



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

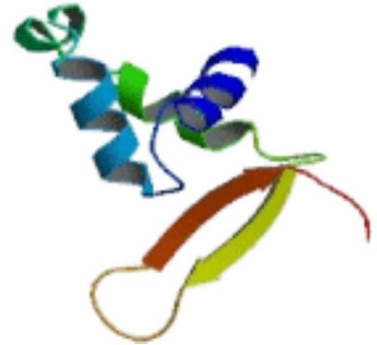
Associated Conditions & Disorders

- 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

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What is FOXC1 and FOXC1 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)

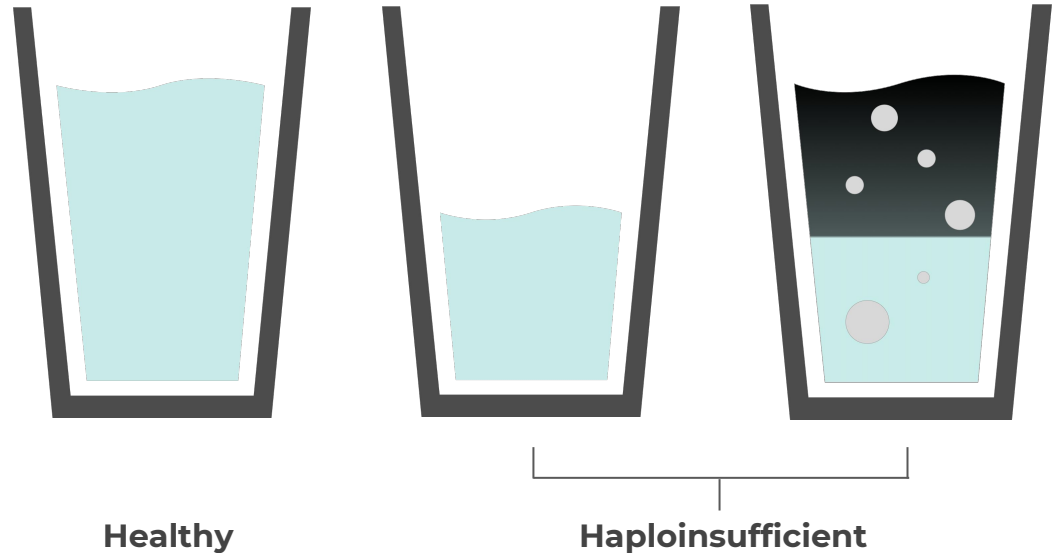
- Mutations, or 'pathogenic variants', are spelling errors that change the instruction, and impact how genes work
- These variants have been observed in FOXG1 affected patients:

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**



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The International FOXP2
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 *FOXP2* 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 FOXP1 on the Brain**

What does a FOXP1 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 FOXP1 Symptoms**

What happens if we trial already FDA-approved medication on neurons developed from FOXP1 patient tissue samples?



Ongoing FOXP1 research projects

Understand the Biological Impact of FOXP1



Boston Children's Hospital

Professor, Univ of California, San Diego

Develop patient-derived iPS neurons to characterize impact of FOXP1-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 FOXP1 mutations in iPS neurons and animal models, and characterize outcomes

Flora Vaccarino, MD

Professor, Yale School of Medicine

iPS neurons to model neurodevelopmental disorders; FOXP1 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 FOXP1 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 FOXP1

Improve FOXP1 Symptoms



Sandra Acosta-Verdugo, PhD

Post-Doctoral Fellow, Northwestern University

Functional characterization of FOXP1 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 FOXP1 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



Million dollar question

If we can figure out how to fix the FOXP1 gene or improve its protein level/activity, can new brain cells be formed? (Cells that were not formed due to FOXP1 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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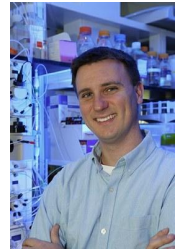


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Questions? Want to help?

If you have a researcher we should contact, or questions about the science of FOXP1 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.