Overview of Collaborative Moebius Syndrome Research Initiatives
# Extramural Collaborative Team

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<th>Mount Sinai</th>
<th>Boston Children’s Hospital</th>
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<td>• Ethylin Wang Jabs</td>
<td>• Elizabeth Engle</td>
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<td>• Erin Brittain</td>
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<td>• Cristel Crespo-Chapel</td>
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<td>• Monica Erazo</td>
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<td>• Bryn Webb</td>
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<td>• Zhongyang Zhang</td>
<td>• Sherin Shaaban</td>
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<td>• Alan Tenney</td>
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NIH Intramural Collaborative Team

• Irini Manoli
• Brian P. Brooks
• Carlo Pierpaoli
• Eva Baker
• Carol Bassim
• Barbara B. Biesecker
• Lori L. Bonnycastle
• Carmen C. Brewer
• John A. Butman
• Wade W. Chien
• Peter S. Chines
• Francis S. Collins
• Flavia Facio
• Kathleen Farrell
• Edmond J. FitzGibbon
• Andrea L. Gropman
• Elizabeth Hutchinson
• Mina S. Jain
• Shruti Japee
• Kelly A. King
• Tanya J. Lehky
• Janice Lee
• Denise K. Liberton
• Rashmi Mishra
• Zhen Ni
• Narisu Narisu
• Scott M. Paul
• Neda Sadeghi
• Joseph Snow
• Beth Solomon
• Angela Summers
• Amy J. Swift
• Camilo Toro
• Audrey Thurm
• Carol Van Ryzin
• Chris K. Zalewski
Moebius Syndrome Conference Families

2016
Definition of Moebius Syndrome

- Minimum criteria of Moebius syndrome:
  - Congenital, uni- or bilateral non-progressive facial weakness and limited abduction of the eye(s).
  - Normal vertical eye movements and no ptosis
  - Incidence: 2 to 20 cases per million births

Von Graefe 1880, Mobius 1988, Miller 2007
Additional Features of Moebius

- Eye movement disorders and lacrimal dysfunction
- Facial movement deficits
- Hearing deficits
- Speech clarity disorder/feeding and swallowing difficulties/oral-facial
- Sensory deficits
- Developmental delay
- Autism spectrum disorders
- Sleep disorders
- Psychiatric disorders
- Club foot
- Arthrogryposis
- Poland anomaly
- Hand anomalies
- Klippel-Feil
- Dental
Causes of Moebius Syndrome and Related Facial Weakness Disorders

• Etiologies
  – Embryology/ Developmental Biology
    • Rhombencephalic maldevelopment
    • Neuronal misguidance and migration defects
    • Muscle abnormalities
  – Environmental Exposures
  – Genetics
NIH/NICHD U01 HD079068

Birth Defects: Moebius Syndrome and Related Facial Weakness Disorders

(MPIs Brooks, Engle, Jabs, Manoli, Pierpaoli)
Overall Goal

• Hypothesis: Identification of genetic factors in Moebius syndrome and related conditions will elucidate the underlying cause of the abnormal facial nerve or muscle development related to these conditions

• Goal: Define the molecular bases of a cohort of patients with birth defects that alter facial movement and expression.
Specific Aim 1

• Generation of a merged registry for the individuals and families with Moebius syndrome and related conditions of facial weakness from MSMC, BCH and NIH.

- REDCap to create and manage a secure web-based registry of participants and their phenotypes and biosamples to be shared among investigators.

- Better define the phenotypic spectrum of these conditions and develop clinically homogeneous subgroups to enable phenotype-genotype correlation analysis.

- 24 patients and family members will be selected to undergo extensive evaluation each year for a total of 72 families during the course of this 3 year project.
Participation at the Moebius Syndrome Conference

- Informed Consent – Collaboration among Mount Sinai, Boston Children’s Hospital and National Institutes of Health
  - de-identified or anonymous
  - information and samples stored for future studies
  - REDCap secure collaborative database
  - dbGaP scientific public database
- Medical history questionnaire
- Physical examination
- Eye examination
- Photography and 3-dimensional imaging studies
- Emotion processing survey
- Sampling – saliva or blood
Enrollment

Total of 516 individuals from 169 families enrolled

• 204 affected individuals and 312 family members

• 17 multiplex families

ClinicalTrials.gov (ID: NCT02055248)
Moebius Syndrome Foundation

L’association Moebius France
Specific Aim 2 - Phenotyping

- Multisystem characterization and neuroimaging of selected patients and their families at the NIH Clinical Center using a standardized protocol.

- Genetics, ophthalmology, and neurology examination;
- Audiology, otolaryngology, dentistry, craniofacial surgery, speech pathology;
- Rehabilitation medicine and psychiatry evaluations;
- Neurocognitive and autism screening assessments
- Electromyography, nerve conduction, and blink reflex studies.
- Imaging studies to be performed are MRI of the brain, orbit, internal auditory canals, and posterior fossa, and 3D-CT of the craniofacial region.
- Specialized tests including video-scopy of eye movements, and brain diffusion tensor and tractography to investigate CNs and central white matter fiber tract anomalies.
Clinical Evaluation

143 participants had full clinical evaluations at the NIH Clinical Center.

192 have been enrolled (72 probands and 96 family members as well as 24 healthy controls) for brain imaging data analysis.

Areas of interest:
- mirror movements (Webb et al. 2014)
- sleep disorders
- emotion processing
Specific Aim 3 - Genomics

• Whole exome sequencing from well characterized patients/families by NIH National Intramural Sequencing Center (NISC)

- Data jointly analyzed and validated among the three sites to identify causal gene mutations and associated developmental pathways.

- An additional 350 probands will be screened for mutations in candidate genes by MSMC and BCH.
Whole Exome Sequencing Data

- U01 funded for WES to be performed at NISC on a total of 216 samples from 72 trios

- Exomes done to date at NIH, Boston, and Sinai:
  Total 165 = from 46 families with 44 trios

Single Nucleotide Polymorphism (SNP) Array Data

- SNP arrays done to date at NIH, Boston, and Sinai
  Total of 150 from 31 families with 27 trios
Whole Genome Sequencing Data

Gabriella Miller Kids First Pediatric Research
WGS at the Baylor Sequencing Center
X01HL132377, PI Engle

• 43 families
  - 38 trios
  - 3 multiplex nuclear families
  - 2 multi-generation families

• 142 individuals

New York Genome Center U01

• 3 multiplex families
• 12 individuals
Specific Aim 4

- Association of specific clinical characteristics with gene mutations and pathways to identify important clinical phenotype-genotype correlations
Congenital Facial Weakness (CFW)

A defect in myoblast fusion underlies Carey-Fineman-Ziter syndrome.


Identification of STAC3 variants in non-Native American families with overlapping features of Carey-Fineman-Ziter syndrome and Moebius syndrome.

Abstracts


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Acknowledgements

- Intramural and extramural members of the “Moebius Syndrome Collaborative Research Group”
- Moebius Syndrome Foundation
- Participants and families in the study