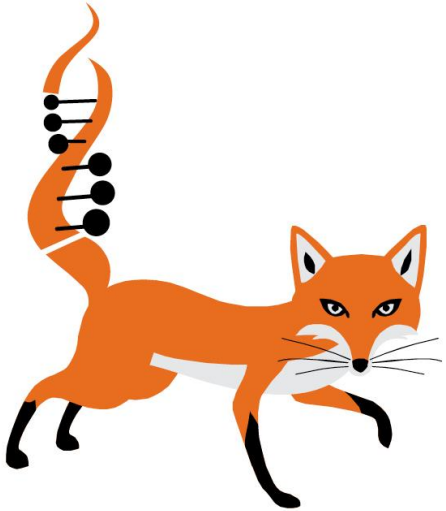


INTERNATIONAL
FOXG1
FOUNDATION®

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

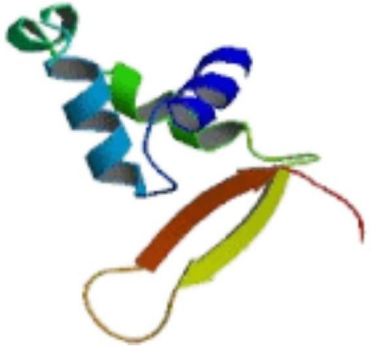
- Low Muscle tone leads to gastroesophageal tract causing reflux, constipation
- Many individuals require feeding tube placement

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 280 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)

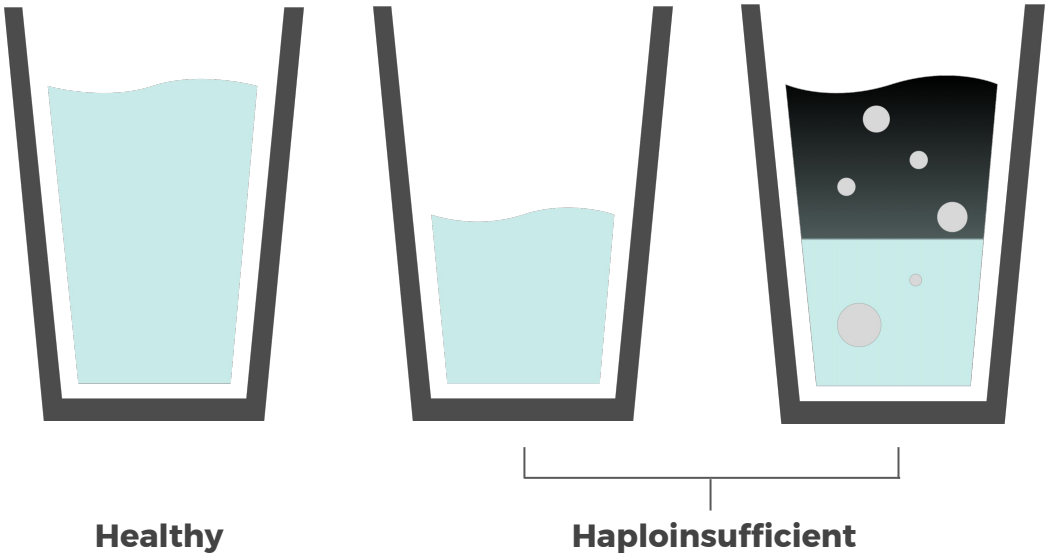
- Mutations, or ‘pathogenic variants’, are spelling errors that change the instruction, and impact how genes work
- These variants have been observed in FOXG1 affected patients:

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

- We 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)
- We are experimenting with CRISPR to edit genes (correct the root problem)

What IFF is funding research for

1. **Understand the Biological Impact of FOXG1**
   What neurons and cells are affected? What other genes are tied to FOXG1? How do different parts of the body react to different mutation types?

2. **Utilize Gene Therapies for Cures**
   Exploit existing gene therapies to better understand *FOXG1* function, and to develop novel treatment strategies:
   - saRNA- and AAV-*Foxg1*-mediated approaches to boost protein expression
   - CRISPR/Cas9 editing as a tool to correct *FOXG1* mutations in neurons
   - RNAi as a tool to silence dysfunctional protein

3. **Improve FOXG1 Symptoms**
   Identify biological pathways that can be modulated with existing compounds. Trial available drugs and hormones to improve symptoms.

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

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*

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

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.

FOXG1 Clinical Database

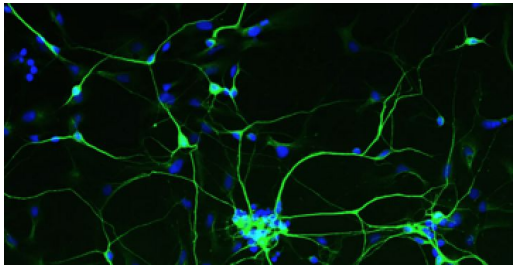
- The development of a public clinical database that researchers have access to will be critical for proposal developments

- This anonymous database will contain medical and statistical information, compiled by clinicians, such as:
  - Type of mutation
  - Skill levels
  - A listing of symptoms and percentages affected
  - Occurrence per country

- This project will occur during the same time as the current research projects

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 at Boston Children's Hospital and Stanford Children's Health 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℠

Stanford Children's Health

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

Dr. Heather Olson, ***MD, MS, Children's Hospital Boston, Assistant in Neurology, Instructor of Neurology, Harvard Medical School.***

HARVARD MEDICAL SCHOOL

Dr. Orrin Devinsky, ***MD. NYU Langone Medical Center, Professor, Department of Neurology, Department of Neurosurgery, Department of Psychiatry, Chief of Service, NYU Epilepsy Service.***

NYU Langone MEDICAL CENTER

Dr. Walter Kaufmann, ***Ravenel Boykin Curry Chair in Genetic Therapeutics, Professor of Neurology, Greenwood Genetic Center.***

Greenwood Genetic Center

Elli Brimble, ***MSc, MS, CGC, Lucile Packard Children's Hospital at Stanford*** has joined us as the foundation's ***Genetics Liaison.***

Stanford MEDICINE

Questions? Want to help?

If you have questions about the science of FOXG1 please contact Adam Haar at a.e.haar@gmail.com.

If you have a researcher we should contact, biotech ideas, or want to help fundraise, please contact Nasha Fitter at nasha.fitter@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.