Decoding FOXG1 and IFF Research Strategy
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
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.
What is FOXG1 and FOXG1 Syndrome? The Science
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:

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<tr>
<th>Healthy</th>
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<th>Duplication</th>
<th>Missense</th>
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<td>A typical healthy gene</td>
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**Diagram**

- **Healthy**: A typical healthy gene.
- **Deletion**: A part, or the entire gene is missing.
- **Duplication**: A part, or the entire gene is duplicated.
- **Missense**: One copy has the wrong letter.
- **Frameshift**: Reading frame shifted.
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)
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 |
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<td>Develop patient-derived iP5 neurons to characterize impact of FOXG1-disruption, and to provide a substrate for drug screening</td>
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|                                         | 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 |
|                                         | 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 iP5 neurons and animal models, and characterize outcomes |
|                                         | Flora Vaccarino, MD  
Professor, Yale School of Medicine |
|                                         | iP5 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 iP5 cortical neurons to model morphologic and electrophysiologic sequelae of FOXG1 disruption, with special interest in cortical development |
| Utilize Gene Therapies for Cures | |
| Sandra Acosta-Verdugo, PhD  
Post-Doctoral Fellow, Northwestern University |
|                                         | Functional characterization of FOXG1 regulatory elements to identify possible therapeutic targets |
| Improve FOXG1 Symptoms | |
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
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

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

Dr. Alex Paciorkowski, Senior Instructor of Neurology, Pediatrics, and Biomedical Genetics at the University of Rochester Medical Center.

Dr. Jeffrey Neul, Annette Schaffer Eskind Chair; Director, Vanderbilt Kennedy Center; Professor of Pediatrics, Division of Neurology

Dr. Steven Gray, Ph.D. Molecular Biology, UNC School of Medicine, Gray Lab, Assistant Professor, Department of Ophthalmology.

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