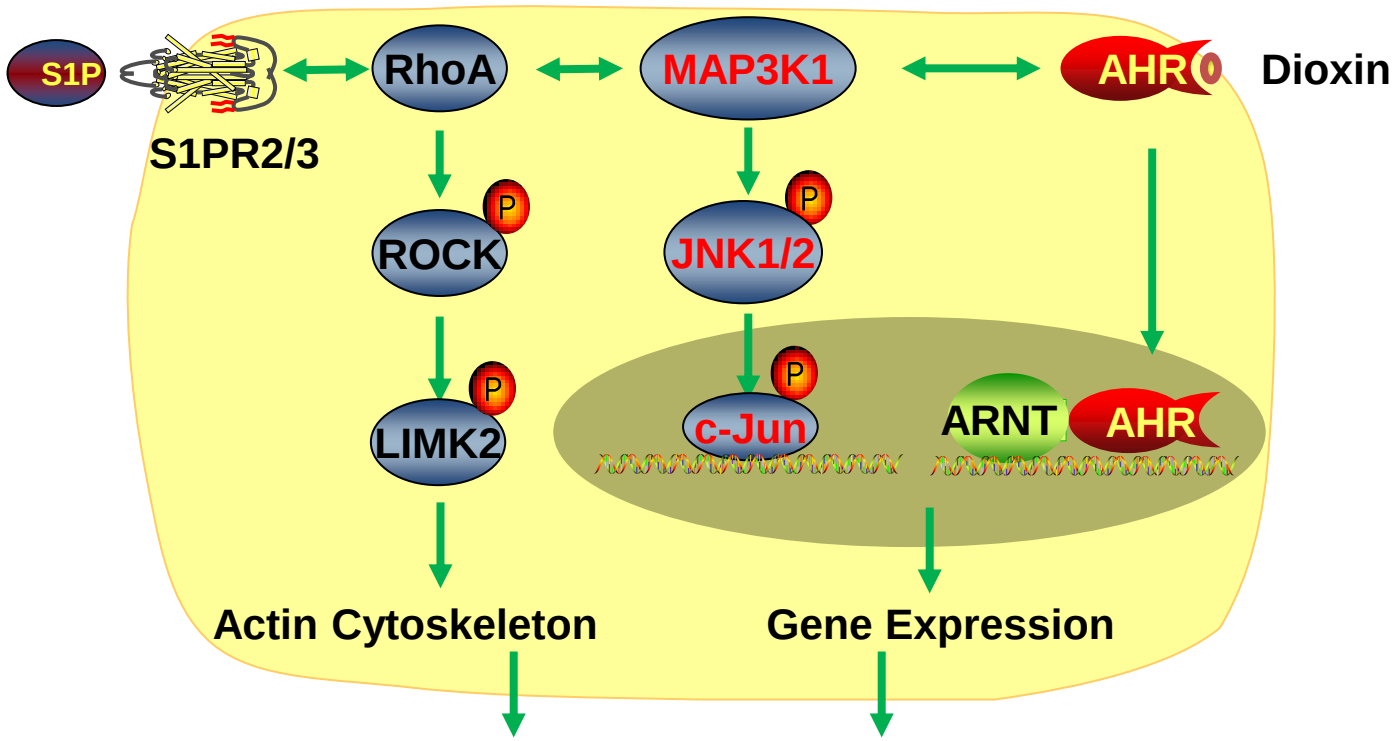
Dioxin Targeting the JNK Pathways



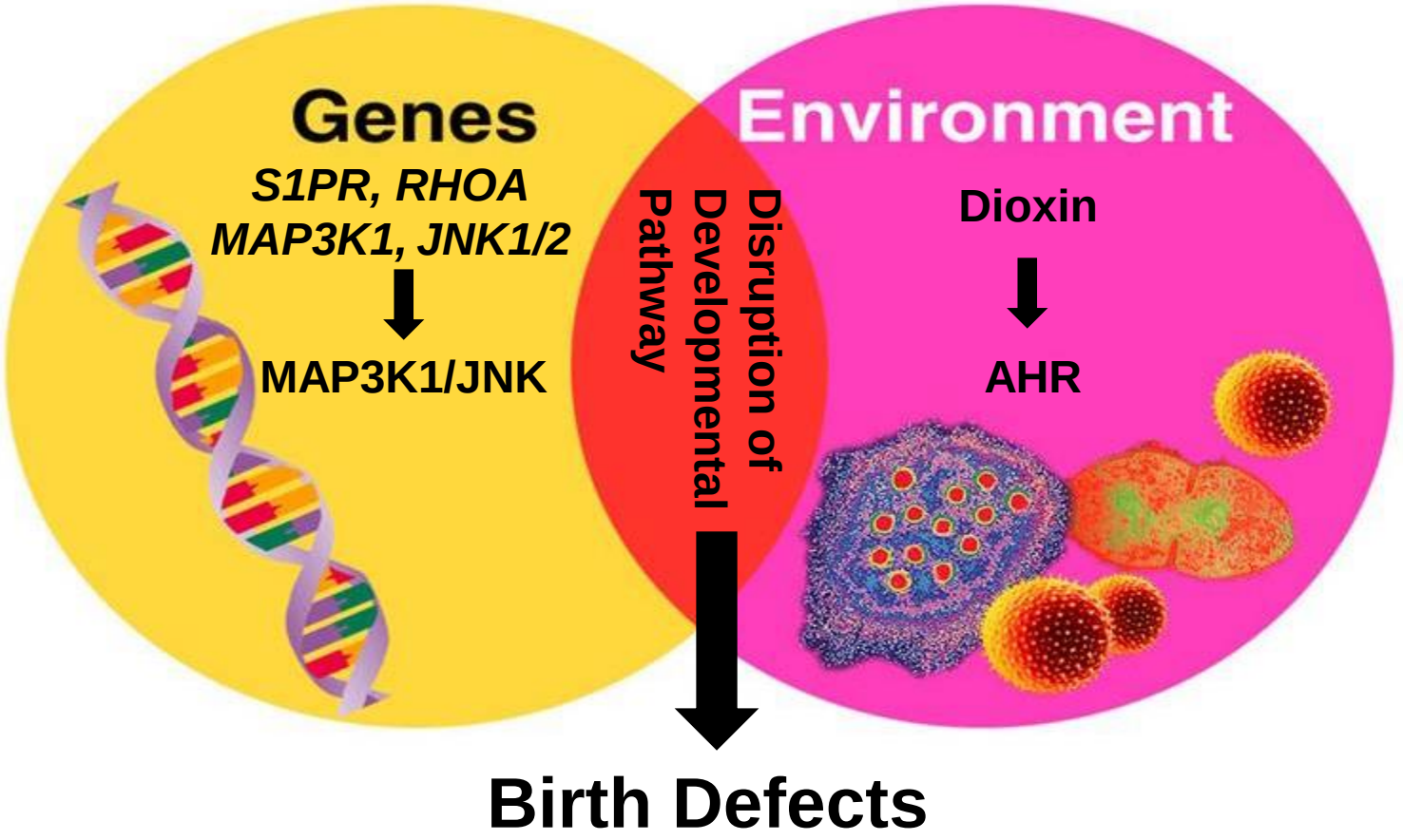




Gene-Gene and Gene-Environment Interactions in Morphogenesis



Gene-Environment Interactions and Developmental Toxicity



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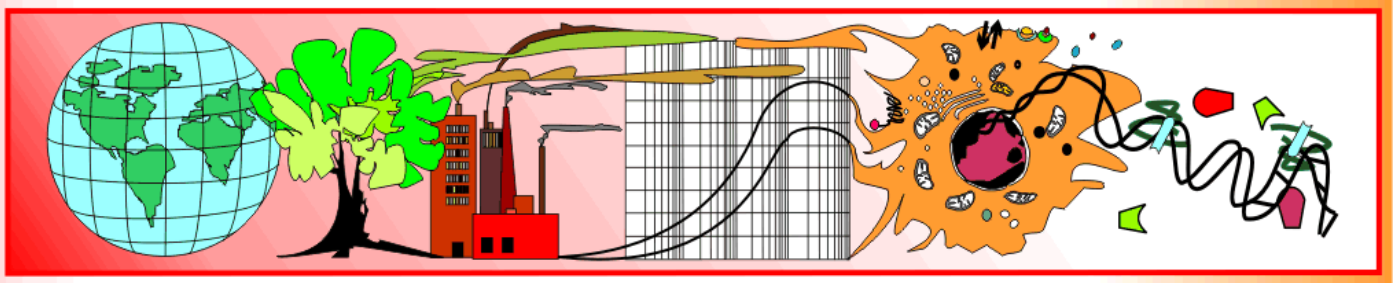

Acknowledgements

Lab member

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