**BIOGRAPHICAL SKETCH**

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NAME: Nara Lygia de Macena Sobreira

eRA COMMONS USER NAME (credential, e.g., agency login): nsobrei2

POSITION TITLE: Assistant Professor of Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| School of Medical Sciences - University of Pernambuco (UPE). Brazil. | MD | 06/2003 | Medicine |
| Genetic Medicine Clinical Resident – São Paulo Hospital (UNIFESP). São Paulo. Brazil. | Clinical Geneticist | 01/2007 | Clinical Genetics |
| Johns Hopkins University, School of Medicine - McKusick-Nathans Department of Genetic Medicine – Human Genetics Program | PhD | 07/2012 | Human Genetics |
| Johns Hopkins University, School of Medicine - McKusick-Nathans Department of Genetic Medicine | Postdoc | 06/2013 | Human Genetics |
| Johns Hopkins Hospital Genetic Medicine | Residency | 06/2015 | Medical Genetics |

**A. Personal Statement**

I graduated from the University of Pernambuco School of Medicine, then completed Clinical Genetics Residency at Paulista School of Medicine (UNIFESP). In 2007, I started my PhD in Human Genetics at Johns Hopkins followed by a one-year postdoc and a two-year Clinical Genetics Fellowship also at Johns Hopkins School of Medicine. During my PhD, I had the privilege to work with Dr. David Valle using next generation sequencing to elucidate the molecular basis of rare Mendelian phenotypes and in 2010 I discovered *PTPN11* as the gene responsible for metachondromatosis (an enchondromatoses) by using whole genome sequencing. Since July 2015, I am an Assistant Professor of the McKusick-Nathans Department of Genetic Medicine at Johns Hopkins School of Medicine with primary interest in rare Mendelian phenotypes, analysis of next-generation sequencing, and functional testing of candidate causative variants. As an early-stage investigator, my main clinical and research focus is on identifying the genetic bases of rare phenotypes. In the last nine years, I have worked extensively on developing strategies to better analyze the variants identified by next-generation sequencing and on novel strategies for data sharing. I participated on the development of PhenoDB, a phenotypic and genomic database and created PhenoDB Variant Analysis Tool used worldwide. I am also one of the creators of GeneMatcher, VariantMatcher and one of the co-founders of the Matchmaker Exchange, all intended to share next-generation sequencing data. I have also worked extensively on functional studies that evaluate the possible pathogenic effects of the candidate causative variants. Since 2009 I have also had the privilege to work with Dr. Ada Hamosh at OMIM, first as a scientific writer and now as the Deputy Scientific Director of Phenotypes. I am Board Certified by the Brazilian Board of Medical Genetics and by the American Board of Medical Genetics and Genomics. I am member of the American Society of Human Genetics. I have published numerous peer-reviewed journal articles and book chapters and have presented my work at national and international meetings.

Ongoing and recently completed projects that I would like to highlight include:

R03CA256535
Sobreira (PI)
07/01/21 - 06/30/23

Genome-wide Sequencing to Identify the Genes Responsible for Enchondromatoses and Related Malignant Tumors

1U24HG012184-01
Sobreira (PI)
9/1/21-8/31/26
GeneMatcher, VariantMatcher and PhenoDB, implementation of new features and connections

2U41HG006627
Hamosh (PI), Role: co-investigator (Deputy Scientific Director of Phenotypes)
08/01/17 – 05/31/22
Online Mendelian Inheritance in Man

UM1HG006542
Valle (PI), Role: co-investigator
2/01/15-11/30/21
Baylor Johns Hopkins Center for Mendelian Genetics

PVO-2A-201
Sobreira (PI)
08/01/18 – 07/31/20
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Palovarotene in Subjects with Multiple Osteochondromas

X01HL140546-01A1
Jelin (PI), Role: co-investigator
03/31/18 - 04/01/19
Single gene pathogenic variants associated with BEEC (Bladder extrophy, Epispadias, Complex)

1X01HL140517-01
Sobreira (PI)
03/31/17 - 04/01/18
Genome-wide Sequencing to Identify the Genes Responsible for Enchondromatoses and Related Malignant Tumors

1X01HL140519-01
Siegel (PI), Role: co-investigator
03/31/17 - 04/01/18
Genomic analysis of a cohort with infantile hemangiomas associated with multi-organ structural birth defects

Citations:


1. Posey JE, O'Donnell-Luria AH, Chong JX, Harel T, Jhangiani SN, Coban Akdemir ZH, Buyske S, Pehlivan D, Carvalho CMB, Baxter S, **Sobreira N**, Liu P, Wu N, Rosenfeld JA, Kumar S, Avramopoulos D, White JJ, Doheny KF, Witmer PD, Boehm C, Sutton VR, Muzny DM, Boerwinkle E, Günel M, Nickerson DA, Mane S, MacArthur DG, Gibbs RA, Hamosh A, Lifton RP, Matise TC, Rehm HL, Gerstein M, Bamshad MJ, Valle D, Lupski JR; Centers for Mendelian Genomics. Insights into genetics, human biology and disease gleaned from family based genomic studies. Genet Med. 2019 Apr;21(4):798-812. PMCID: PMC6691975.
2. El Abiad JM, Robbins SM, Cohen B, Levin AS, Valle DL, Morris CD, **de Macena Sobreira NL**. Natural history of Ollier disease and Maffucci syndrome: Patient survey and review of clinical literature. Am J Med Genet A. 2020 Mar 7. PMID: 32144835. PMCID pending.
3. 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. A defect in myoblast fusion

underlies Carey-Fineman-Ziter syndrome. Nat Commun. 2017 Jul 6;8:16077. PMID: 28681861. PMCID: PMC5504296.

4. Gould RA, Aziz H, Woods CE, Seman-Senderos MA, Sparks E, Preuss C, Wünnemann F, Bedja D, Moats CR, McClymont SA, Rose R, **Sobreira N**, Ling H, MacCarrick G, Kumar AA, Luyckx I, Cannaerts E, Verstraeten A, Björk HM, Lehsau AC, Jaskula-Ranga V, Lauridsen H, Shah AA, Bennett CL, Ellinor PT, Lin H, Isselbacher EM, Lino Cardenas CL, Butcher JT, Hughes GC, Lindsay ME; Baylor-Hopkins Center for Mendelian Genomics; MIBAVA Leducq Consortium, Mertens L, Franco-Cereceda A, Verhagen JMA, Wessels M, Mohamed SA, Eriksson P, Mital S, Van Laer L, Loeys BL, Andelfinger G, McCallion AS, Dietz HC. ROBO4 variants predispose individuals to bicuspid aortic valve and thoracic aortic aneurysm. Nat Genet. 2019 Jan;51(1):42-50. PMID: 30455415. PMCID: PMC6309588.

**B. Positions, Scientific Appointments, and Honors**

## Positions and Scientific Appointments

2003-2004 Family Health Program Doctor, Jardim City, CE-Brazil
2007-2007 Clinical Geneticist, APAE (Associacao dos Pais e Amigos dos Excepcionais) de Sao Paulo, Sao Paulo, SP-Brazil (Center for Mental Retardation Children)
2009-2015 OMIM Scientific Writer, OMIM, Baltimore, MD
2012-Present PhenoDB Creator (www.phenodb.org)
2013-Present GeneMatcher Creator (www.genematcher.org)
2015-Present OMIM Deputy Scientific Director of Phenotypes
2015-Present Assistant Professor, Johns Hopkins University, School of Medicine - McKusick-Nathans Institute of Genetic Medicine, Baltimore, MD
2018-Present VariantMatcher Creator (www.variantmatcher.org)

### Other Experience and Professional Memberships

2008-Present Member, American Human Genetics Society
2011-Present Chair, Baylor-Hopkins Center for Mendelian Genomics Analysis Review Committee
2011-Present Member, Baylor-Hopkins Center for Mendelian Genomics Phenotypic Review Committee
2014-Present Member, ClinGen Consortium, Actionability Working Group
2014-Present Member, Global Alliance, Discovery Working Group

### Honors

1999 Assistant Instructor of Cytology, School of Medical Sciences - University of Pernambuco (UPE), Recife, PE-Brazil
2000 Scholar in the Scientific Initiation Scholarship Institutional Program – PIBIC (Contract FACEPE/CNPq), Recife, PE-Brazil
2001 Scholar in the Scientific Initiation Scholarship Institutional Program – PIBIC (Contract FACEPE/CNPq), Recife, PE-Brazil
2005 Collaborator in a project sponsored by CNPq, Sao Paulo, SP-Brazil
2009 FASEB MARC Program Travel Award - ASHG 2009 Annual Meeting
2011 Research Fellowship Award Number F31HD068133 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development.
2017 National Institutes of Health - Common Fund's Gabriella Miller Kids First Pediatric Research Program – Award number 1 X01 HL140517-01 (PI)
2018 MD-GEM Wolfe Street Competition (PI)
2018 2018 Johns Hopkins Discovery Award (PI)
2018 125 Living the Hopkins Mission Honorees

**C. Contributions to Science**

**1. Description of the natural history of rare novel Mendelian disorders.** My early publications during my Medical Genetics Residency are already related to the description the natural history of rare novel Mendelian disorders. These publications allow other clinicians and researchers to understand the clinical variability of these phenotypes to provide better care for patients around the world. More recently, I published my work on

the description of the natural history of Ollier disease and Maffucci syndrome. I served as the primary investigator or co-investigator in all of the studies that led to these publications.

a. **Sobreira NL**, Brunoni D, Cernach MC, Perez AB. Finlay-Marks (SEN) syndrome: a sporadic case and the delineation of the syndrome. Am J Med Genet A. 2006 Feb 1;140(3):300-2. PMID: 16411189. PMCID pending.

b. Carvalho DR, Speck-Martins CE, Brum JM, Ferreira CR, **Sobreira NLM**. Spondyloepimetaphyseal dysplasia with elevated plasma lysosomal enzymes caused by homozygous variant in MBTPS1. Am J Med Genet A. 2020 Jul;182(7):1796-1800. PMID: 32420688. PMCID pending.

c. Perrone E, Perez ABA, D'Almeida V, de Mello CB, Jacobina MAA, Loureiro RM, Burlin S, Migliavacca M, do Amaral Virmond L, Graziadio C, Pedroso JL, Mendes EL, Gomy I, **de Macena Sobreira NL**. Clinical and molecular evaluation of 13 Brazilian patients with Gomez-López-Hernández syndrome. Am J Med Genet A. 2021 Apr;185(4):1047-1058. PMID: 3338192. PMCID pending.

d. El Abiad JM, Robbins SM, Cohen B, Levin AS, Valle DL, Morris CD, **de Macena Sobreira NL**. Natural history of Ollier disease and Maffucci syndrome: Patient survey and review of clinical literature. Am J Med Genet A. 2020 Mar 7. PMID: 32144835. PMCID pending.

**2. Analysis of whole genome and exome sequencing data.** Later, during my PhD, I started working with next-generation sequencing analysis. These publications are related to my work using whole exome and whole genome sequencing to understand the molecular bases of rare Mendelian disorders. They show that I have identified many novel Mendelian genes associated with known and novel Mendelian phenotypes, including the discovery of the gene responsible for one of the enchondromatoses, metachondromatosis.

a. **Sobreira NL**, Cirulli ET, Avramopoulos D, Wohler E, Oswald GL, Stevens EL, Ge D, Shianna KV, Smith JP, Maia JM, Gumbs CE, Pevsner J, Thomas G, Valle D, Hoover-Fong JE, Goldstein DB. Whole-genome sequencing of a single proband together with linkage analysis identifies a Mendelian disease gene. PLoS Genet. 2010 Jun 17;6(6):e1000991. PMCID: PMC2887469.

b. Hoover-Fong J, **Sobreira N (co-first author)**, Jurgens J, Modaff P, Blout C, Moser A, Kim OH, Cho TJ, Cho SY, Kim SJ, Jin DK, Kitoh H, Park WY, Ling H, Hetrick KN, Doheny KF, Valle D, Pauli RM. Mutations in PCYT1A, Encoding a Key Regulator of Phosphatidylcholine Metabolism, Cause Spondylometaphyseal Dysplasia with Cone-Rod Dystrophy. Am J Hum Genet. 2014 Jan 2;94(1):105-12. PMCID: PMC3882727.

c. 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**. Identification of *STAC3* variants in non-Native American families with overlapping features of Carey-Fineman-Ziter syndrome and Moebius syndrome. Am J Med Genet A. 2017 Oct;173(10):2763-2771. PMCID: PMC5843189.

d. Carvalho DR, Medeiros JEG, Ribeiro DSM, Martins BJAF, **Sobreira NLM**. Additional features of Gillespie syndrome in two Brazilian siblings with a novel ITPR1 homozygous pathogenic variant. Eur J Med Genet. 2018 Mar;61(3):134-138. doi: 10.1016/j.ejmg.2017.11.005. Epub 2017 Nov 21. PMID: 29169895. PMCID pending.

3. **Whole genome and exome sequencing analysis tools and phenotypic and genomic data sharing.** I have worked extensively on developing strategies to better analyze the variants identified by next-generation sequencing. As part of this work, I participated on the development of PhenoDB and created PhenoDB Variant Analysis Tool. These platforms are widely used worldwide. I have also been involved with the important work of phenotypic and genomic data sharing around the world and I am one of the creators of GeneMatcher, the creator of VariantMatcher and one of the co-founders of the Matchmaker Exchange.

a. **Sobreira N**, Schiettecatte F, Boehm C, Valle D, Hamosh A. New Tools for Mendelian Disease Gene Identification: PhenoDB Variant Analysis Module; and GeneMatcher, A Web-based Tool for Linking Investigators with an Interest in the Same Gene. Hum Mutat. 2015 Feb 14. PMCID: PMC4820250.

b. **Sobreira NLM**, Arachchi H, Buske OJ, Chong JX, Hutton B, Foreman J, Schiettecatte F, Groza T, Jacobsen JOB, Haendel MA, Boycott KM, Hamosh A, Rehm HL; Matchmaker Exchange Consortium. Matchmaker Exchange. Curr Protoc Hum Genet. 2017 Oct 18;95:9.31.1-9.31.15. PMCID: PMC6016856.

c. Au PY, You J, Caluseriu O, Schwartzentruber J, Majewski J, Bernier FP, Ferguson M, Valle D, Parboosingh JS, **Sobreira N**, Innes AM, Kline AD. GeneMatcher aids in the identification of a new malformation syndrome with intellectual disability, unique facial dysmorphisms, and skeletal and connective tissue abnormalities caused by de novo variants in HNRNPK. Human mutation. 2015; 36(10):1009-14. PMCID: PMC4589226.

d. Tanaka AJ, Cho MT, Millan F, Juusola J, Retterer K, Joshi C, Niyazov D, Garnica A, Gratz E, Deardorff M, Wilkins A, Ortiz-Gonzalez X, Mathews K, Panzer K, Brilstra E, van Gassen KL, Volker-Touw CM, van Binsbergen E, **Sobreira N**, Hamosh A, McKnight D, Monaghan KG, Chung WK. Mutations in *SPATA5* Are Associated with Microcephaly, Intellectual Disability, Seizures, and Hearing Loss. Am J Hum Genet. 2015 Sep 3;97(3):457-64. PMCID: PMC4564988.

**4. Functional investigation of causative variants.** In addition to the identification of disease causative variants, I have worked on the cell-based and mouse-based models to investigate the effect of the identified variants.

a. 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. A defect in myoblast fusion underlies Carey-Fineman-Ziter syndrome. Nat Commun. 2017 Jul 6;8:16077. PMID: 28681861. PMCID: PMC5504296.

b. Patients with a Kabuki syndrome phenotype demonstrate DNA methylation abnormalities. **Sobreira N**, Brucato M, Zhang L, Ladd-Acosta C, Ongaco C, Romm J, Doheny KF, Mingroni-Netto RC, Bertola D, Kim CA, Perez AB, Melaragno MI, Valle D, Meloni VA, Bjornsson HT. Eur J Hum Genet. 2017 Dec;25(12):1335-1344. PMID: 29255178. PMCID: PMC5865196.

c. Gould RA, Aziz H, Woods CE, Seman-Senderos MA, Sparks E, Preuss C, Wünnemann F, Bedja D, Moats CR, McClymont SA, Rose R, **Sobreira N**, Ling H, MacCarrick G, Kumar AA, Luyckx I, Cannaerts E, Verstraeten A, Björk HM, Lehsau AC, Jaskula-Ranga V, Lauridsen H, Shah AA, Bennett CL, Ellinor PT, Lin H, Isselbacher EM, Lino Cardenas CL, Butcher JT, Hughes GC, Lindsay ME; Baylor-Hopkins Center for Mendelian Genomics; MIBAVA Leducq Consortium, Mertens L, Franco-Cereceda A, Verhagen JMA, Wessels M, Mohamed SA, Eriksson P, Mital S, Van Laer L, Loeys BL, Andelfinger G, McCallion AS, Dietz HC. ROBO4 variants predispose individuals to bicuspid aortic valve and thoracic aortic aneurysm. Nat Genet. 2019 Jan;51(1):42-50. PMID: 30455415. PMCID: PMC6309588.

d. Martin EMMA, Enriquez A, Sparrow DB, Humphreys DT, McInerney-Leo AM, Leo PJ, Duncan EL, Iyer KR, Greasby JA, Ip E, Giannoulatou E, Sheng D, Wohler E, Dimartino C, Amiel J, Capri Y, Lehalle D, Mory A, Wilnai Y, Lebenthal Y, Gharavi AG, Krzemień GG, Miklaszewska M, Steiner RD, Raggio C, Blank R, Baris Feldman H, Milo Rasouly H, **Sobreira NLM**, Jobling R, Gordon CT, Giampietro PF, Dunwoodie SL, Chapman G. Heterozygous loss of WBP11 function causes multiple congenital defects in humans and mice. Hum Mol Genet. 2020 Dec 4;29(22):3662-3678. PMCID: PMC7823106 (available on 2021-12-04).

**Complete List of Published Work in MyBibliography** (100 publications):
https://www.ncbi.nlm.nih.gov/myncbi/nara.sobreira.1/bibliography/public/