A FAMILY-FRIENDLY GUIDE TO NEW DYRK1A RESEARCH

RECENT PUBLISHED FINDINGS AND A TIGER UPDATE

RACHEL EARL, PHD

DYRK1A FAMILY MEETUP, JUNE 2019
EXCITING NEW RESEARCH ON DYRK1A IS BEING PUBLISHED EACH YEAR!!

BUT TRYING TO UNDERSTAND IT CAN FEEL LIKE
RECENT THEMES IN DYRK1A RESEARCH

1. BRAIN CELL GROWTH
2. MISSENSE MUTATIONS
3. MOUSE MODELS

FIRST LET’S TALK ABOUT THE BASICS!
THEME 1: BRAIN CELL GROWTH

DIFFERENT BRAIN CELLS DO DIFFERENT THINGS

PART OF TYPICAL DEVELOPMENT REQUIRES THE RIGHT NEURONS TO MIGRATE TO THE RIGHT PLACE IN THE BRAIN.
DYRK1A IMPACTS THE WAY NEURONS GROW

• DYRK1A expressed early in development of embryo
• Development of dendrites and axon are impacted
• Migration of neurons to where they need to be in the brain also disrupted

Dang et al., 2018; Arranz et al., 2019
DYRK1A IMPACTS TYPE OF NEURONS

• More excitatory neurons than there should be
• Imbalance of excitatory and inhibitory neurons also found in ASD
• Other genes influenced by DYRK1A affect axon growth and communication between neurons.

Arranz et al., 2019
THEME 2: MISSENSE MUTATIONS

What is a missense mutation?

DNA sequence → Amino acids → Protein → Brain and body development

"MISSENSE MUTATION MAY OR MAY NOT DISRUPT DEVELOPMENT"
PATHOGENIC MISSENSE MUTATIONS ARE IN A SPECIFIC REGION OF THE GENE

- Missense mutations located in prime protein-coding region
  - Catalytic domain
- Pathogenic mutations likely effect the stability of the protein domain

Evers et al., 2017; Widowati et al., 2018
FIRST HALF OF GENE IS MOST CRITICAL TO DEVELOPMENT

- Pathogenic mutations occurred more often on one side of the gene (where the protein-coding region is) while natural mutations occurred on the other end.

[Non-disease causing mutations]

[Pathogenic mutations]
DYRK1A ANIMAL MODELS

IMPORTANT PRECURSOR TO PHARMACOLOGICAL TREATMENTS
**THEME 3: ANIMAL MODELS**

- Animal models are a very important bridge for determining how genetic disruptions influence development.

- A successful animal model can also be used for testing future pharmacological treatments for people.

**DYRK1A +/-**
- Two functional copies of genes

**DYRK1A +/+**
- Researchers ask how do the two types of mice compare in development and behavioral characteristics?

**DYRK1A +/-**
- Only one functional copy of gene
MOUSE MODELS SHOW SAME CLINICAL FEATURES AS HUMANS

- Mice with only one working copy of *DYRK1A* (instead of the typical two) **show impairments consistent with those seen in people:**
  - cognitive flexibility (difficulty completing mazes)
  - decreased vocalizations (fewer complex vocalizations)
  - febrile seizures (seizures associated with fever)

Raveau et al., 2018
ASD-LIKE SYMPTOMS IN DYRK1A +/- MICE

DYRK1A +/- mice showed:

• Social impairments
  • Reduced exploration when new mice introduced
  • Increased escape behaviors when confronted with another mice in tube
  • Reduced sniffing of other mice

• Repetitive behaviors (marble burying, self-grooming) in DYRK1A +/- mice

Raveau et al., 2018; Arranz et al., 2019
ASD-LIKE SYMPTOMS IN DYRK1A +/- MICE

Raveau et al., 2018; Arranz et al., 2019
SUMMARY

• Research across a variety of fields are zooming in on both what’s going on genetically and what’s going on behaviorally for DYRK1A.

• Better understanding of DYRK1A’s impact at the cellular level will help us down the road identify pharmacological treatments that could target the areas that DYRK1A affects.

• Families like yours participating in research make ALL the difference in our ability to understand DYRK1A better.
ONGOING TIGER STUDY RESEARCH

17 patients with DYRK1A and their parents have completed the TIGER study

12/17 of those patients have completed EEG

10 new families participating this weekend!!
FINDINGS FROM OUR 2017 DYRK1A PAPER

Earl et al., 2017
FINDINGS FROM OUR 2017 DYRK1A PAPER

The DYRK1A phenotype is unique

Earl et al., 2017
FINDINGS FROM OUR 2017 DYRK1A PAPER

Those with DYRK1A mutations have distinct facial features

Earl et al., 2017
FINDINGS FROM OUR 2017 DYRK1A PAPER

Those with *DYRK1A* mutations have distinct facial features

- p.Ala498Profs*61
- p.Asn151Lysfs*12
- c.665-8_665-3delTCTTTTC
- p.Leu295Phe
- p.Ile468Aspfs*17
- p.Arg255*

Earl et al., 2017
THANK YOU!
WE COULD NOT DO THIS RESEARCH WITHOUT YOU AND WE DO IT FOR YOU!
WE WANT TO LEARN MORE FROM YOU!

Participate in our research!

Contact us by:
Email: rablab@uw.edu
Phone: 206-616-2889
Website: http://depts.washington.edu/rablab/