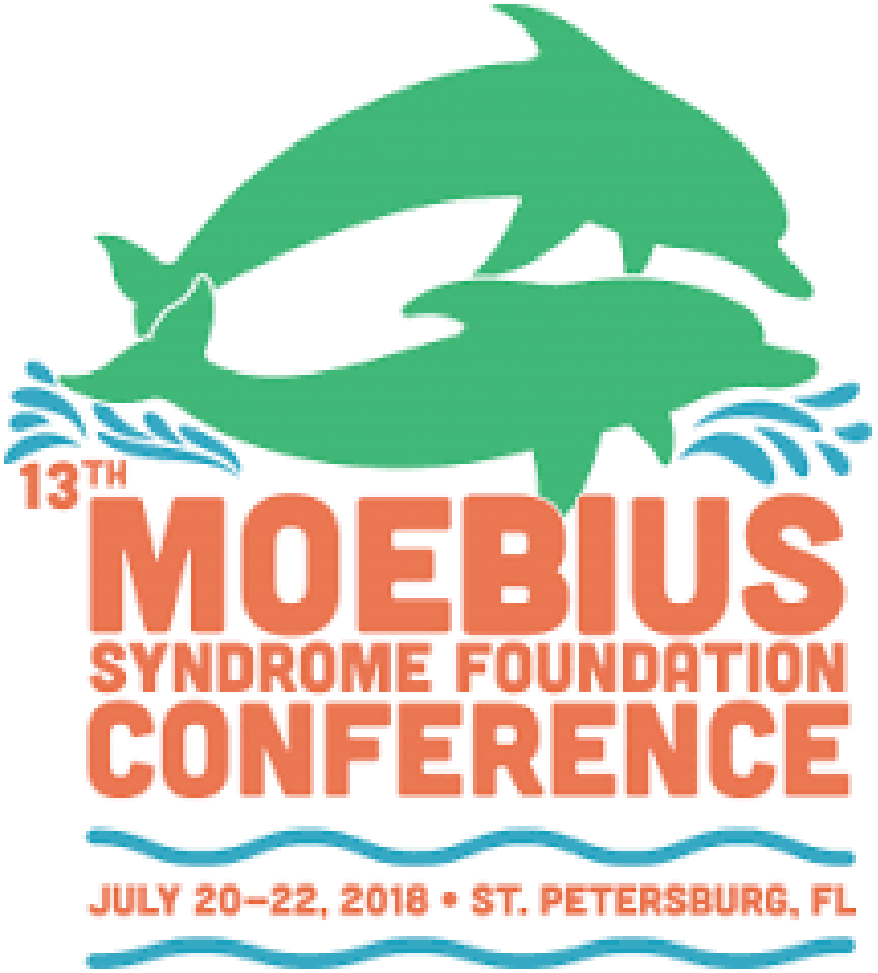
Overview of Collaborative Moebius Syndrome Research Initiatives



Moebius Syndrome Research Consortium

2018

Extramural Collaborative Team

Mount Sinai

- Ethylin Wang Jabs
- Erin Brittain
- Cristel Crespo-Chapel
- Monica Erazo
- Shirley Felix
- Tamiesha Frempong
- Ke Hao
- Monica Huertas
- Lisa Karger
- Thomas Naidich
- Ying Ru
- Janet Rucker
- Ananya Swaroop
- Sierra White
- Bryn Webb
- Zhongyang Zhang

Boston Children's Hospital

- Elizabeth Engle
- Caroline Andrews
- Brenda Barry
- Sarah Bekele
- Jo Chan
- Tammy Chu
- Silvio Alessandro Di Gioia
- David Hunter
- Julie Jurgens
- Arthur Lee
- Sarah MacKinnon
- Carla Nyquist
- Darren Oystreck
- Caroline Robson
- Matthew Rose
- Sherin Shaaban
- Alan Tenney

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-identifed 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 el. 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.

Di Gioia SA, Connors S, Matsunami N, Cannavino J, Rose MF, Gilette NM, Artoni P, de Macena Sobreira NL, Chan WM, Webb BD, Robson CD, Cheng L, Van Ryzin C, Ramirez-Martinez A, Mohassel P, Leppert M, Scholand MB, Grunseich C, Ferreira CR, Hartman T, Hayes IM, Morgan T, Markie DM, Fagiolini M, Swift A, Chines PS, Speck-Martins CE, Collins FS, Jabs EW, Bönnemann CG, Olson EN; **Moebius Syndrome Research Consortium**, Carey JC, Robertson SP, Manoli I, Engle EC. Nat Commun. 2017 Jul 6;8:16077. doi: 10.1038/ncomms16077. PMID: 28681861

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

Telegrafi A, Webb BD, Robbins SM, Speck-Martins CE, FitzPatrick D, Fleming L, Redett R, Dufke A, Houge G, van Harssel JJT, Verloes A, Robles A, Manoli I, Engle EC; **Moebius Syndrome Research Consortium**, Jabs EW, Valle D, Carey J, Hoover-Fong JE, Sobreira NLM. Am J Med Genet A. 2017 Oct;173(10):2763-2771. doi: 10.1002/ajmg.a.38375. Epub 2017 Aug 4. PMID: 28777491

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Bassim, C.W., Manoli, I., Chalmers, N.I., Leikin, J., Van Ryzin, C., Brown, R., Engle, E.C., Jabs, E.W., Lee, J.S and **Moebius Syndrome Collaborative Research Group**: Craniofacial and dental findings in congenital facial weakness disorders. **IADR/AADR Annual Meeting**, 2015

Manoli, I., Webb, B.D., Van Ryzin, C., Andrews, C., Erazo, M., Lee, J., Brooks, B., Hunter, D. G., Rucker, J.C., Frempong, T., MacKinnon, S., Oystrek, D., Pierpaoli, C., Sadeghi, N., Paul, S., Bassim, C., Fitzgibbon, E., Gropman, A., Toro, C., Collins, F.S., Engle, E.C., Jabs, E.W. and the **Moebius Syndrome Collaborative Research Group**: Moebius and related syndromes: exploring the genetic causes and phenotypic spectrum of congenital facial weakness. **Am College of Med Genet**, 2016.

Van Ryzin, C., Manoli, I., Webb, B.D., Gaspar, H., Lee, J., Pierpaoli ,C., Sadeghi, N., Robson, C., Nadich, T., Fitzgibbon, E., Toro, C., Whitman, M., Jabs, E.W., Engle, E.C. and the **Moebius Syndrome Collaborative Research Group**: TUBB3 mutations other than p.E140K cause Kallmann syndrome of variable penetrance as part of syndromic congenital fibrosis of extraocular muscles, type 3 (CFEOM3). **Am College of Med Genet**, 2016.

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Sadeghi, N., Manoli, I., Hutchinson, E., van Ryzin, C., Thomas, C., Irfanoglu, O., Nayak, A., Collins, F.S., Liu, C.-Y., Jabs, E.W., Engle, E.C., Pierpaoli, C. and the **Moebius Collaborative Research Group**: Brain morphometry driven by DTI data in Moebius syndrome and hereditary congenital facial paresis. **Organization for Human Brain Mapping**, 2017.

Facio, F.M., Webb, B.D., Barry, B.J., Biesecker, B.B., Van Ryzin, C., **Moebius Syndrome Collaborative Research Consortium**, Engle, E.C., Manoli, I., Jabs, E.W., and Collins, F.S.: Is this Moebius Syndrome? Exploring the phenotypic spectrum of congenital facial weakness disorders, and the resulting implications for genetic counseling. **National Society of Genetic Counselors 36th Annual Conference**, 2017.

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Mount Sinai

Boston Children's Hospital
Until every child is well™

HARVARD MEDICAL SCHOOL

MOEBIUS SYNDROME FOUNDATION

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National Institute of Child Health & Human Development

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