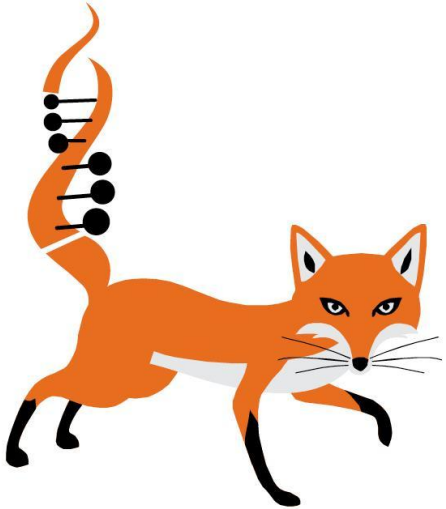

INTERNATIONAL
FOXG1
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# Decoding FOXG1 and IFF Research Strategy

# FOXG1 vs. Foxg1- What Capitalization Means

How a gene is capitalized is important, it allows the reader to gain insight into exactly what the author is trying to say.

- FOXG1- refers to the gene and syndrome in humans
- Foxg1- refers to the gene and syndrome in mouse and rat animal models
- *FOXG1* and *Foxg1 in italics*- refers to the proteins, not the gene itself

# FOXG1 Syndrome – Phenotype (Visible Human Symptoms)

**Microcephaly and Structural Brain Abnormalities**

- Small head and partial or full loss of the corpus callosum (inhibiting communication of left and right brain)

**Epilepsy/Seizures**

- Infantile Spasms and life-threatening seizures resistant to drugs and surgical treatments that regress skills

**Gross Motor/Fine Motor Delays**

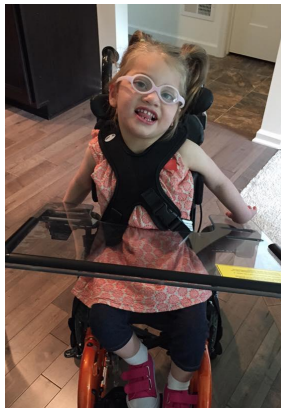
- Low muscle tone leads to little or no sitting, walking, talking or purposeful use of hands
- Strabismus, poor eye contact and Cortical Visual Impairment

**Feeding Issues**

- Low Muscle tone leads to gastroesophageal tract causing reflux, constipation
- Many individuals require feeding tube placement

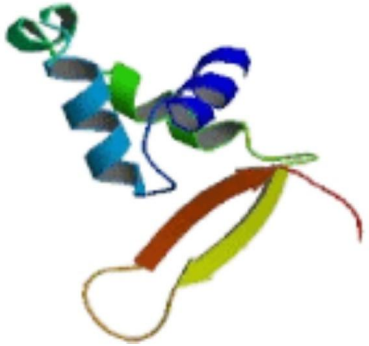
**Associated Conditions & Disorders**

- Autism Spectrum Disorders (ASD)
- Sensory Processing Disorder (SPD)
- Movement disorders



# FOXG1 Syndrome – History and Landscape

- FOXG1 gene discovered in 1995 by Dr. Alessandra Renieri, University of Siena, Italy
- Shown as cause of Congenital RETT/FOXG1 Syndrome in 2005
- Formerly called Congenital RETT Syndrome, has since been proven that FOXG1 Syndrome is a sister to RETT Syndrome and does not fall under the RETT umbrella
- Currently 360  cases reported worldwide.
    - This number steadily increasing as more children are tested for Autism Spectrum Disorder (ASD), and other genetic disorders.



FOXG1 Gene Representation

# What is FOXG1 and FOXG1 Syndrome? The Science

# FOXG1 tells the Brain How to Develop

FOXG1 is one of the **earliest transcription factors** that gives rise to Telencephalon - where the cerebrum develops prenatally

- Transcription factors are the set of instructions that bind DNA to regulate the expression of other genes
- The Cerebrum is **What makes us human**. It is the largest and most important part of brain, controlling the central nervous system.

# FOXG1 Genotype (Gene Mutation)

- Mutations, or ‘pathogenic variants’, are spelling errors that change the instruction, and impact how genes work
- These variants have been observed in FOXG1 affected patients:

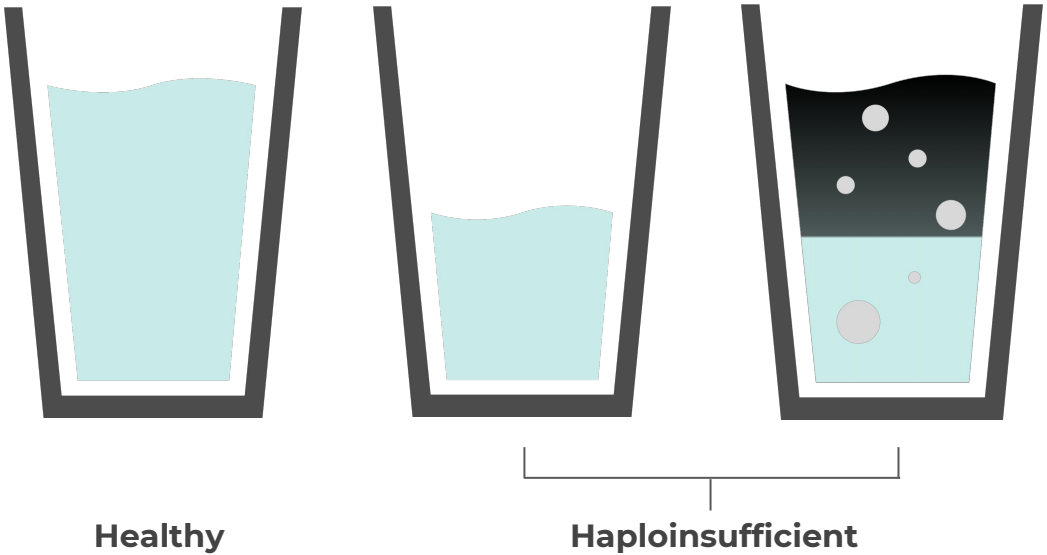
| Healthy | Deletion | Duplication | Missense | Frameshift |
|---|---|---|---|---|
| A typical healthy gene | A part, or the entire gene is missing | A part, or the entire gene is duplicated | One copy has the wrong letter | Reading frame shifted |
|  |  |  |  |  |

# *FOXG1* Protein

The FOXG1 gene encodes (gives instructions) to a protein called **Forkhead box G1 (aka *FOXG1* protein).**

- Protein becomes ***haploinsufficient***: prevents production of the FOXG1 protein and/or impairs the protein's function

- These outcomes are referred to as **FOXG1 Syndrome**



The International FOXG1 Foundation is leading in cutting edge research to find a cure.

# We are in a New Era of Scientific Discovery

Over the last five years, science has made massive strides

- Scientists can safely deliver medicine to the brain through vectors (targeting a specific point)
- Technology exists to increase or decrease *FOXG1* protein levels (saRNA and iRNA therapies)
- Researchers are experimenting with CRISPR to edit genes (correct the root problem)

# What IFF is funding research for

1. **Understanding the Impact of FOXG1 on the Brain**
   What does a FOXG1 brain look like? What are the structural abnormalities, and how do they relate to behavioral symptoms? What happens when we attempt to turn the gene back “on”?

2. **Developing a Public Clinical Database**
   - This is critical for research proposal developments
   - Will contain medical and statistical data, such as:
     - Skill levels,
     - Type of mutation,
     - A listing of symptoms and percentages affected,
     - Occurrence per country

3. **Improve FOXG1 Symptoms**
   What happens if we trial already FDA-approved medication on neurons developed from FOXG1 patient tissue samples?

# Ongoing FOXG1 research projects

## Understand the Biological Impact of FOXG1

**Boston Children's Hospital**
*Professor, Univ of California, San Diego*

Develop patient-derived iPS neurons to characterize impact of FOXG1-disruption, and to provide a substrate for drug screening

**Jeffrey Neul, MD, PhD**
*Professor, Univ of California, San Diego*

Generate a *Foxg1*-deletion mouse model to characterize molecular, developmental, and behavioral outcomes of *Foxg1* disruption and subsequent correction

**Alessandra Renieri, MD, PhD**
*Professor, Univ of Siena*

Employ CRISPR/Cas9-mediated approach to correct *FOXG1* mutations in iPS neurons and animal models, and characterize outcomes

**Flora Vaccarino, MD**
*Professor, Yale School of Medicine*

iPS neurons to model neurodevelopmental disorders; *FOXG1* in the pathogenesis of autism spectrum disorders and head circumference

**Antonello Mallamaci, PhD**
*Associate Professor, SISSA*

**Roberta Cilio, MD, PhD**
*Director of Pediatric Epilepsy Research, UCSF*

Generate patient-derived iPS cortical neurons to model morphologic and electrophysiologic sequelae of *FOXG1* disruption, with special interest in cortical development

## Utilize Gene Therapies for Cures

**Guangping Gao, PhD**
*Professor, Univ of Mass. Medical School*

Develop saRNA + AAV-mediated gene therapies for neurodevelopmental disorders, including *FOXG1*

## Improve FOXG1 Symptoms

**Sandra Acosta-Verdugo, PhD**
*Post-Doctoral Fellow, Northwestern University*

Functional characterization of FOXG1 regulatory elements to identify possible therapeutic targets

# Natural History Study

- In October of 2014 the National Institute of Health awarded a $29 million five-year grant to study FOXG1 Syndrome, MECP2 Duplication Syndrome, CDKL5 Syndrome and Rett Syndrome.

- The goals of this grant are:
  - to understand the core clinical features of each disorder
  - to identify if there are any treatments that can improve quality of life
  - to understand the link between symptoms and brain imaging/eeg variations.

# IFF is creating assets to help scientists

- Publically available *Foxg1* deletion **mouse models** and well characterized **iPSC lines** for molecular/behavioural research and pre-clinical trials
- *FOXG1* clinics to accumulate accurate clinical data
- RETT associated Natural History Study to characterize outcomes across patients lifespan, and to explore possible genotype-phenotype correlations
- Active social network of affected families that can be reached immediately
- Building of public facing clinical and patient derived database

Boston Children's Hospital
Until every child is well™

UNIVERSITY of ROCHESTER MEDICAL CENTER

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for Research on Human Development

# Million dollar question

If we can figure out how to fix the FOXG1 gene or improve its protein level/activity, can new brain cells be formed? (Cells that were not formed due to FOXG1 Syndrome) Can cells re-generate?

Currently this is unknown; we will learn more over next few years through research experiments

# FOXG1 Could Be Linked to Autism and Other Brain Disorders

- Disrupted GABA neurons lead to Autism, Schizophrenia and Epilepsy
- Functional FOXG1 Genes have been shown to regulate the balance of GABA neurons

While FOXG1 Syndrome is a rare condition, **its linkage to other disorders may help us attract scientific/biotech focus and investment**

Mariana J, *et al.* 2015. FOXG1-dependent dysregulation of GABA/Glutamate neuron differentiation in autism spectrum disorders. *Cell.*162:375-390.

# FOXG1 Foundation Scientific Advisory Board

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HARVARD MEDICAL SCHOOL

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Greenwood Genetic Center

***Dr Sookyong Koh****, MD, Ph.D., Marcus Professor in Neurology, Associate Professor, Division of Neurology, Dept of Pediatrics, Emory University School of Medicine*

EMORY UNIVERSITY SCHOOL OF MEDICINE

# Questions? Want to help?

If you have a researcher we should contact, or questions about the science of FOXG1 please contact Adam Haar at adam.haar@foxg1.org.

It takes millions of dollars to get to clinical trials. Rare diseases like Dravet have been successful through parents working together to raise funds.