

AWARD NUMBER: W81XWH-21-1-0438

TITLE: Genetics of Frontotemporal Degeneration in Diverse Populations

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CONTRACTING ORGANIZATION: University of Miami, Miami, FL

REPORT DATE: July 2022

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command  
Fort Detrick, Maryland 21702-5012

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<b>REPORT DOCUMENTATION PAGE</b>			<i>Form Approved</i> OMB No. 0704-0188		
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<b>1. REPORT DATE</b> July 2022		<b>2. REPORT TYPE</b> Annual		<b>3. DATES COVERED</b> 01Jul2021-30Jun2022	
<b>4. TITLE AND SUBTITLE</b>  Genetics of Frontotemporal Degeneration in Diverse Populations			<b>5a. CONTRACT NUMBER</b>		
			<b>5b. GRANT NUMBER</b> W81XWH-21-1-0438		
			<b>5c. PROGRAM ELEMENT NUMBER</b>		
<b>6. AUTHOR(S)</b> Dr. Margaret Pericak-Vance, PhD Nuytemans, Karen  E-Mail: knuytemans@med.miami.edu			<b>5d. PROJECT NUMBER</b>		
			<b>5e. TASK NUMBER</b>		
			<b>5f. WORK UNIT NUMBER</b>		
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b>  University of Miami UNIVERSITY OF MIAMI-MEDICAL RESEARCH A 1600 NW 10 AVE MIAMI FL 33136-1015			<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>		
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b>  U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012			<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>		
			<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>		
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b> Approved for Public Release; Distribution Unlimited					
<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b>  Genomic analyses in diverse populations of frontotemporal dementia patients are currently lacking. Here we present the first report on creation of a (Caribbean) Hispanic cohort through enrollment in the greater South Florida area and Puerto Rico as well as well the first genomic analyses using genotyping and whole genome sequencing approaches. Enrollment was delayed due to COVID-19 hesitancy but plans are in place to improve in the next reporting period. Further efforts to increase outreach are being developed. Preliminary analyses indicate good representation of diverse genetic ancestries in the dataset and no known FTD mutations in genes originally identified in European FTD patients were identified so far. Whole genome sequencing and genotyping on the full cohort is currently ongoing.					
<b>15. SUBJECT TERMS</b> Hispanic FTD cohort establishment; no known mutations through genotyping and whole genome sequencing					
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>	<b>18. NUMBER OF PAGES</b>	<b>19a. NAME OF RESPONSIBLE PERSON</b>
<b>a. REPORT</b>	<b>b. ABSTRACT</b>	<b>c. THIS PAGE</b>			USAMRDC
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## 1. INTRODUCTION:

Approximately 5% of all dementia patients present with Frontotemporal dementia (FTD) with a substantial minority (~10-20%) developing FTD before the age of 65. Existing FTD genomics efforts are using genome wide genotyping and sequencing to increase knowledge about genetic variation contributing to FTD. The identified variants only explain up to 25% of disease. Additionally, noticeably understudied in these efforts is the assessment of genetic factors in underrepresented populations including Hispanics (HI) and African Americans (AA). The lack of study in HI is concerning given their status as the largest minority in the US. The failure to include diverse racial/ethnic populations in genetics studies will exacerbate existing health disparities amongst HI and AA and limit the scope of benefits from such studies. Furthermore, since HI—especially those of Caribbean background—are admixed groups (i.e., European, African and Amerindian ancestry) this will inform our understanding of genetic factors in individuals with non-NHW genetic backgrounds. **We set out to create of a cohort of HI FTD to (a) determine contribution of FTD variants originally identified in European ancestry patients in these populations and (b) identify novel FTD variants on European, Amerindian or African background.** For this purpose we will recruit ~120 FTD patients throughout South Florida and Puerto Rico and perform genome wide genotyping and sequencing to determine underlying disease associated variants. Demographics for Florida show a clear enrichment for Caribbean versus Central or mainland HI. This proposal will leverage all in-house ascertainment and genomic expertise, pipelines and data that are available through the ADSP (-FUS) projects and FTD consortia.

2. **KEYWORDS:** Frontotemporal dementia; genomics; diversity; health disparity; ancestry; genotyping; whole genome sequencing; Hispanic;

## 3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**

In the first year of the award we proposed to do the following:

<b>Specific Aim 1: Establish HI FTD cohort by expanding local diverse dataset.</b>	<b>Timeline months</b>	<b>Initiating PI</b>	<b>Partner PI</b>	<b>% completed</b>
<b>Major Task 1: Ascertain 120 FTD patients</b>				
Subtask 1. Obtain approval from USAMRDC ORP HRPO	1-3	Dr. Nuytemans		100
Subtask 2. Set up outreach efforts in South Florida and Puerto Rico (and maintain)	1-6 (-48)	(Dr. Nuytemans)	Dr. Pericak-Vance / Dr. Cuccaro	99
Subtask 3. Enroll patients in Florida	4-40		Dr. Pericak-Vance / Dr. Cuccaro	22
Subtask 4. Enroll patients in Puerto Rico	4-40		Dr. Pericak-Vance / Dr. Cuccaro	22
<b>Major Task 2: Adjudicate FTD cases</b>				
Subtask 1. Obtain full clinical assessments for all patients	4-48		Dr. Vance / Dr. Cuccaro	18
Subtask 2. Perform adjudication for enrolled patients	4-48		Dr. Vance / Dr. Cuccaro	15
<b>Specific Aim 3: Perform whole genome sequencing and admixture mapping to identify novel putative disease variants.</b>				
<b>Major Task 5: Perform family analyses</b>				
Subtask 2. Perform whole genome sequencing on samples.	8-42	Subaward. Dr. Dalgard		6

- What was accomplished under these goals?

## **Major Task 1: Ascertain 120 FTD patients**

### **Initiating PI (Nuytemans):**

- **IRB approvals;** all necessary approvals were obtained both internally at UM and at DOD. All proposed clinical research forms developed by the National Alzheimer's Coordinating Center (NACC) were included in these approvals; both uniform data set forms and FTLD module forms.
- **Set up outreach efforts in South Florida and Puerto Rico;**

#### South Florida:

- a) Dr. Nuytemans and Dr. Martinez (clinical coordinator) are present at all UMH Neurology Memory Disorders project meetings (monthly) and attended the yearly Neurology assembly.
- b) Dr. Nuytemans provides day-to-day communication with Dr. Galvin (Director of the Memory Disorders Division) regarding the dementia projects at HHG.

#### Puerto Rico:

- a) Both Dr. Nuytemans and Dr. Pericak-Vance traveled with the clinical team to Puerto Rico to meet with Dr. Acosta and set up a formal collaboration. Dr. Acosta has been added as consultant to Dr. Pericak-Vance's partnering PI grant.
- b) During this visit, Dr. Nuytemans discussed the project with Dr. Acosta and outlined specific interest areas for the grant. In this discussion, enrollment of FTD cases with a long history of progressive frontotemporal degeneration (prior to full symptomology) was brought up and will be added as a specific focal point.

### **Partnering PI (Pericak-Vance):**

- **Set up outreach efforts in South Florida and Puerto Rico;**

#### South Florida:

- a) Dr. Nuytemans and Dr. Martinez (clinical coordinator) are present at all UMH Neurology Memory Disorders project meetings (monthly) and attended the yearly Neurology assembly.
- b) Dr. Martinez visited three additional neurology offices in the greater Miami area (including adult care centers) to interact with practicing clinicians.
- c) Dr. Martinez has set up an outreach program with a local radio station reaching the Hispanic population in South Florida, broadcasting four larger interviews about the study, Frontotemporal dementia and genomics over the course of 4 months, as well as daily small ads regarding the study. These interviews and ads will start broadcasting in September 2022.
- d) Dr. Martinez works closely with the HHG AD team to identify additional outreach opportunities for the HHG dementia research studies in general. Efforts to present our study on NextDoor in Miami regions with larger Hispanic population are current ongoing.

#### Puerto Rico:

- a) Both Dr. Nuytemans and Dr. Pericak-Vance traveled with the clinical team to Puerto Rico to meet with Dr. Acosta and set up a formal collaboration. Dr. Acosta has been added as consultant to Dr. Pericak-Vance's partnering PI grant.
- **Enroll patients in South Florida;**
    - a) In the period of July 2021 to June 2022, a total of 15 FTD patients were enrolled in the FTD study (13 Hispanic and 2 Non-Hispanic White (NHW)) through our collaborations with Neurology and previously established representation of the study on TrialMatch and Association of FTD website. Additionally, we identified five patients ascertained in the AD study that were adjudicated by the clinical consensus board to have a FTD diagnosis.
    - b) Prior efforts and databases:  
Through prior Miami HHG efforts, we had already ascertained 27 FTD patients (14 NHW, 12 Hispanic and 1 black), and 11 patients from the AD study that were re-adjudicated as FTD patients (4 NHW, 7 Hispanic). These samples will be included in the analyses proposed here.

Additionally, we obtained clinical information and DNA for 31 FTD patients from the Alzheimer Disease Centers through NACC and National Centralized Repository for Alzheimer's Disease (NCRAD) (22 Hispanic, 8 African ancestry, 1 Amerindian). These samples will be included in the analyses proposed here.

c) Amongst these samples, we currently have 2 families with more than one affected.

**- Enroll patients in Puerto Rico;**

Dr. Martinez enrolled three FTD patients in the first preliminary visit to Puerto Rico. To catch up from COVID-19 hesitancy delays, a larger ascertainment trip has been planned for end of August 2022.

**Major Task 2: Adjudicate FTD cases**

**Partnering PI (Pericak-Vance):**

**- Obtain full clinical assessments:**

- a) Dr. Martinez has been trained on all NACC clinical research forms and has completed all forms for all new ascertainment to the patient's ability. Previous individuals from the AD study with adjudicated changed diagnosis of FTD do not have these clinical data available. Continuing on, these individuals will have data available for the Uniform DataSet forms, but not the FTLD module specific form.
- b) Dr. Cuccaro actively works with Dr. Martinez to streamline the assessments of new patients to allow for easy harmonization with the local AD projects as well as the larger AD consortia. Dr. Cuccaro and Dr. Vance are co-MPIs on the larger Harmonization effort grants within these AD consortia (U24-AG074855-01).

**- Perform adjudication for enrolled patients:**

- a) Full clinical assessment is being performed as described above. The NACC clinical research forms are currently being integrated in the HHG's clinical database (Chimera). The large number of novel forms has presented the development team with a large work burden and implementation of the last forms is still ongoing.
- b) Manual adjudication reports are currently being made for presentation to the Clinical Consensus Board. Dr. Cuccaro is actively working with Dr. Martinez to streamline an automatic report extracting pertinent information from the breadth of forms from the Chimera database once all forms are active therein.
- c) We acknowledge the delay in development of the electronic forms and the subsequent report for adjudication has delayed adjudicated of the full dataset. We anticipate this being resolved in the first quarter of the second year.

**Major Task 5: Perform family analyses**

**Initiating PI (Nuytemans):**

**Whole genome analyses:**

- a) Some delay in enrollment due to COVID-19 hesitancy was accrued, so samples ascertained in the first year of this award were only just out for sequencing at USUHS in July 2022 (Q1 of year 2). This include both the sample enrolled under the FTD study, those samples enrolled under AD study but adjudicated as FTD as well as a few FTD samples from the NCRAD collection.
- b) We had previously completed genotyping and genome sequencing on samples already available at HHG (same study mechanisms as described above). As these data will be included in the analyses presented here, we will provide some preliminary results for those here.
  - We completed the Global Diversity Assay with Neurobooster (GDA+Neuro) content on 16 FTD (7 NHW, 1 black, 8 Hispanic) as well as the 31 NCRAD samples. Additionally, Global Screening Array genotyping data is available for those AD enrolled samples with FTD adjudicated diagnosis. Global ancestry analyses using the GDA+Neuro genotyping data shows our dataset has a wide representation of African, Amerindian and European ancestry (Figure 1; red, green and blue color respectively).



**Figure 1. Principal component analyses of FTD cohort genotyping data.**

- We also completed whole genome sequencing on 19 HIHG samples (16 NHW, 3 Hispanic) and 24 NCRAD samples (6 Black, 1 Amerindian, 17 Hispanic). We did not identify any carriers of known pathogenic mutations in the known FTD genes (originally identified in European descent samples); *MAPT*, *GRN*, etc. We did identify 3 *PSEN1* putative pathogenic variants (p.I249L/p.A431E) or VUS (p.D333G) in 2 Hispanic and 1 Black patient, all of which were previously identified in other FTD patients as well. Local ancestry analysis indicated these are located on European background. Further analyses for potential novel variants in these genes are currently ongoing.
- c) *C9orf72* genotyping in the new dataset and the previously available dataset did not identify any carriers of the repeat expansion. Additional analyses in the final larger cohort will be needed to determine the impact of this variant in the Hispanic population.
- **What opportunities for training and professional development has the project provided?**
  - a) *Nothing to Report.*
- **How were the results disseminated to communities of interest?**
  - a) *Nothing to Report.* Abstracts of preliminary results in previous data and current data was submitted in February for presentation at the Alzheimer Association International Conference in August 2022 in San Diego, CA; and in June for presentation at the American Society for Human Genetics meeting in October 2022 in Los Angeles, CA.
- **What do you plan to do during the next reporting period to accomplish the goals?**

#### Initiating PI (Nuytemans):

##### Aim 1 (enrollment).

- Complete establishment of collaborations with additional datasets for inclusion here (ALLFTD diverse samples, EFIGA, MHAS, etc.). These collaborations are already in place, we await DNA shipment for inclusion in genomic analyses.

##### Aim 2 (genotyping).

- Genotyping using the Global Screening Array (in accordance with the large AD consortia) will be completed for all new enrollments and analyzed for global and local ancestry.

##### Aim 3 (family analyses).

- Whole genome sequencing will be completed for the dataset enrolled in the first year and a second dataset (enrollment in Y2) will be sent to USUHS as well. For those families with multiple affecteds we will begin sharing analyses (and linkage analyses for those families large enough).

### **Partnering PI (Pericak-Vance):**

#### Aim 1 (enrollment).

- Completion of the radio program outreach efforts.
- Continue outreach to the local neurology offices.
- Complete the already scheduled larger ascertainment trip to Puerto Rico (August 2022) and schedule additional more frequent trips.
- Finalizing implementation of all NACC forms and establishment of the automated adjudication forms is expected early on in Y2 Q1.

#### Aim 3 (family analyses).

- Dr. Martinez will continue to identify potential families with multiple affecteds and expand those families were possible to include in these analyses.

### **4. IMPACT:**

- o **What was the impact on the development of the principal discipline(s) of the project?**

Our preliminary results indicate that the Hispanic patients carry some of the variants originally described in European patients. However, we do not observe the C9orf72 repeat expansion in this cohort. Together these data indicate that there are likely to be novel variants on the African or Amerindian background and/or more recent on the European background in the Hispanic population; as we have seen in the Alzheimer Disease field. Therefore, inclusion of diverse, admixed populations is extremely valuable for all communities with similar ancestries.

- o **What was the impact on other disciplines?**

a) *Nothing to Report.*

- o **What was the impact on technology transfer?**

a) *Nothing to Report.*

- o **What was the impact on society beyond science and technology?**

a) *Nothing to report*

### **5. CHANGES/PROBLEMS:**

- o **Changes in approach and reasons for change**

a) *Nothing to report.*

- o **Actual or anticipated problems or delays and actions or plans to resolve them**

The presence of COVID-19 has impacted our ability to ramp up ascertainment early on, given hesitancy of potential participants both locally and in PR to meet with our researchers for enrollment. We anticipate trying to compensate for this in the next few years by organizing slightly larger ascertainment trips to PR and re-contacting previously hesitant participants.

- o **Changes that had a significant impact on expenditures**

Given the delay in ascertainment due to COVID also the planned genotyping and sequencing efforts are delayed. Both are planned for the next batch of samples in July-August. Additionally, we hired a new analyst few months into the award.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
  - a) *Nothing to report.*

## 6. PRODUCTS:

- **Publications, conference papers, and presentations**
  - a) **Journal publications.** *Nothing to Report.*
  - b) **Books or other non-periodical, one-time publications.** *Nothing to Report.*
  - c) **Other publications, conference papers, and presentations.** Abstracts of preliminary results in previous data and current data was submitted in February for presentation at the Alzheimer Association International Conference in August 2022 in San Diego, CA; and in June for presentation at the American Society for Human Genetics meeting in October 2022 in Los Angeles, CA.
- **Website(s) or other Internet site(s)**  
*Nothing to Report.*
- **Technologies or techniques**  
*Nothing to Report.*
- **Inventions, patent applications, and/or licenses**  
*Nothing to Report.*
- **Other Products**  
For all new enrollments we have obtain full clinical assessment information (NACC Uniform DataSet and FTLD module) as per participant’s ability. Additionally, we have collected blood for DNA and RNA extraction as well as plasma and peripheral blood mononuclear cells (for creation of iPSCs). We will generate genomic data that will be shared with the greater research community upon completion of the project (and per participant’s consent).

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	<i>Karen Nuytemans</i>
Project Role:	Contact PI
Researcher Identifier (e.g. ORCID ID):	Eracommons; knuytemans
Nearest person month worked:	2
Contribution to Project:	Establish collaborations, face of the study and manage genomic analyses
Name:	<i>Margaret Pericak-Vance</i>
Project Role:	<i>MPI</i>
Researcher Identifier (e.g. ORCID ID):	<i>Eracommons; mpvance</i>

Nearest person month worked:	<i>1</i>
Contribution to Project:	Establish collaborations, manage clinical ascertainment
Name:	<i>Anisley Martinez</i>
Project Role:	<i>Clinical research coordinator</i>
Nearest person month worked:	<i>12</i>
Contribution to Project:	Enrollment of all patients in South Florida and Puerto Rico
Name:	<i>Sergio Tejada</i>
Project Role:	<i>Clinical research manager</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	Manage ascertainment efforts in Puerto Rico across all dementia studies at HIHG
Name:	<i>Derek Van Booven</i>
Project Role:	<i>Bioinformatics</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	Initial processing of Whole Genome sequencing data. Provides any bioinformatics input.
Name:	<i>Esther Gu</i>
Project Role:	<i>Research analyst</i>
Nearest person month worked:	<i>5</i>
Contribution to Project:	Detailed analyses of Whole genome analysis, genotyping analyses including global and local ancestry analyses and sharing analyses; as well as management of information in database on back-end.

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  - a) Previously pending grants have been awarded and are active for Dr. Nuytemans (Alzheimer Association AARG-22-923768, FDOH 22A15, NIH U01 AG072579-01), Dr. Pericak-Vance (U19 AG074865, U01 AG072579), Dr. Vance (NIH U01 AG066767-02S2, U01 AG072579-01, U19 AG074865, U01 NS125580-01), Dr. Griswold (NIH U01 AG072579-01, U19AG074865, 1RF1AG070935, R01DC009645, 2U54AG052427) and Dr. Cuccaro (U01 AG066767-02S2, U24-AG074855-01). These efforts are minimal.
  - b) Previously active grants were closed for Dr. Nuytemans (M2000789, ZEN-19-591586, A2018425S), Dr. Vance (ZEN-19-591586, A2018425S, RF1 AG058066, R01 AG054080, 1RF1 AG054074), Dr. Pericak-Vance/Cuccaro/ Grsiwold (A2018425S, RF1 AG058066, R01 AG054080, 1RF1 AG054074),
  - c) None of these changes significantly impact the efforts on this project.
- **What other organizations were involved as partners?**
  - a) *Nothing to Report.*

## 8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** *Duplicate reports are submitted in both PIs accounts.*

## 9. APPENDICES:

*Appendix: abstract submitted to AAIC 2022 (San Diego, CA; July 31- August 4). Poster presentation and to ASHG 2022 (Los Angeles, CA; October 25-29) Format TBD.*

**Authors:** Anisley Martinez<sup>1</sup>, Farid Rajabli<sup>1</sup>, Esther Gu<sup>1</sup>, Sergio Tejada<sup>1</sup>, Heriberto Acosta<sup>4</sup>, Bernard Baumel<sup>3</sup>, Christian Camargo<sup>3</sup>, Xiaoyan Sun<sup>3</sup>, Jeffery M. Vance<sup>1,2</sup>, Michael L. Cuccaro<sup>1,2</sup>, Margaret A. Pericak-Vance<sup>1,2</sup>, Karen Nuytemans<sup>1,2</sup>

**Affiliations:** 1) John P. Hussman Institute for Human Genomics, 2) Dr. John T. Macdonald Department of Human Genetics, 3) Department of Neurology, University of Miami, Miami, FL, USA; 4) Caribbean Center for the Study of Memory and Cognition, San Juan, PR

**Title:** Characterization of a diverse Frontotemporal Dementia cohort, enriched for Caribbean Hispanic patients.

### Abstract body:

#### Background:

The vast majority of biomedical data currently available for any disease is derived from studies in non-Hispanic white (NHW) populations. Specifically, clinical information, genetic factors as well as biomarkers for frontotemporal dementia (FTD) have been studied predominantly in those NHW populations. To increase representation in biomedical research, we set out to enroll and characterize a diverse FTD patient cohort enriched for Caribbean Hispanic patients.

#### Method:

Our current cohort consists of 89 FTD patients (30% NHW, 67% Hispanic), with continuing enrollment from the University of Miami Hospital Neurology Department in Miami, FL and the Caribbean Center for the Study of Memory and Cognition in San Juan, PR. All patients were evaluated using NACC approved Uniform Data Set (UDS) or equivalent in their preferred language. For ~65% of the cohort we also completed the NACC FTD module forms. We generated genotyping data (Illumina GDA+Neurobooster array) as well as whole genome sequencing and plasma biomarker data (Quanterix Simoa Neuroplex-3; A $\beta$ 40, A $\beta$ 42, and total tau) for a subset of the cohort.

#### Results:

Initial genetic analyses showed none of the Hispanic patients are carriers of known FTD mutations originally identified in NHW patients, including the *C9orf72* repeat expansion and reported pathogenic variants in *MAPT* or *GRN*. We did not identify a significant difference in age-at-onset or Clinical Dementia Rating scores at time of enrollment between NHW and Hispanic patients. Additionally, biomarker data on A $\beta$ 40/A $\beta$ 42 ratio and total tau levels in a subset of 22 FTD patients (~12/10 Hispanic/NHW) did not show significantly different levels between patients of both ethnicities.

#### Conclusion:

Genetic analyses of FTD in underrepresented population groups is necessary as genetic information from research in NHW is not always generalizable across race/ethnicity. We are currently working to expand our efforts to include identification of novel genetic risk factors for FTD in the Hispanic patients using whole genome sequencing, full evaluation of the Neuroplex as well as p-tau181 and NfL biomarkers in the complete cohort and comparison of clinical presentations between ethnicities. The biomedical characterization of FTD across race/ethnicity will help the understanding of disease mechanisms in all patients ultimately preventing further health disparities.