
www.thejansensfoundation.org

- A rare disease
- Miles and miles of desert sand
- No Google
- No “expert opinions”


Christmas, 2009

No Sign of Disease

**Arshaan Adam  (A good man)**


Christmas, 2010

A Diagnosis at last

**Jahan Adam (Savior)**

# Jansen Metaphyseal Chondrodysplasia (JMC)

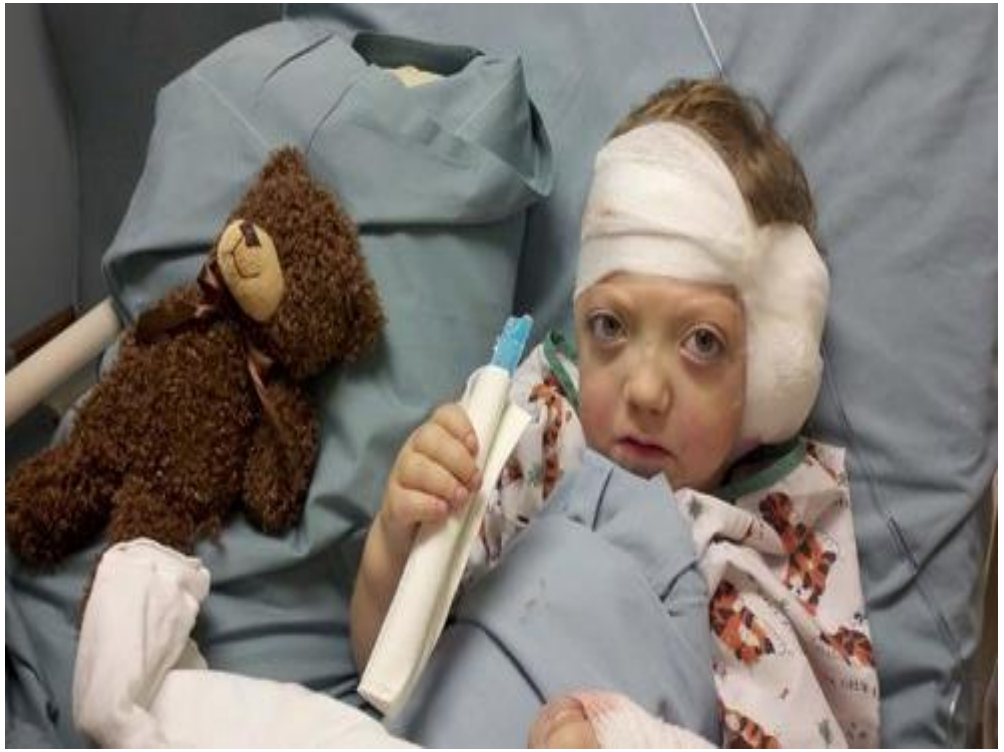
- A rare disease of bone and mineral ion physiology
- ~ 30 patients known to date
- Autosomal dominant, caused by activating mutations in the PTH/PTHrP receptor (PTHR1)
- Short stature, skeletal abnormalities, hypercalcemia/hypercalciuria, nephrocalcinosis, renal disease.


Rare Disease Day 2016, NIH

Dr. Harald Jueppner had been researching Jansen's Disease for 20 years, but ***never*** met a patient.


A.I. Dupont Hospital 2016, Delaware

# The Jansen's Foundation formed in February, 2017.



**Jansen's patient recovering from eardrum reconstruction, was born with craniosynostosis - the fusion of the skull's bones, and at two years old had to have his skull broken to make room for his brain to grow.**

Text Source: National Organization for Rare Diseases website, https://rarediseases.org/rare-diseases/jansen-type-metaphyseal-chondrodysplasia/.
Picture Source: Jansen's Foundation website:

# Jansen's Foundation and MGH

**Connected with the research team at MGH, and has been supporting the research efforts.**

ORIGINAL ARTICLE

## Jansen Metaphyseal Chondrodysplasia due to Heterozygous H223R-PTH1R Mutations With or Without Overt Hypercalcemia

Sheela Nampoothiri, Eduardo Fernández-Rebollo, Dhanya Yesodharan, Thomas J. Gardella, Eric T. Rush, Craig B. Langman, and Harald Jüppner

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**Context:** Jansen's metaphyseal chondrodysplasia (JMC) is a rare skeletal dysplasia characterized by abnormal endochondral bone formation and typically severe hypercalcemia despite normal/low levels of PTH. Five different heterozygous activating PTH/PTHrP receptor (PTH1R) mutations that change one of three different amino acid residues are known to cause JMC.

**Objectives:** Establishing the diagnosis of JMC during infancy or early childhood can be challenging, especially in the absence of family history and/or overt hypercalcemia. We therefore sought to provide radiographic findings supporting this diagnosis early in life.

**Patients and Methods:** Three patients, a mother and her two sons, had radiographic evidence for JMC. However, obvious hypercalcemia and suppressed PTH levels were encountered only in both affected children. Sanger sequencing and endonuclease (*SphI*) digestion of PCR-amplified genomic DNA were performed to search for the H223R-PTH1R mutation.

**Results:** The heterozygous H223R mutation was identified in all three affected individuals. Surprisingly, however, the now 38-year-old mother was never overtly hypercalcemic and was therefore not diagnosed until her sons were found to be affected by JMC at the ages of 28 months and 40 days, respectively. The presented radiographic findings at different ages will help diagnose other infants/toddlers suspected of having JMC.

**Conclusion:** The H223R mutation is typically associated with profound hypercalcemia despite low/normal PTH levels. However, the findings presented herein show that overt hypercalcemia is not always encountered in JMC, even if caused by this relatively frequent mutation, which is similar to observations with other PTH1R mutations that show less constitutive activity. (***J Clin Endocrinol Metab*** **101: 4283–4289, 2016)**

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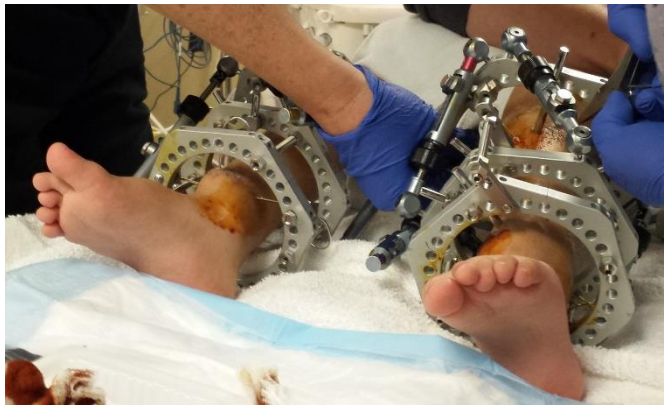
# Children Living with Jansen's

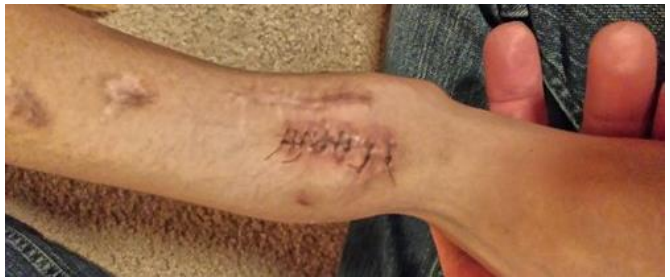
- "During childhood, affected individuals may begin to exhibit progressive stiffening and swelling of many joints and/or an unusual 'waddling gait' and squatting stance."

Jansen's patient's legs pre-surgery

Post-Surgery Recovery



A few months post-surgery, the "Bends" are already back



Text Source: National Organization for Rare Diseases website, https://rarediseases.org/rare-diseases/jansen-type-metaphyseal-chondrodysplasia/.
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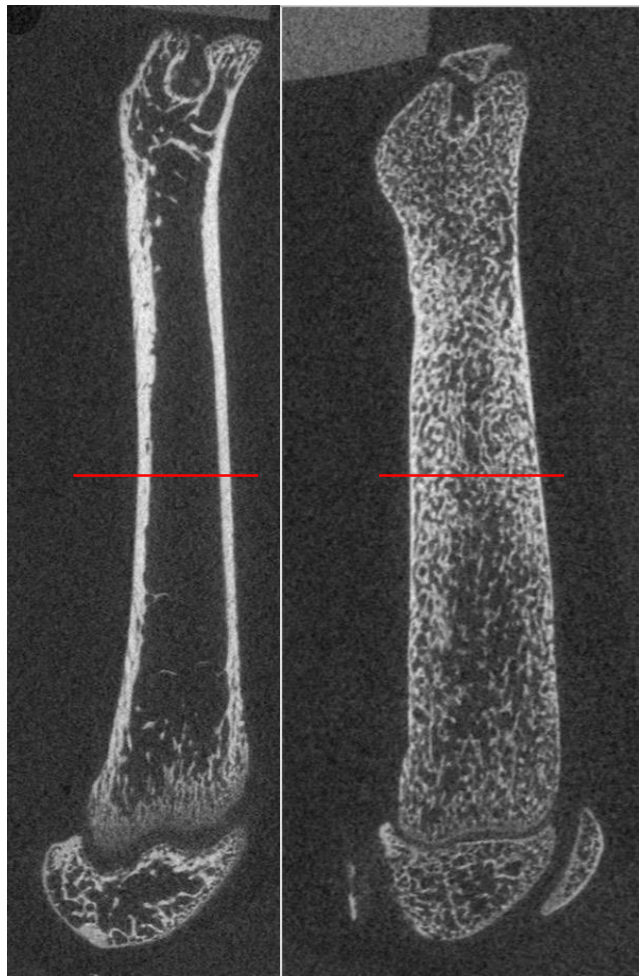
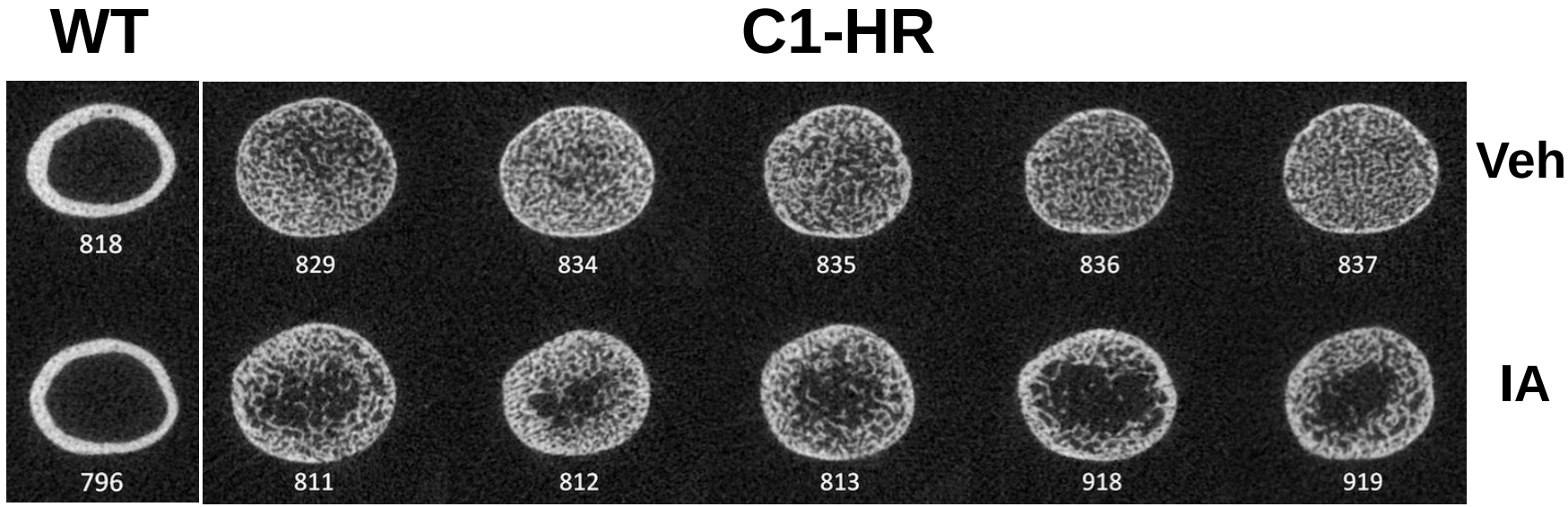
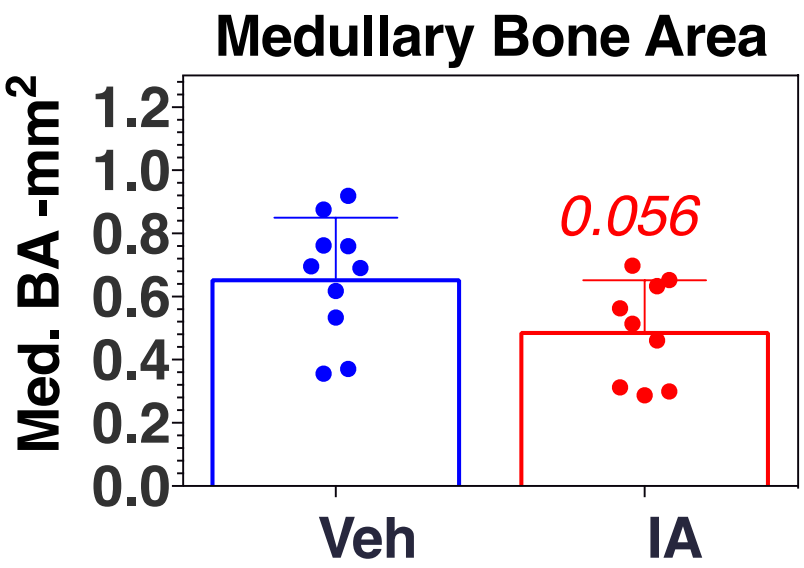
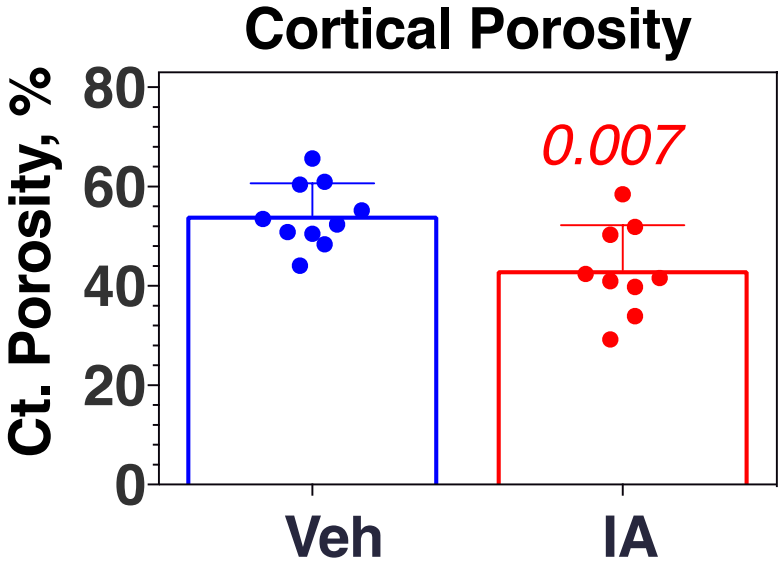
# The Monster Inside


# Inverse agonist (IA) improves bone parameters of C1-HR mice



# The Jansen's Foundation Mission

**The Jansen's Foundations goal is to speed up research process, obtain all the necessary approvals, and to start the first testing of a disease-modifying peptide in an adult patient with Jansen's disease.**

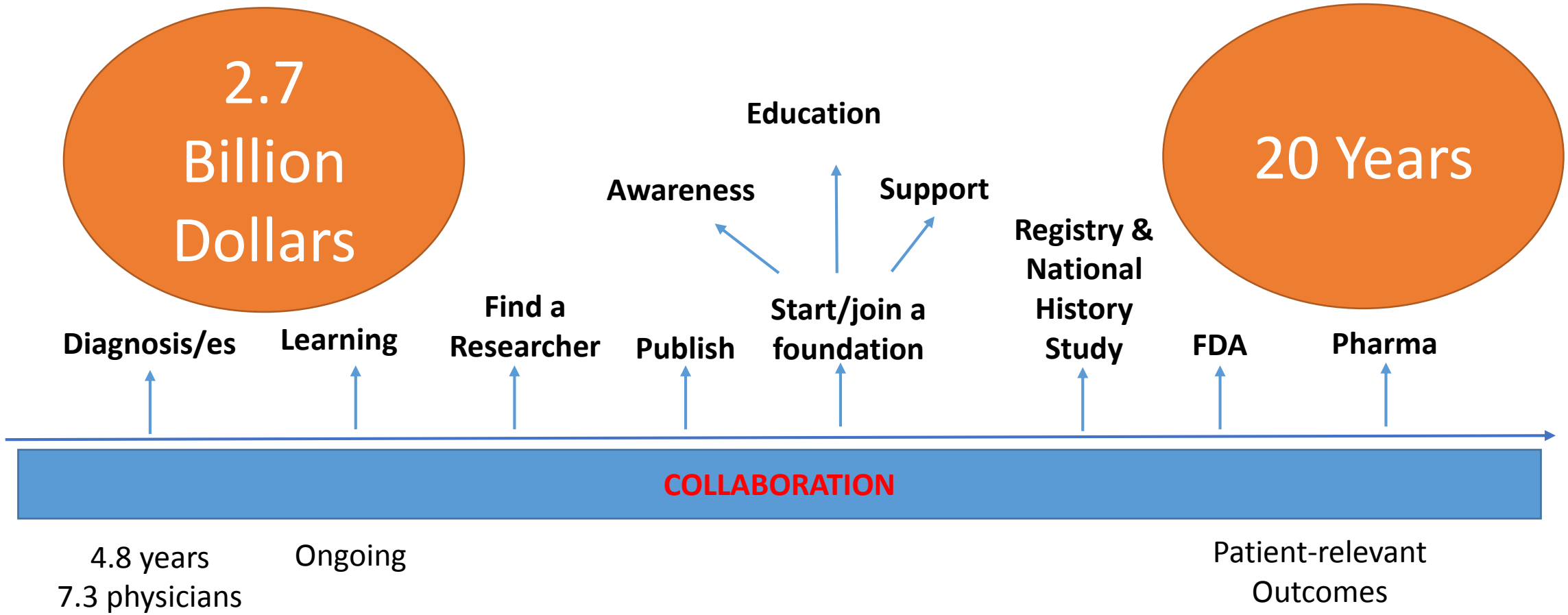
- **Nov. 2017 – RO1 NIH grant – pre-clinical studies**
- **June 2018 – Pre-IND meeting with FDA**
- **Sept 2018 – Patient Registry**
- **December 2018 – Natural History Study**

**2019 – NIH TRND FUNDING**

# Rare Disease Facts

Only 5%

- 1:10 people suffer from a **rare disease** (U.S.)
- 30% will not live to see their 5th birthday.
- **Rare diseases** are responsible for 35% of deaths in the first year of life.
- 50% affected are children.
- Affect over 300 million people worldwide




**Patient Pathway to Cures/Treatment**

# Assumption!!

We are assuming that we have reasons to prevent disease in future people.

# The Case of Pursuing Germline Gene Editing – The Medical Case

**Prevent Genetic Disease**

Roughly 6% of all babies born have a serious birth defect of genetic or partly genetic origin (March of Dimes Global Report on Birth Defects, 2016.)

# The Case of Pursuing Germline Gene Editing – The Medical Case

## Single Gene Disorders

- GGE may be the only way to avoid passing on single gene disorders
  - Approximately 19% of women undergoing IVF only produce one viable embryo.
  - In late onset dominant conditions, like Huntington's disease, some patients carry two copies of the disease-causing gene.

# The Case of Pursuing Germline Gene Editing – The Medical Case

- GGE may have the advantage of preventing disease in subsequent generations, unlike in IVF and PGD.
    - In the case of autosomal recessive disorders, children who are born as the result of PGD are often carriers of the condition their parents selected against.

# The Case of Pursuing Germline Gene Editing – The Medical Case

**Person-Affecting benefits VS Impersonal Benefits**

- Genetic selection replaces one individual with a disease with a healthy individual.
- It does not benefit those with disease. Its benefits are impersonal.
- GGE on the other hand could provide benefits to individuals who would otherwise be born with genetic disorders – it could cure their disorders.
- **It is plausible that person-affecting benefits are more important than impersonal benefits**

# The Case of Pursuing Germline Gene Editing – The Medical Case

## Other Disorders

- GGE allows multiple changes to be made to a single embryo, and could therefore target many different genes simultaneously.
  - IVF and PGD, are not powerful enough to select against polygenic diseases
  - Three out of every ten deaths in those under 70 are caused by chronic diseases, like cancer, diabetes and heart disease.

# The Case of Pursuing Germline Gene Editing – The Research Case

## Unique and Beneficial Role

- GGE could have a unique and beneficial role to play in research.
  - Using gene editing techniques, researchers can investigate the role of genetics in human development
  - GGE could also improve our understanding of genetic diseases


# Warriors of Hope!