SOPHIE'S NEIGHBORHOOD

Moving Mountains to Effectively Treat MCTO

Sophie's Neighborhood

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Timeline to An Ultra Rare Diagnosis
Multicentric Carpotarsal Osteolysis (MCTO)

June 2018 (1yo) – Feb 2019 | **Feb 2019 – Mar 2020** | **Mar 2020 - Present**

Pre- diagnosis

Misdiagnosis
JIA

Post-diagnosis: Absence of an effective medicine

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Who is Sophie? A catalyst for a cure.

- Whole Exome Sequencing
  - ***Diagnosis:***
    - **MCTO** at the age of 2.5 yo
- General prognosis:
  - *Her bones and kidneys would progressively deteriorate*
  - *No known research being funded for a condition this rare*
- **Sophie's Neighborhood 501c3,** was officially formed in April 2020
  - *Formed a Scientific Advisory Board*
  - *Conversed with scientists / authors of literature*
  - *Connected with patients globally*
  - *Began fundraising*
  - *Children's Hospital CO BAMM clinic & Dr. Nina Ma*

This Neighborhood has since set out on the fastest path to inhibiting disease progression and finding an effective treatment

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What is MCTO - What is Known to Date?

- Ultra Rare Genetic Condition
  - Less than 60 people worldwide, majority are children
  - Sophie's case - de novo, spontaneous

- Genetic diagnosis:
  - Invariably mutations in a single copy of the MafB gene, in a very narrow amino acid domain of about 17 base pairs, cause MCTO

- Disease phenotype is variable but generally:
  - "Disappearance" or lack of formation of carpal and tarsal bones, in the hands and feet, plus other bones of the joints
  - Nephropathy – from mild to end stage kidney failure; 2/3 of patients are affected by proteinuria (albuminuria) with progressive loss of kidney function due to damage to kidney filters
  - Craniofacial anomalies are typical. Ocular conditions reported.

- Mechanism:
  - Leading hypothesis is an increase in stability and therefore accumulation (or overabundance) of MAFB, affecting downstream gene expression
  - Effector cell type is unknown and complex. Likely to include:

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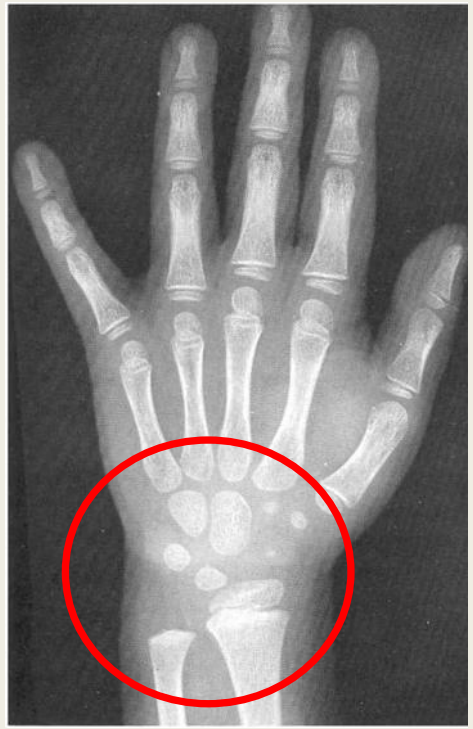
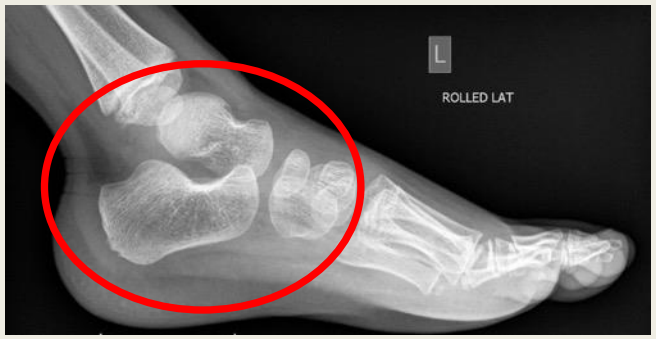
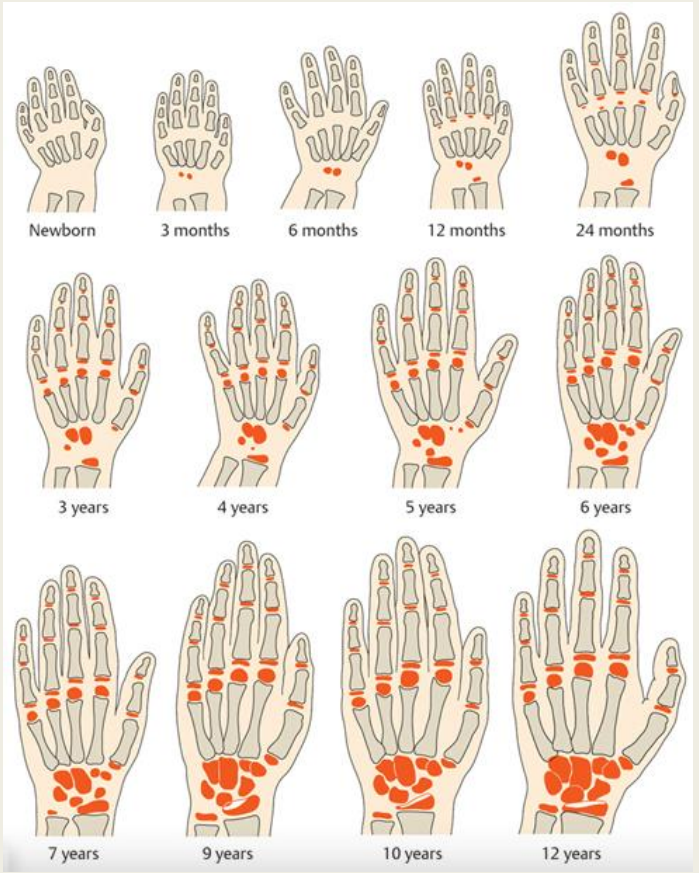
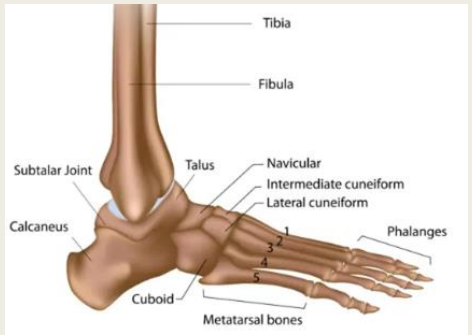
Proclivity to Joint Bones - Hands, Feet and More

4.5 yo
Healthy Child

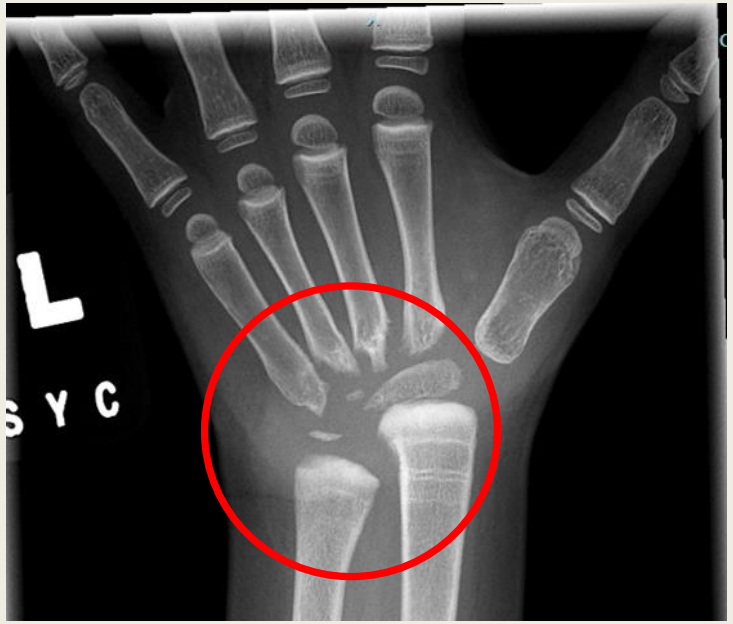


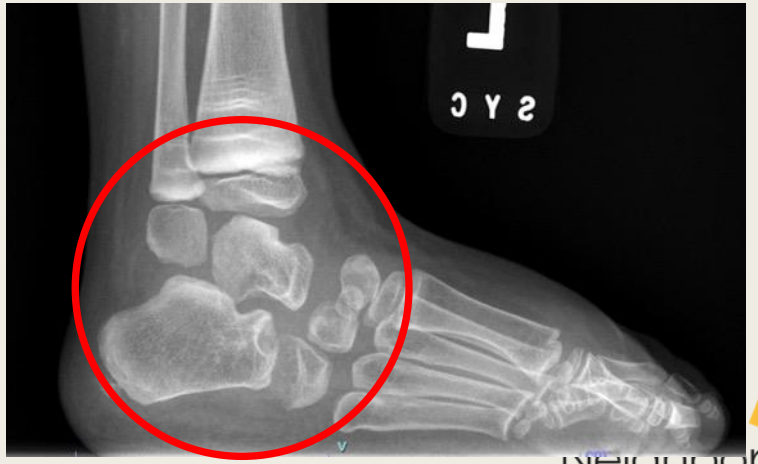






4.5 yo
MCTO patient





Pathway to Action ~ Scientific Team & Partners

Scientific Advisors

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Satoru Takahashi

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April Craft

Christina Jacobsen

Agnieszka Czechowicz

Arpeggio Biosciences

Jackso

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What Are We Doing ~ Discovery Pipeline

MCTO Biomarker Discovery

Somascan proteomic analysis identifying overabundant MafB proteins

somalogic

Nascent RNAseq transcriptomics - cell lines and iPSCs

arpeggio

MCTO patient RNAseq vs healthy control

LINDA CRNIC INSTITUTE for DOWN SYNDROME

In vitro MCTO Reporter Screen

Wild-type and mutant MafB overexpression constructs.

MafB expression cell lines and iPSC development

ARTISAN BIO™

In vitro Screen for Drug Repurposing

BROAD INSTITUTE

arpeggio

In cell Biomarker Characterization

Sample collection from MCTO and control patients and iPSC mechanistic studies

Boston Children's

somalogic

Children's Hospital Colorado

LELAND STANFORD JUNIOR UNIVERSITY 1891

In vivo Validation Studies

Validated MCTO mouse models. Mice generated by CRSPR/Cas9.

筑波大学 University of Tsukuba

The Jackson Laboratory

VE RI TAS HARVARD

Neighborhood

Sophie's Neighborhood Research Objective(s)

1. To **RAPIDLY** identify **EXISTING** therapeutic options for Sophie
2. To develop new options for MCTO treatment if necessary
3. To elucidate MCTO mechanism to inform treatment options

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Why Are We Hopeful Today: Drug Repurposing

- Positive response to anti-inflammatory medicines
  - *Identification of a drug that inhibits the pathway responsible for regulating MafB expression*
- MCTO pathology is likely due to MafB overabundance
- Ongoing studies must prove this, and determine the most effective treatment options
  - *Continue proteomic & transcriptional profiling on:*
    - Sophie's blood samples compared to controls and other MCTO patients
    - Cell lysates containing Sophie's mutation compared to controls

- Once we have a good read out, proceed with High Throughput Screening:
    - Cell lines
    - iPSC differentiations
    - nascent RNA analysis
    - Most risky: determine plausibility of selectively knocking down the mutated copy of MafB with oligonucleotide (ASO/ TMO)

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Additional Research Projects Underway

- Better understand and address pathophysiology of MCTO:
  - *The role of MafB in osteoblasts*
  - *MafB and developmental chondrogenesis*
  - *Identify role of bone marrow by studying MCTO vs WT mice, to ultimately inform experiments using MCTO patient bone marrow*

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THANK YOU!

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