



# Personalized Medicine. What is it?



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The day after the world didn't come to an end.



# Challenges (and opportunities)

# 1. Communication across disciplines





## 2. Information management/interpretation

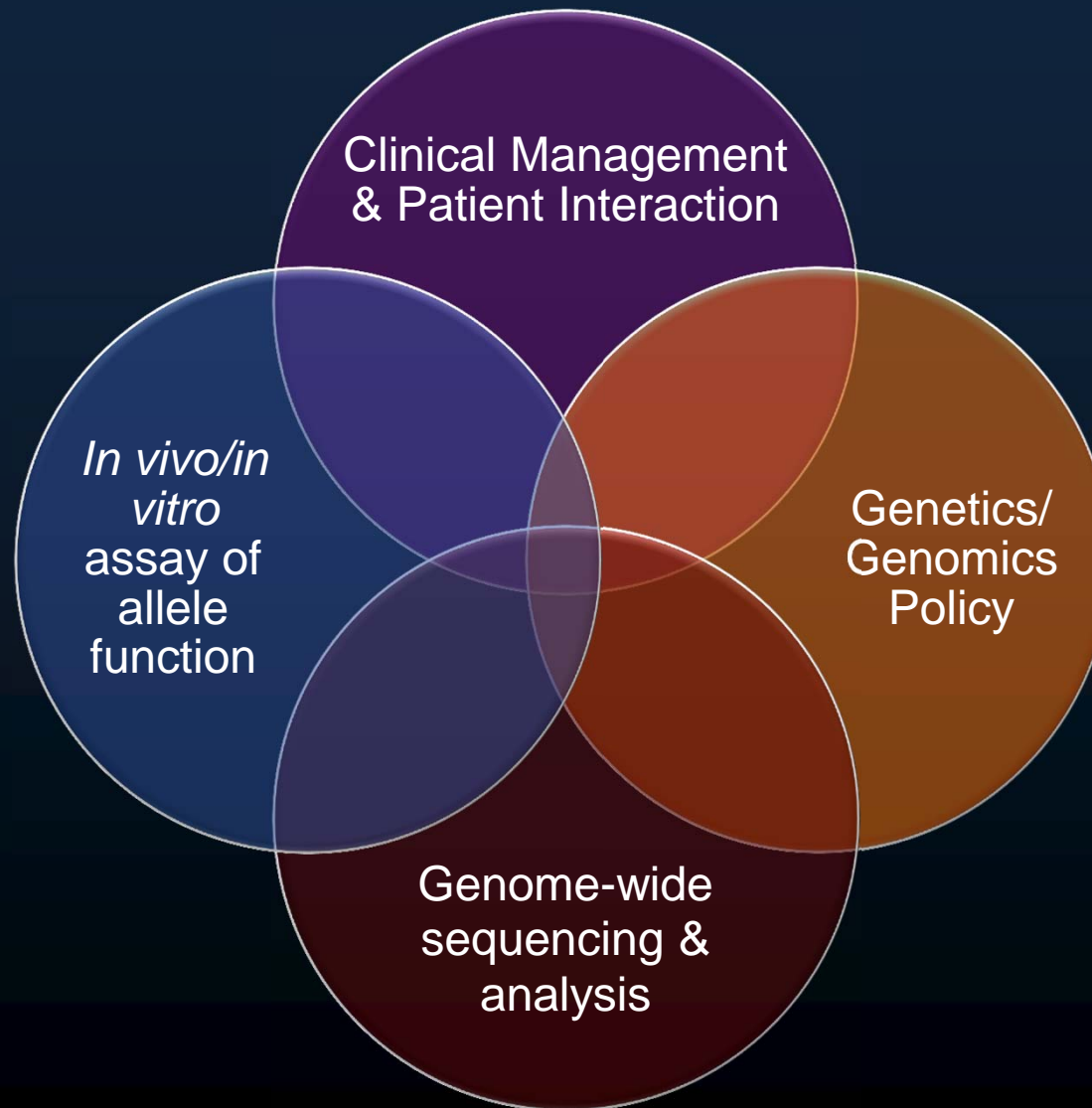


### 3. Ethical transmission of information



# Task Force for Neonatal Genomics

## A hybrid structure at Duke



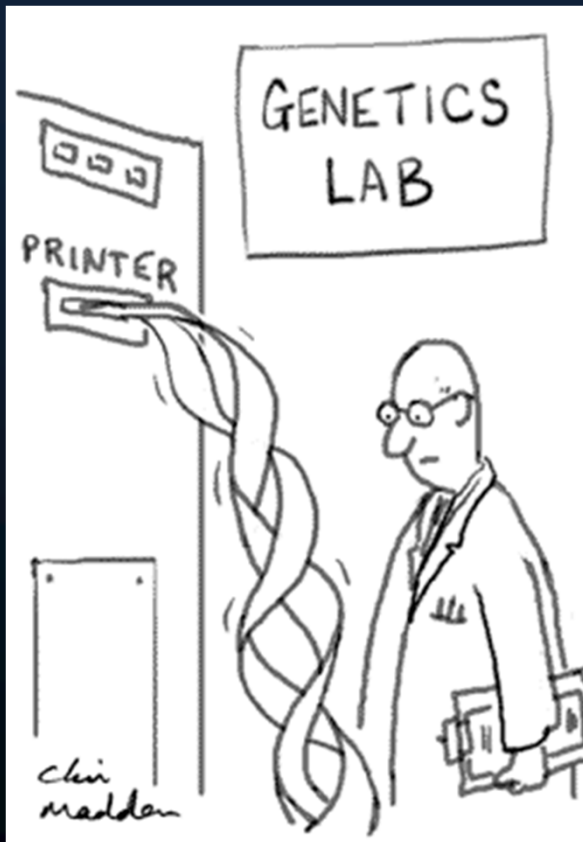
# Four Phases

1. Recruitment
2. Genomics
3. Functional studies
4. Return of Results

All Phases are cyclical  
and Iterative

# Our biggest Challenge

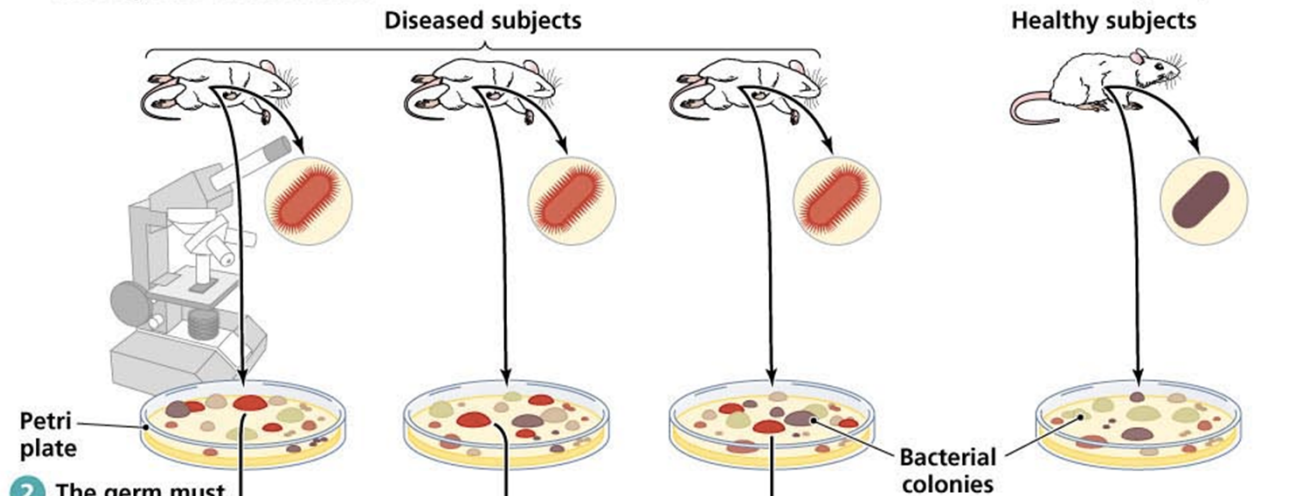
*Our current ability to interpret genetic variation accurately*



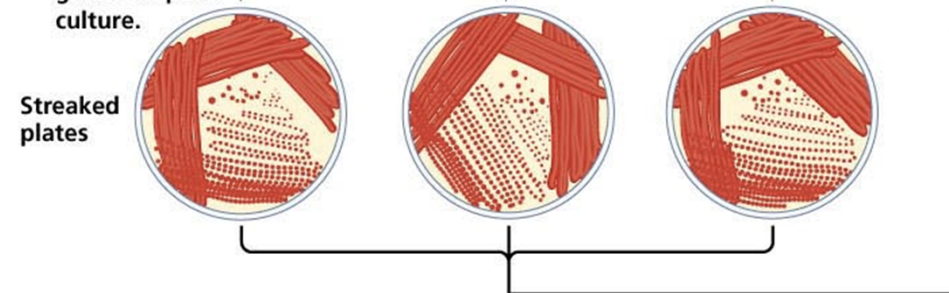
1. Is the gene “relevant” to a disease state
2. Is a DNA variant within a gene altering the function of the encoded protein?
3. How do we answer these questions?

# Applying Koch's Postulates

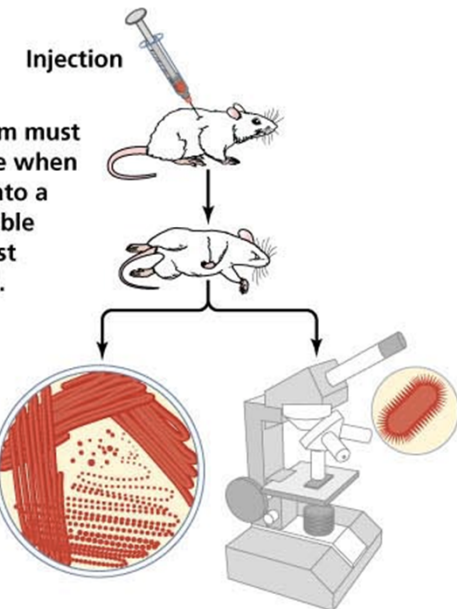
- 1 The suspected germ must be present in every case of the disease.



- 2 The germ must be isolated and grown in pure culture.



- 3 The cultured germ must cause the disease when it is inoculated into a healthy, susceptible experimental host (animal or plant).



- 4 The same germ must be reisolated from the diseased experimental host.



# Animal Models: Which one is the best?



Human



Mouse



Zebrafish



Fruit fly



Worm

<b>Genomic similarity</b>	80%	70%	61%	43%
<b>Number of offspring</b>	10-12	>200	10-20	300
<b>Daily cost per animal</b>	\$0.20	<\$0.01	<\$0.01	<\$0.01

# How well are organ systems conserved?



Human



Mouse



Zebrafish



Fruit fly



Worm

Nervous system	✓ ✓ ✓	✓ ✓	✓	✓
Cardiovascular	✓ ✓ ✓ ✓	✓ ✓	✓ ✓ ✓	✓
Respiratory	✓ ✓ ✓ ✓	✓	✓	✓
Skeletal	✓ ✓ ✓ ✓	✓ ✓	✓	✓
Muscle	✓ ✓ ✓ ✓	✓ ✓ ✓	✓ ✓	✓ ✓
Gastrointestinal	✓ ✓ ✓ ✓	✓ ✓ ✓	✓ ✓	✓ ✓
Renal / urinary	✓ ✓ ✓ ✓	✓ ✓ ✓	✓	✓
Reproductive	✓ ✓ ✓ ✓	✓ ✓	✓	✓
Endocrine	✓ ✓ ✓ ✓	✓ ✓ ✓	✓	✓ ✓
Skin / limbs	✓ ✓ ✓ ✓	✓	✓	✓



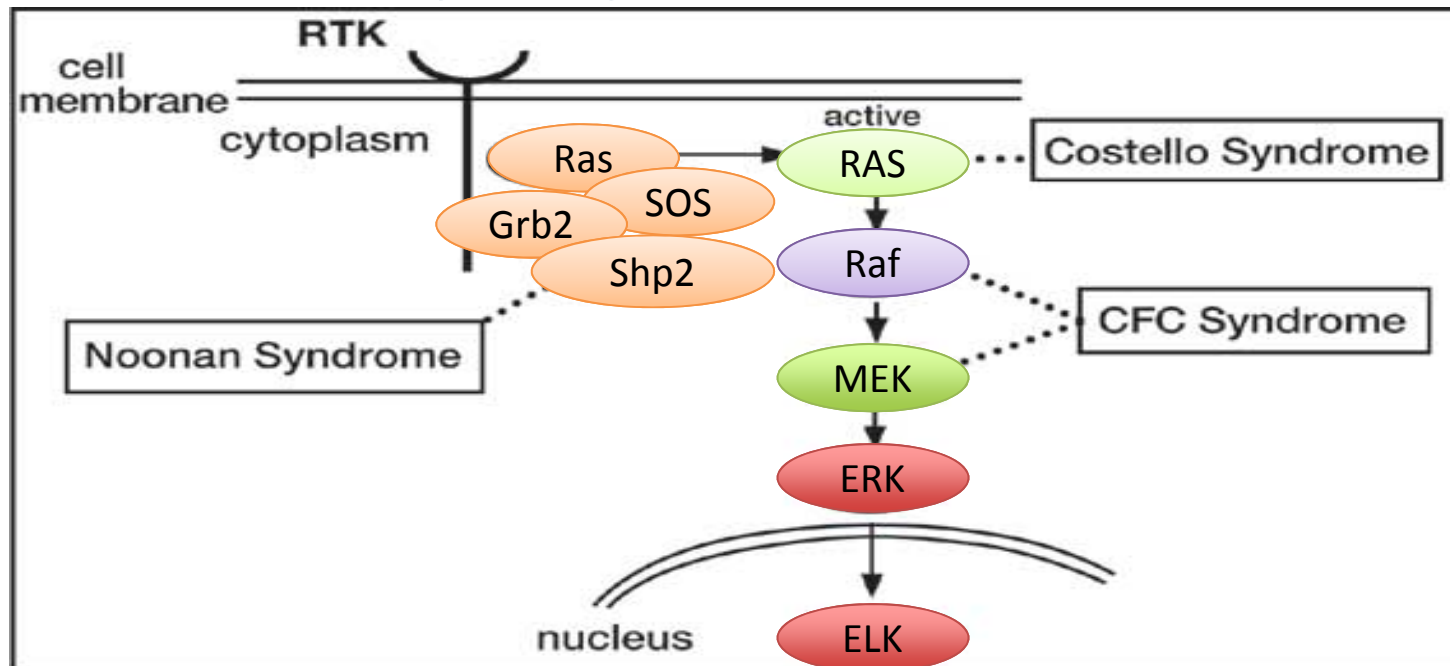
# Discovery New Disease Genes



- Baby with intractable seizures, microcephaly, and small jaw
- Candidate genes have not been described in humans with these symptoms before
- Functional testing showed zebrafish with similar defects and inherited variants of one candidate gene to be pathogenic: *ELK3*

# Testing the “Genomic Hypothesis”

- **ELK3:** ETS proteins function as transcription factors in the RAS/MEK/ERK signaling pathway



Rodriguez-Viciana et al. Science, 311: 1287-1290 (2006).

- **Genomic hypothesis: Proband will exhibit overlapping features**
- **Documented:** characteristic facial features, growth retardation, neurocognitive impairment,
- **Re-evaluation:** gut malrotation, coarse hair

# TFNG Discovery Rate

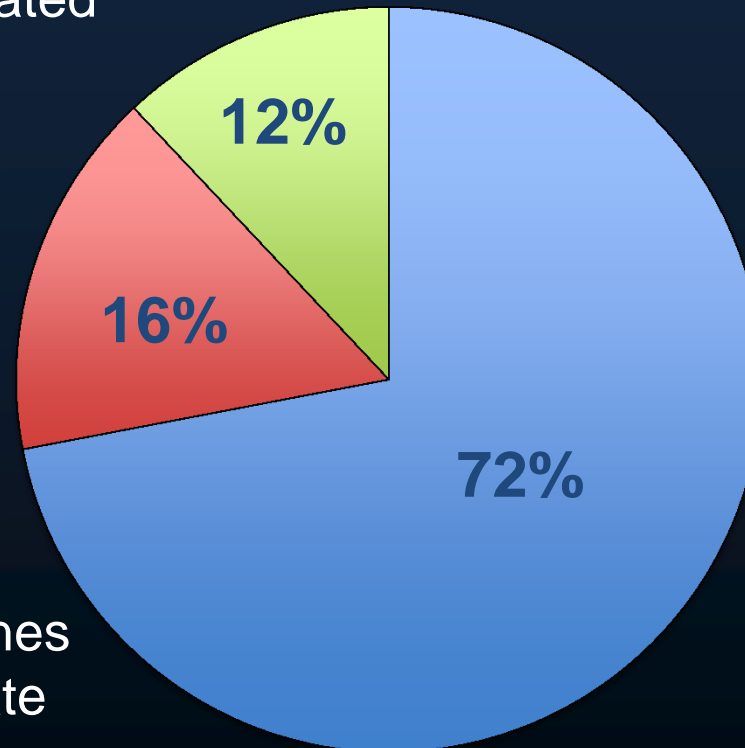
*Data from 238 families*

## ***Inconclusive***

- Genes not associated with disease and unable to test functionally

## ***Maybe causal***

- Novel disease genes harboring candidate pathogenic alleles; no direct functional assay



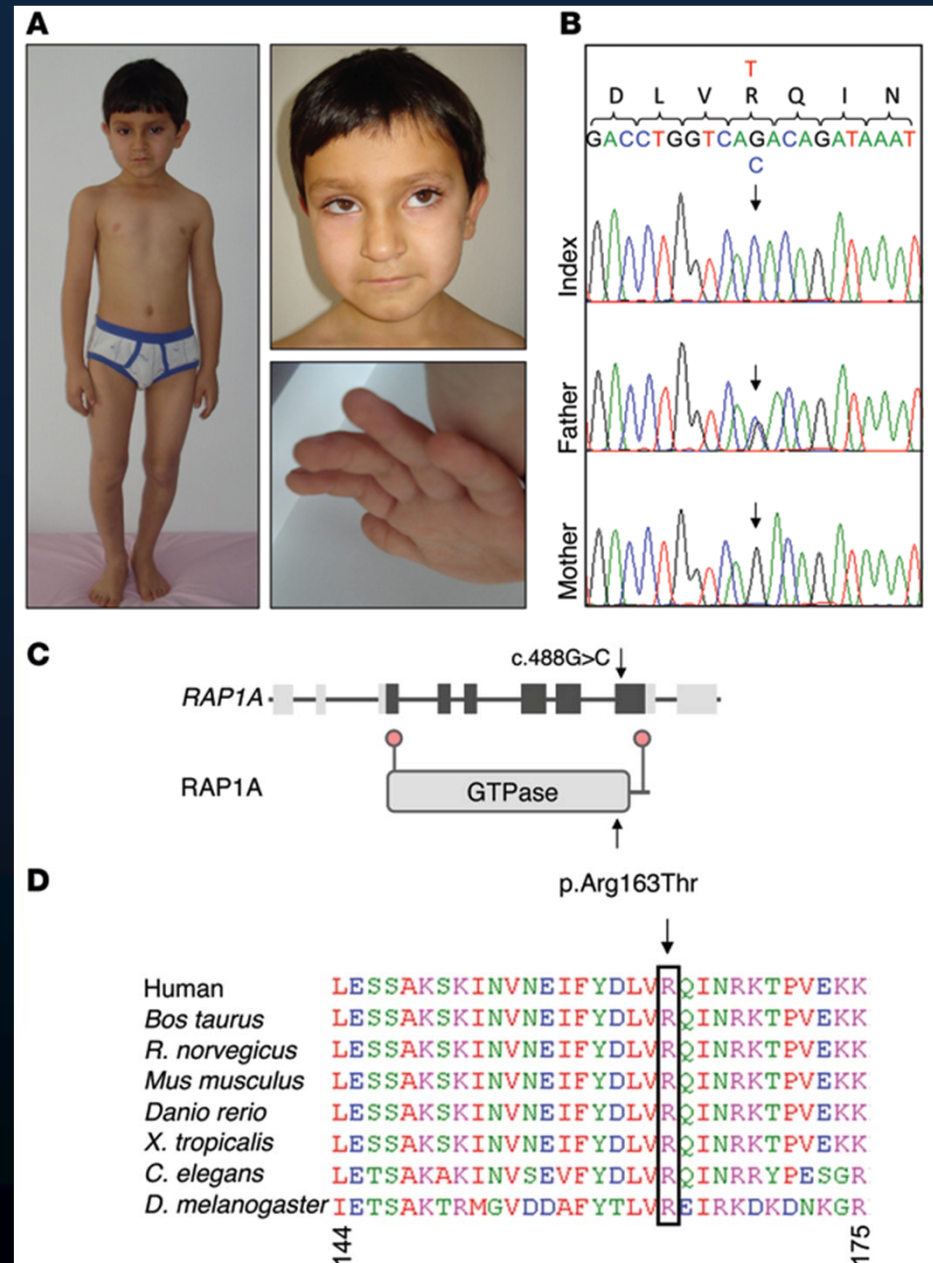
## ***Probably causal***

- Known gene and known mutation
- Known gene and novel functional variants
- Known CNV
- New gene with strong functional evidence

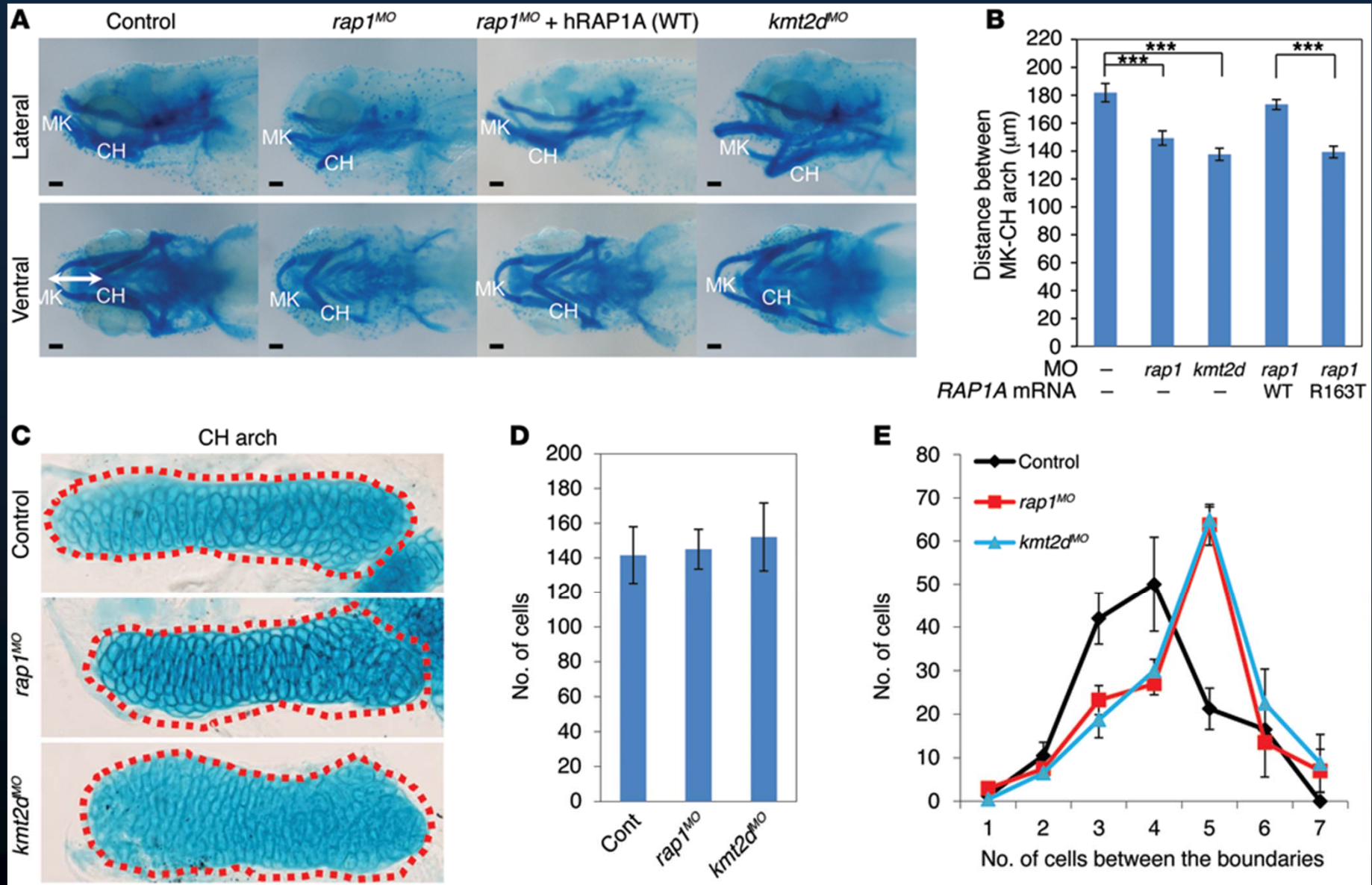
*Can any of this lead to credible therapeutics???*

# Principle: Functional LoF informs drug discovery

2013: gene discovery

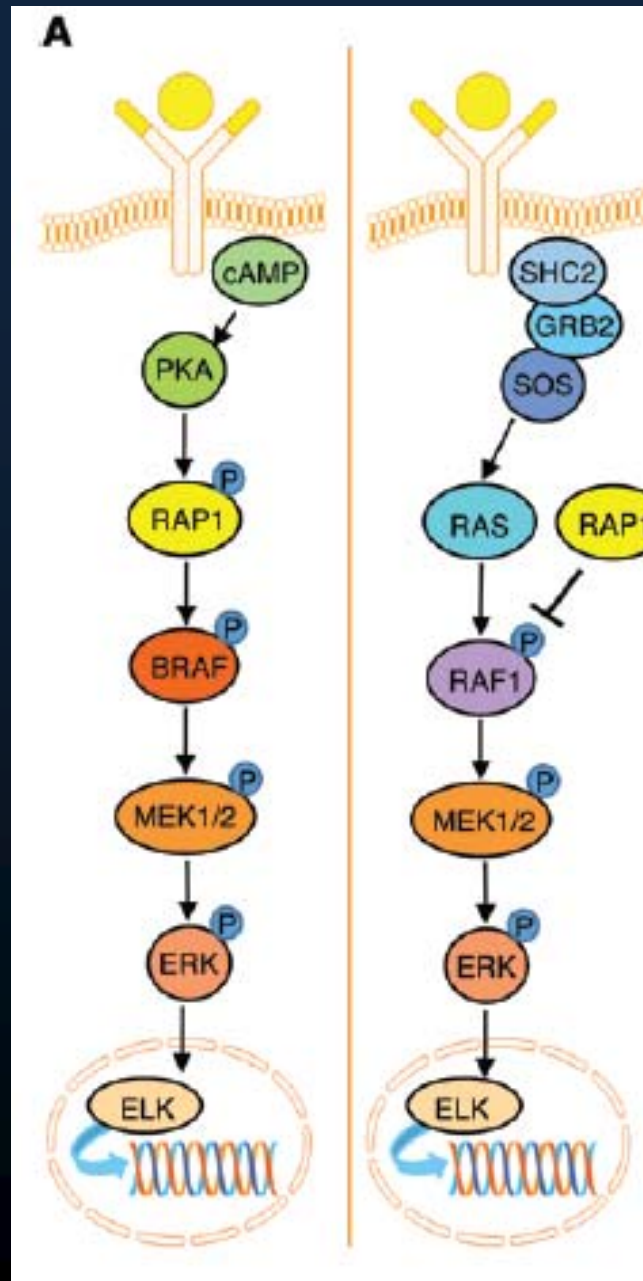


# 2014: Modeling the jaw development of KS in zebrafish

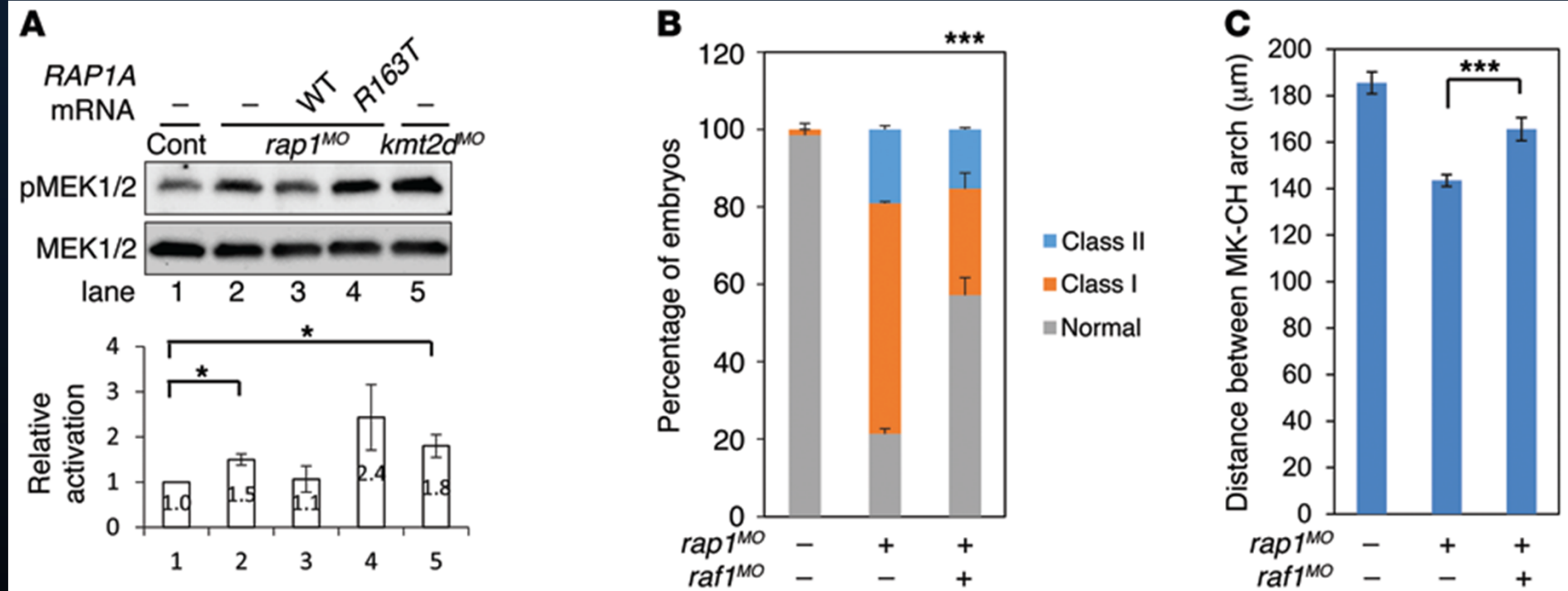




# KS pathophysiology overlap with RASopathies



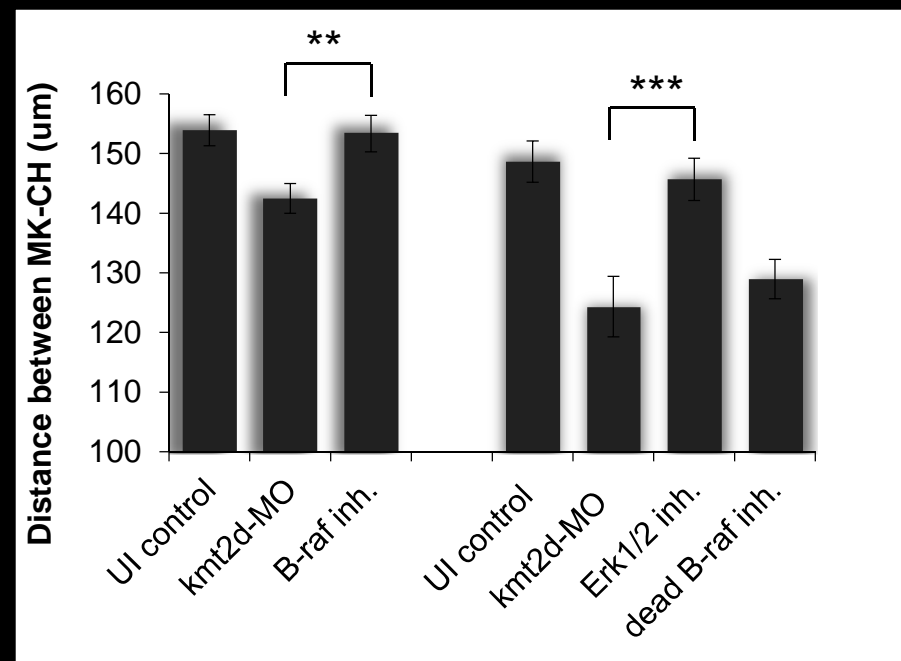
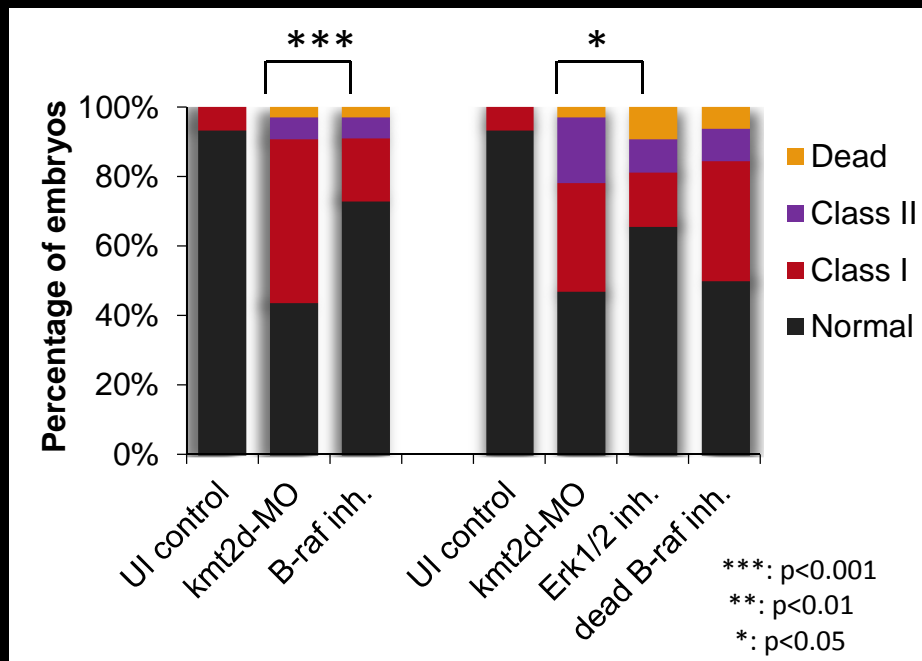
# Pathway-based Genetic Suppressor





# 2014/15: Rescue of CE and jaw defect in *kmt2d* morphants

2 of the 27 compounds consistently rescue CE and jaw defects



“Only” remaining boundary to move to patients is legal/IP

## *So what have we learned in our Travels??*

- *Collaboration and data sharing are key*
- *Community engagement is necessary*
- *Strong genetics and biochemistry*
- *You never know where your “winners” come from*





Thank you