

Early onset dementia: an experience towards the future



FIU
Robert Stempel College
of Public Health
& Social Work

9th Global Health Conference
May 7-9, 2019. *Innovative Results. Global Solutions*

Nik Spencer/Nature

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Bogotá- Colombia





Agenda

- Introduction
- Historical Contextualization
- Colombian experience on Early onset
- New Directions based on our experience

Nik Spencer/Nature

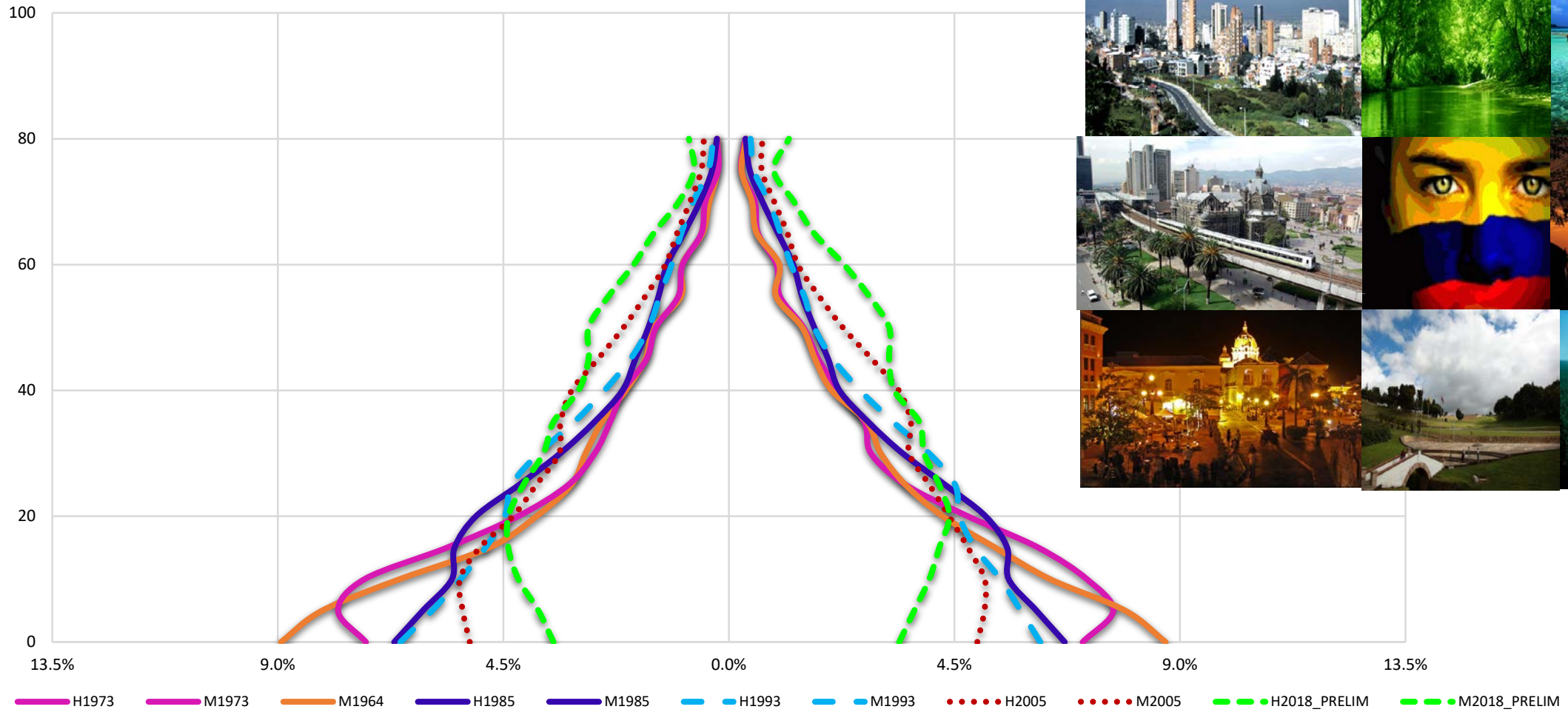
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Population Structure Colombia: 1964-2018



Institute of Public Health. PUJ, 2018

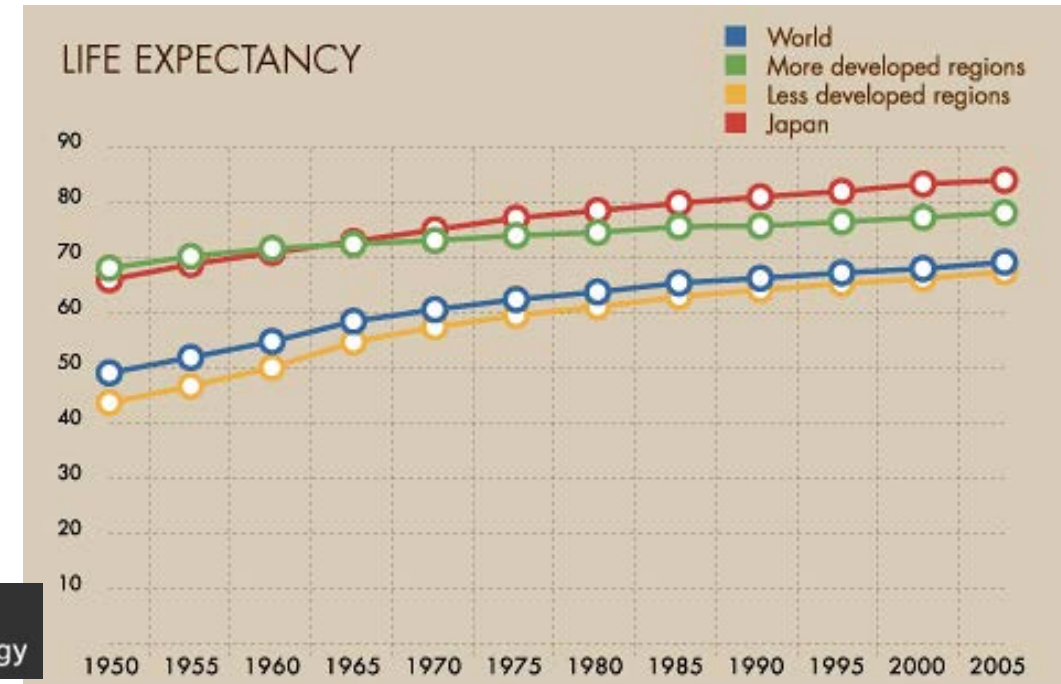
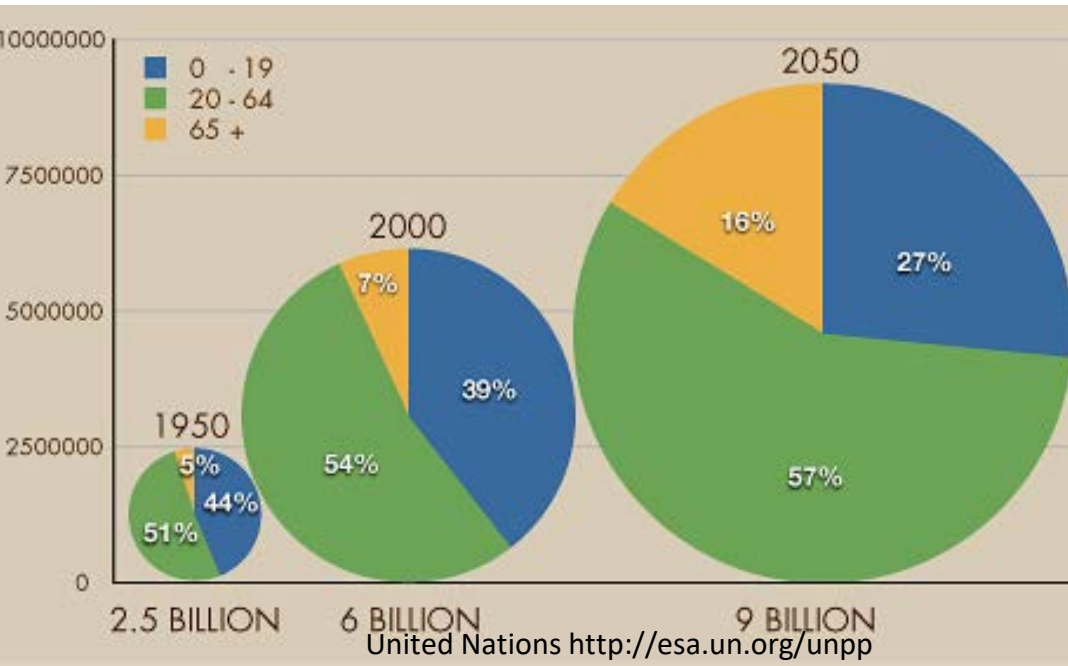


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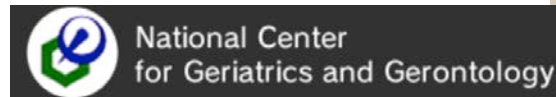




Lessons from an old country- Japan



Neurosciences of Aging - Japan



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Challenges

(1) Research: Mental and physical public health from studies in Neurosciences.

(2) How to maintain independence despite the aging of the brain?

On aging:

(3) What are the mechanisms of cognitive alterations in dementia: relationship of metabolic processes and cognitive functions

(4) Translational Medicine: From basic research to clinical practice.

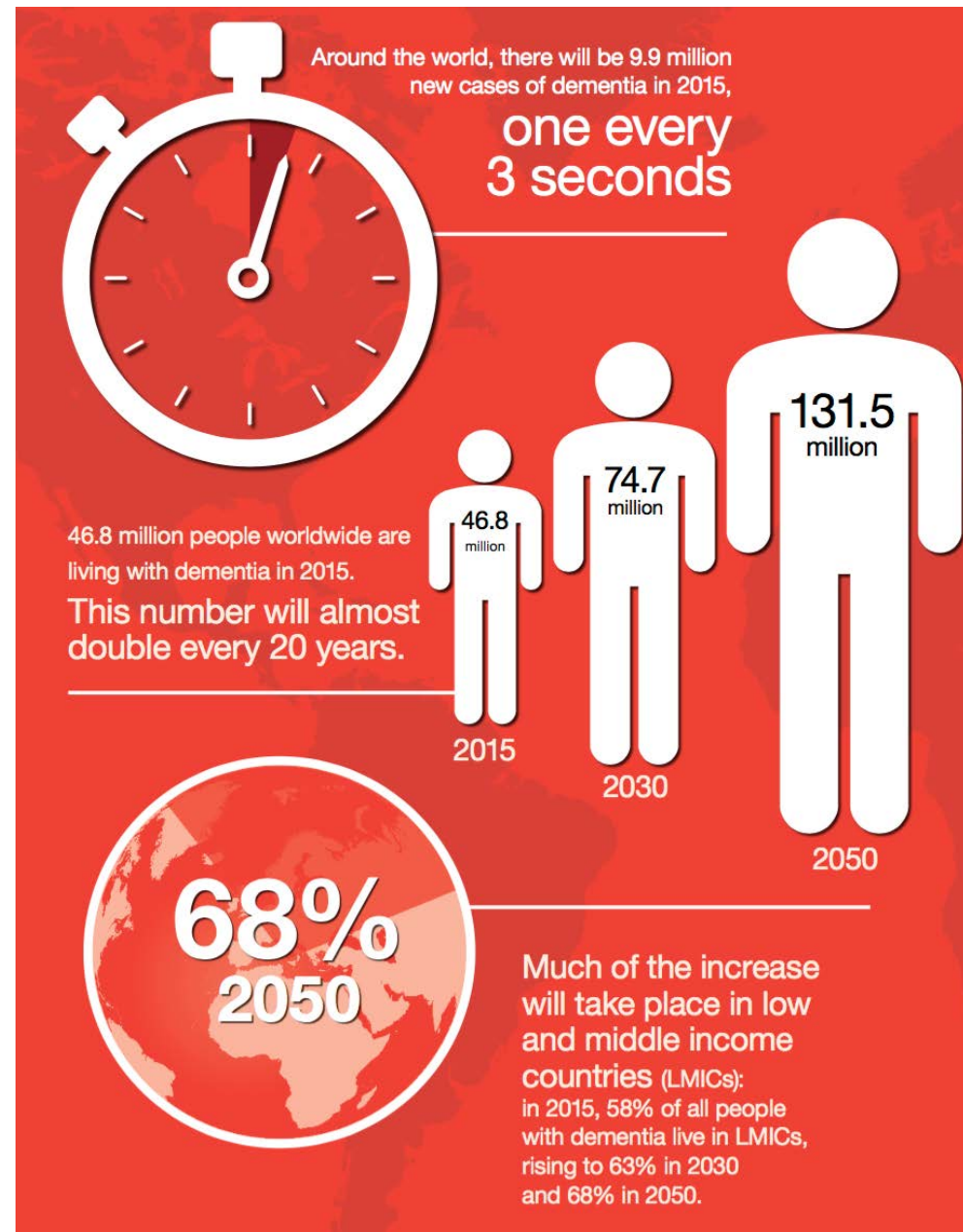
. Create preventive and new interventions for dementia:

. **Pre-dementia stage biomarkers (genetics)**

. Research in regulation of endocrine systems and CNS

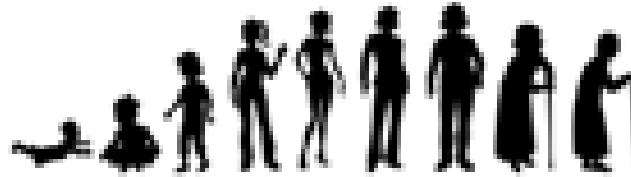
Challenges

On aging:



About 35 years ago, the reaction in USA to the phenomenon of accelerated aging, which followed success in the battle against the so-called killer diseases (TB, smallpox, diphtheria, tetanus), apparently took two paths of reflection:

It is expected to grow old with a large burden of morbidity and its sequelae (cancer, heart disease, diabetes)



It is possible to age, achieving that, gradually it is the fragility *, the only cause of death

Expansion of morbidity

Comprehension of morbidity

* Fragility: Refers to individuals who, without demonstrable disease, have manifested limited **functional reserve** (decreased cardiac reserve, respiratory, effective reaction time) and increased their fragility in the face of external disturbances.

Challenges in PUJ

... so far:

On Young

Onset/Early Onset:

- differential diagnosis by contrasting their behavioral, cognitive and structural neuroimaging findings.

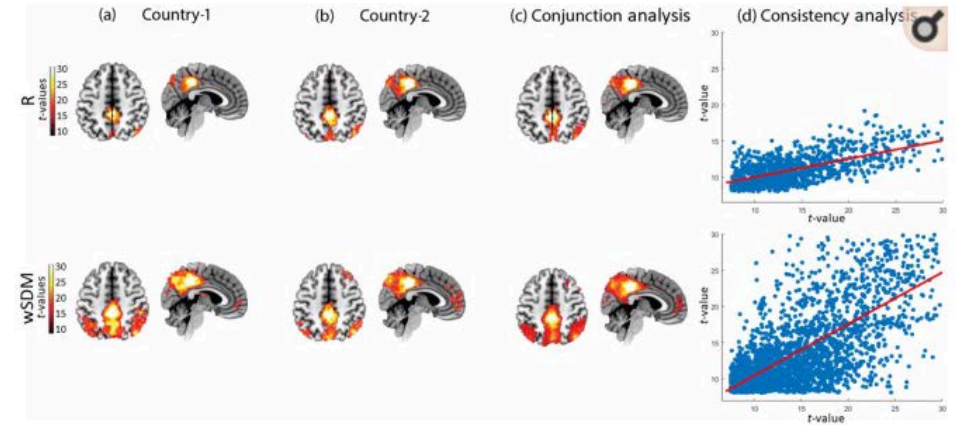
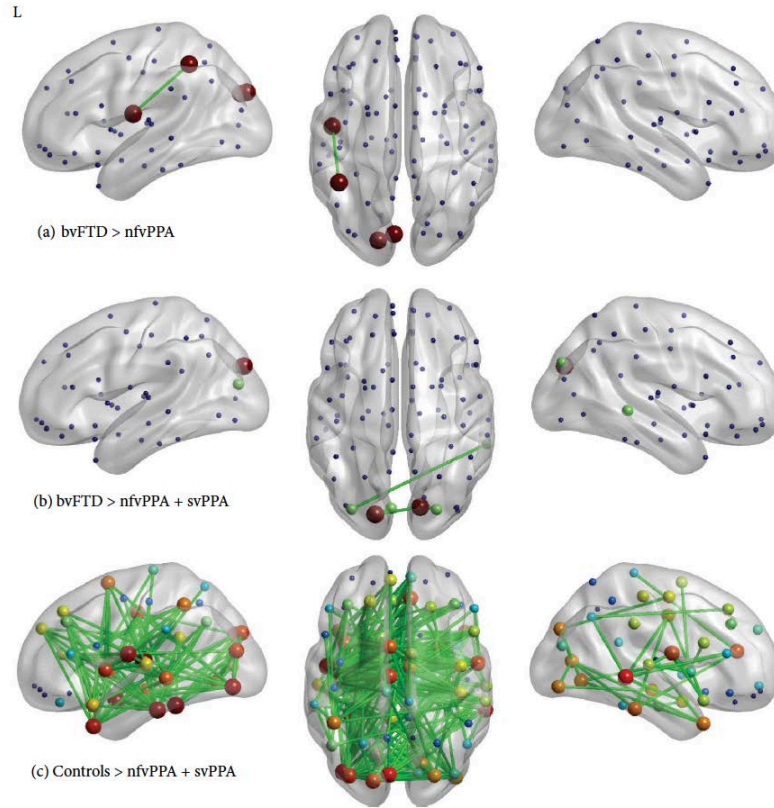
- studying genetics, including and understanding epigenetic

Challenges in

PUJ

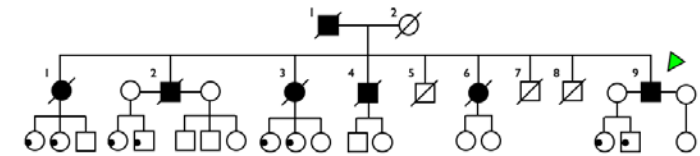
On Young

Onset/Early Onset:



Moguilner S, García AM, Mikulan E, Hesse E, García-Cordero I, Melloni M, Cervetto S, Serrano C, Herrera E, **Reyes P, Matallana D**, Manes F, **Ibáñez A**, Sedeño L. Weighted Symbolic Dependence Metric (wSDM) for fMRI resting-state connectivity: A multicentric validation for frontotemporal dementia. *Sci Rep.* 2018

Reyes P, Ortega-Merchan MP, Rueda A, Uriza F, Santamaria-García H, Matallana D. Functional Connectivity Changes in Behavioral, Semantic, and Non-fluent Variants of Frontotemporal Dementia. *Behav Neurol.* 2018 .



Colombian Familial Dementia with Frontotemporal Features Associated with a Presenilin-1 Mutation.

AAN /2016. Lopez A., Matallana D., Reyes P., Uriza F., Cano C., Van Deerlin, V., Suh, E., McCarty-Wood, E., McMillan, CT, Grossman, M., Rascovsky, K. **PUJ/ U Penn**

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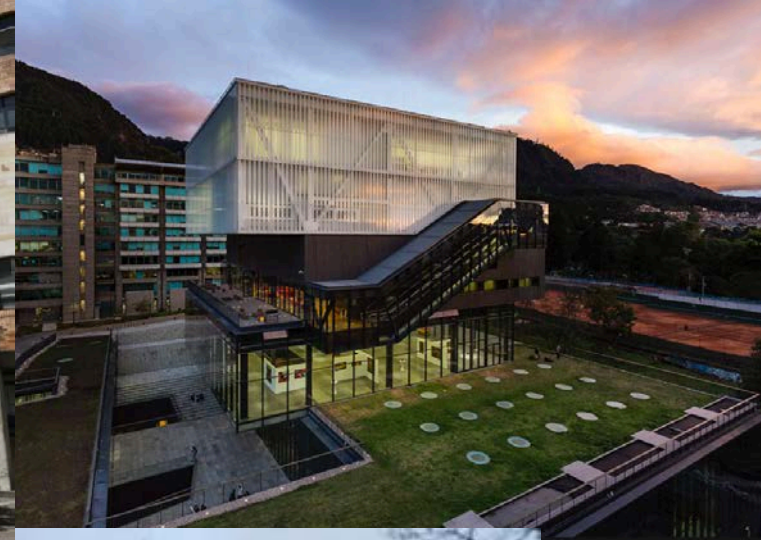
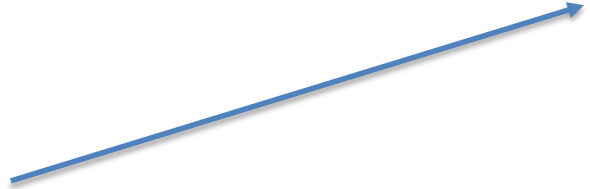


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From 1992 to 1995

Neurological
Institute
from Colombia



1995, Hospital San Ignacio /
Pontificia Universidad Javeriana -
PUJ



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Jacquier, M., Montañes, P., Velandia, F., Velez, P., Van Broeckhoven, Ch (1995): Clinico-pathological and molecular study of a Colombian case of early-onset familial Alzheimer's disease. Poster. CONGRESO PANAMERICANO DE NEUROLOGIA. Guatemala. Octubre 7-13.

Jacquier, M., Matallana, D. Velez, P, Cano, C., Quiroga, F., Pedraza, O., ARTEAGA, C, VAN BROECKHOVEN, Ch. (1996). "Very-early-onset Colombian Familial Alzheimer's Disease: Clinico-molecular case study. Comunicación. XII CONFERENCE ON ALZHEIMER'S DISEASE. Jerusalén. Israel. Octubre 8.

Montañes, P., Jacquier, M. Cano, C. Matallana, D, Villareal, E., .. Van Broeckhoven, C. Neuropsychological profiles of familial and sporadic Alzheimer disease Colombian patients: Correlation with APOE genotypes. Abstract: 52 INTERNATIONAL CONFERENCE ON ALZHEIMERS DISEASE. Amsterdam Julio, 18-23, 1998

Cano,C, Montañes, P., Jacquier,M. Características Funcionales de Pacientes con Demencia Tipo Alzheimer según genotipo APOe. XXII CONGRESO DE LA SOCIEDAD ESPAÑOLA DE GERIATRÍA Y GERONTOLOGÍA. Barcelona, 10-13 de Junio de 1998.

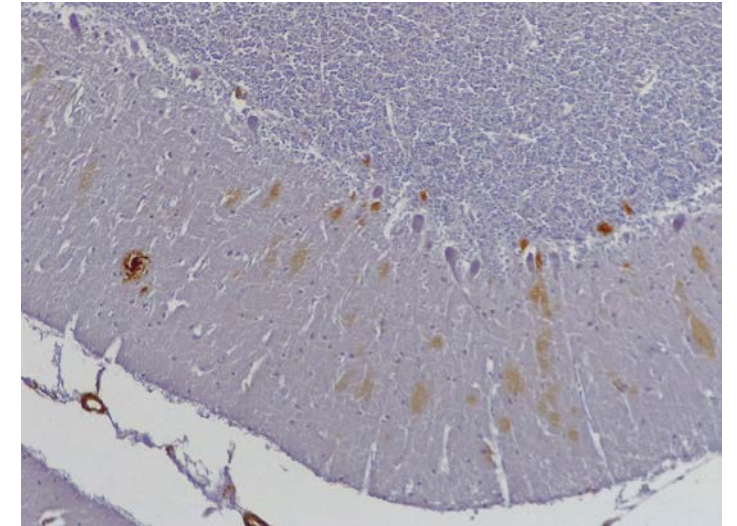
Torres O., Serrano M., Arango D.,Villareal E., Rodríguez N., Velez P., Montañes P., Matallana D., Rascovski, K., Cano C., Quimbay D., Arteaga C., Van Broeckhoven. C., Jacquier M (1998): Análisis mutacional del gen de la presenilina 1 (ps-1) por polimorfismo conformacional de cadena sencilla (pccs) en casos colombianos de enfermedad de Alzheimer familiar y esporádica y sujetos control: patogenicidad de la mutación e318g (exon 9) (1998). XV CONGRESO COLOMBIANO DE MEDICINA INTERNA .Cartagena .Colombia. Octubre 8 a 11.

Torres, O, Cano, C, Arango, D, Montañes, P, Sinchi, A, Bahamon, A Suescun, S, Jacquier, M. (2000). Apoe and lipid profiles in probable and possible Alzheimer patients versus controls in Bogotá, Colombia. WORLD ALZHEIMER CONGRESS 2000, WASHINGTON, JULIO 9-16. ABSTRACTS: NEUROBIOLOGY OF AGING. V21, P.S162.

Jacquier M, Arango D, Villareal E, Torres O, Serrano ML, Cruts M, Montanes P, Cano C, Rodriguez MN, Serneels S, Van Broeckhoven C. APOE epsilon4 and Alzheimer's disease: positive association in a Colombian clinical series and review of the Latin-American studies.ARQ NEUROPSIQUIATR 2001 Mar;59(1):11-7

Arango D, Cruts M, Torres O, Backhovens H, Serrano ML, Villareal E, Montanes P, Matallana D, Cano C, Van Broeckhoven C, Jacquier M. Systematic genetic study of Alzheimer disease in Latin America: mutation frequencies of the amyloid beta precursor protein and presenilin genes in Colombia. AM J MED GENET 2001 Oct 1;103(2):138-43

Alzheimer disease in Colombia: Clinico-Molecular Studies



Irwin D., Raskovsky K., Matallana D., Cano C. Santamaría-García H., Iragori A., Santacruz JM, et. al. (2019) PSN1 Amyloide Plaque. Colombian Familial Dementia with Frontotemporal Features Associated with a Presenilin-1 Mutation.



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THE AGEING INSTITUTE: 2000



Academic unit of the
medicine faculty, with a
clear focus on
interdisciplinary work in
normal and pathological
aging

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Research Lines

- 1) Clinic and psychopathology
- 2) Aging and its vicissitudes
- 3) Longevity Modalities of mental health care
- 4) Intervention methods
- 5) Neurobiology of behavior control
- 6) Neuropsychology of dementias
- 7) Professional and formative work
- 8) Public and social mental health
- 9) Assessment and diagnosis of normal and pathological aging**



2011 "INTELLECTUS"

Satellite center of memory and cognition

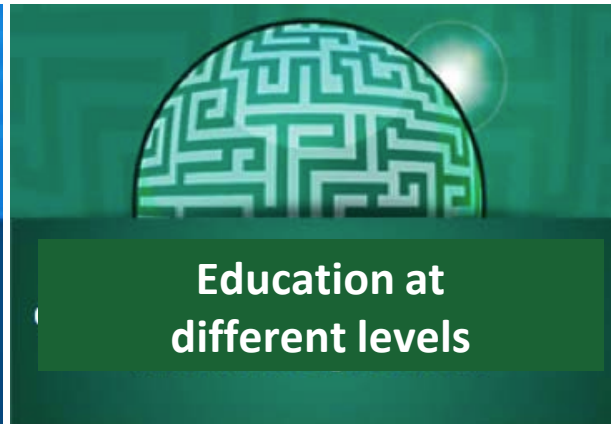
50 professionals in different areas and services



Research



Clinical assistance



**Education at
different levels**

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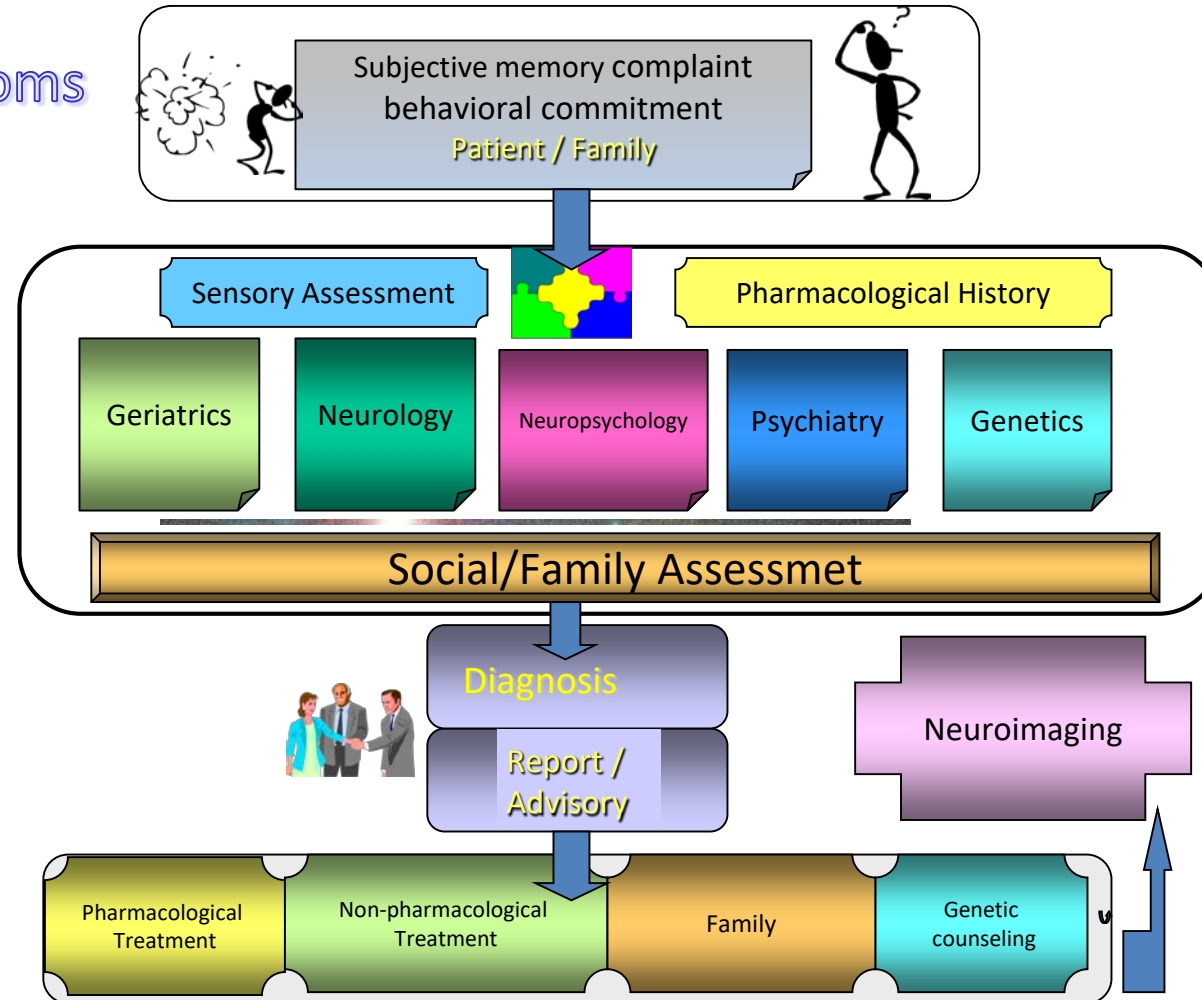
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Symptoms

1050 new patients/year
All Public Health systems pay a one day diagnosis

Interdisciplinary Assessment Intervention



Trabajo original

Actuales retos diagnósticos a partir de un análisis de características Socio-demográficas de 2453 pacientes de una Clínica de Memoria y Cognición

Current diagnostic challenges from an analysis of social-demographic characteristics of 2453 patients in a Memory and Cognition Hospital

Lizet Paola Moreno Moreno (1), Diana Lucia Matallana Eslava (1,2), Carlos Alberto Cano Gutierrez (1,2)

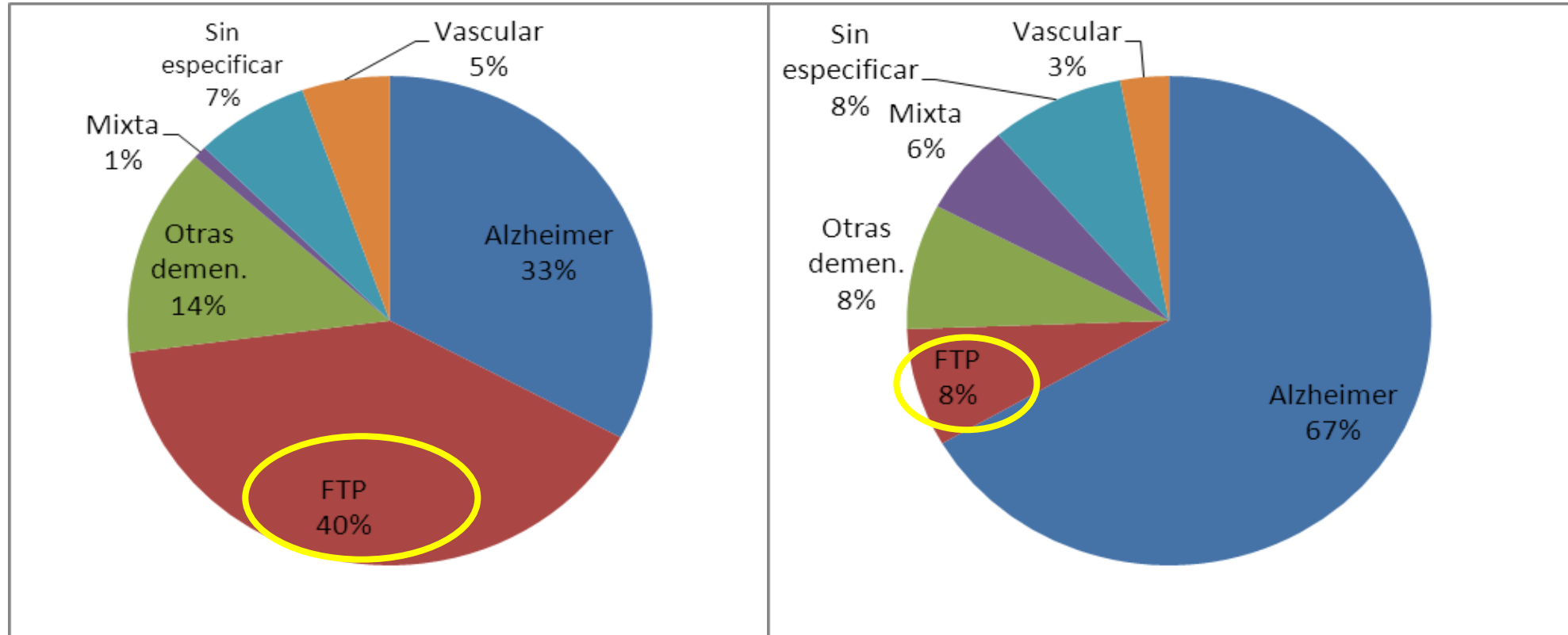
SUMMARY

INTRODUCTION AND OBJECTIVES: The number of patients in earlier stages of the disease who consult to the memory clinic has increased. This poses a challenge to differentiate, not only between types of dementia, but also between conditions which may share characteristics with dementia-related illnesses. Starting from a descriptive study the current diagnostic challenges are proposed in order to then analyze sociodemographic characteristics, the results of assessment and diagnosis made by consensus of the patients who were attended for the first time in the memory clinic program at the Hospital Universitario San Ignacio in Bogotá, Colombia (CM PUJ-HUSI).

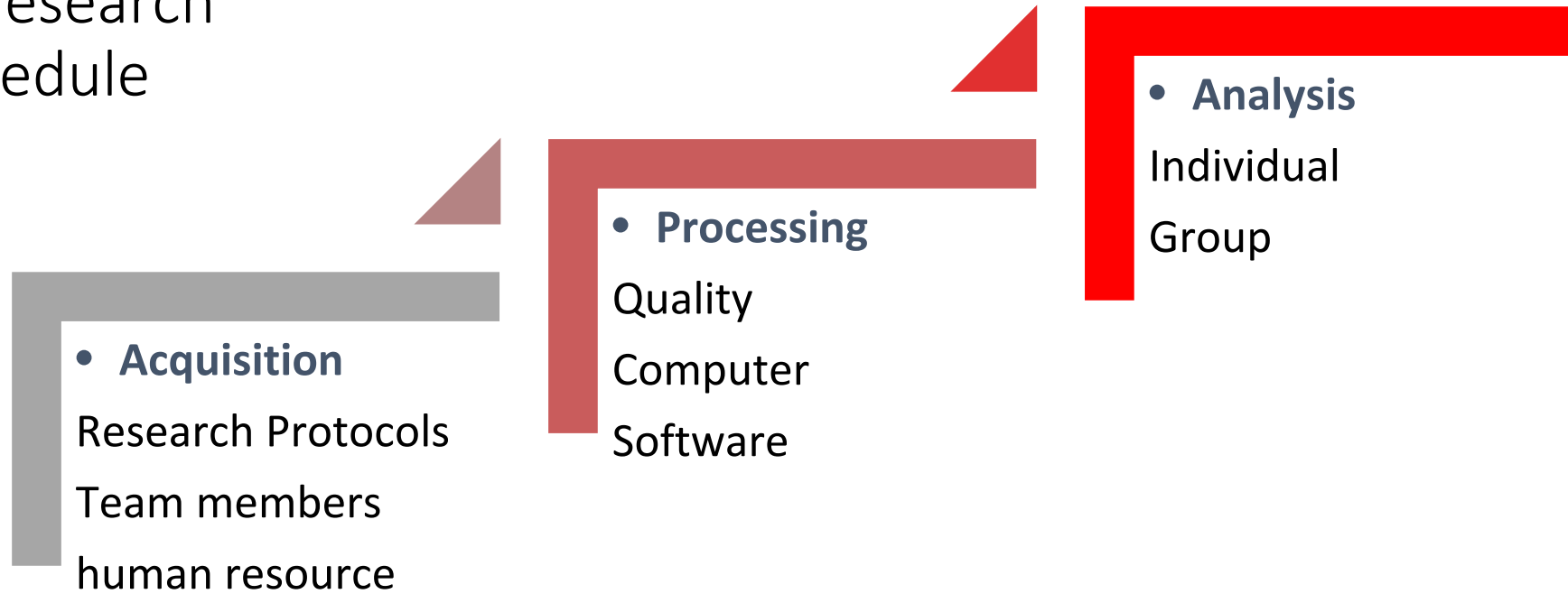
MATERIALS AND METHODS: A descriptive cross-sectional study was performed on the group of patients who were attended for the first time in the CM PUJ-HUSI, from September 1996 to May 2014.

RESULTS: Alzheimer's dementia is the most frequent diagnosis (43,45%), but frontotemporal dementia has been increasing over the years, with less psychiatric diagnoses. The scales applied for the evaluation of the patients are, in different proportions, altered in all groups of patients, including those who were considered normal.

Types of dementia in people under 65 years of age (left) and over 65 years (right)



Clinical and research
Our own schedule



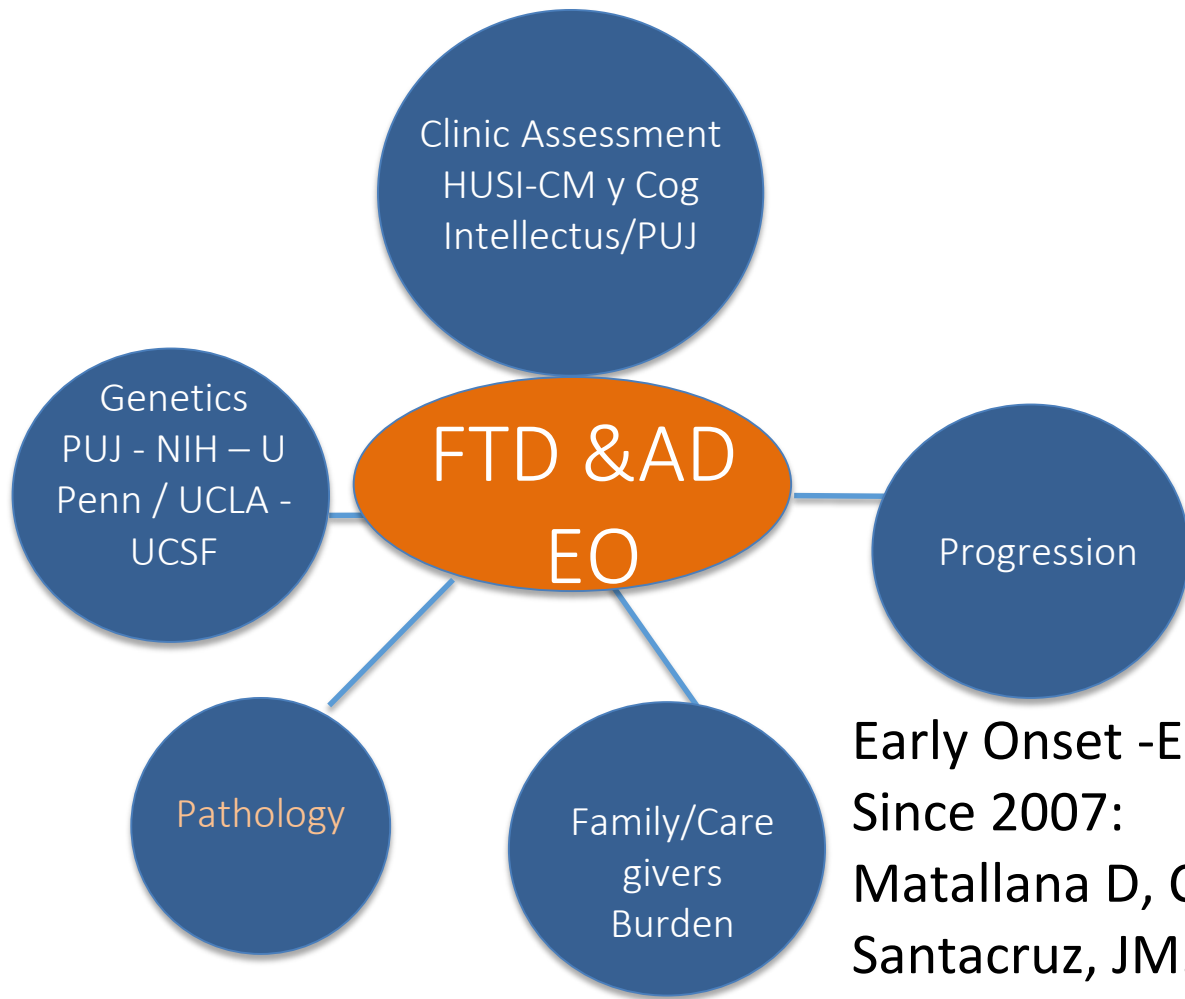
To our own experience

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- Project 1 2007 – 2011 PUJ
- Project 2 2008 – 2011 Colciencias PUJ
- Project 3 2011 – 2017 Colciencias PUJ
- Project 4 2015 – 2016 PUJ Pos Doc
- Project 5 2014 – 2018 Fogarty NIH/U PENN – PUJ
- Proyect 6 2018 – 2019 - 2020 PUJ- HUSI-INCyT- UCLA UCSF

Early Onset -EO-
Since 2007:

Matallana D, Cano C., Reyes P.,
Santacruz, JM., Santamaría-García H., Iragorri A., et. al.

Academic Partners in Colombia. U de Antioquia: **Lopera F.**

U de Los Andes: Báez. S.In Latin

America. Argentina – INCyT/INECO: **Ibáñez A.**



First Symptoms and Neurocognitive Correlates of Behavioral Variant Frontotemporal Dementia

Hernando Santamaría-García^{a,b,c,k}, Pablo Reyes^{a,k}, Adolfo García^{b,c,m}, Sandra Baez^{b,c}, Angela Martínez^{a,l}, José Manuel Santacruz^{a,k,n}, Andrea Slachevsky^{c,f,g,o,p}, Mariano Sigman^a, Diana Matallana^{a,k,q} and Agustín Ibáñez^{b,c,d,i,j,*}



Integration of Intention and Outcome for Moral Judgment in Frontotemporal Dementia: Brain Structural Signatures

Sandra Baez^{a,b,c}, Philipp Kanske^a, Diana Matallana^a, Patricia Montañes^a, Pablo Reyes^a, Andrea Slachevsky^{a,b}, Cristian Matus^o, Nora Silvana Vigliecca^{a,h}, Teresa Torralba^{a,q}, Facundo Manes^{a,i,j}, Agustín Ibáñez^{b,c,d,i,j,k,l,m,n,p}



Brain Network Organization and Social Executive Performance in Frontotemporal Dementia

aca Sedeño,^{1,2,3} Blas Couto,^{1,2,3} Indira García-Cordero,¹ Margherita Melloni,^{1,2,3} Sandra Baez,^{1,2,3} an Pablo Morales Sepúlveda,² Daniel Friman,^{2,4} David Huepe,² Esteban Harada,^{2,5} Diana Matallana,⁶ Rodrigo Kujal,² ressa Torralba,^{2,6,8} Dante Chialvo,^{3,7} Mariano Sigman,⁸ Olivier Piguet,^{9,10} Facundo Manes,^{11,12,13} AND Agustín Ibáñez^{2,3,3,11}

Journal List • Behav Neurosci • v:2018; 2018 • PMC5902123



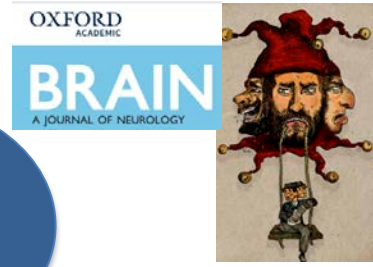
Behav Neurosci. 2018; 2018: 9684129.
 Published online 2018 Apr 1. doi: 10.1155/2018/9684129

Functional Connectivity Changes in Behavioral, Semantic, and Nonfluent Variants of Frontotemporal Dementia

P. Reyes,^{1, 2} M. P. Ortega-Merchan,¹ A. Rueda,³ F. Uriza,¹ Hernando Santamaría-García,^{2, 4, 5} N. Rojas-Serran,² J. Rodríguez-Santos,² M. C. Velasco-León,² J. D. Rodríguez-Parras,² D. E. Mora-Díaz,² and D. Matallana²

Primary empathy deficits in frontotemporal dementia

Sandra Baez^{1,2,3,1}, Facundo Manes^{1,2,3,4}, David Huepe^{2,5}, Teresa Torralba^{1,2}, Natalia Fiorentino^{1,2}, Fabian Richter⁶, Daniela Huepe-Artigas^{2,5}, Jesica Ferrari¹, Patricia Montañes^{1,6}, Pablo Reyes¹, Diana Matallana^{1,8}, Nora S. Vigliecca^{1,9}, Jean Decety¹⁰ and Agustín Ibáñez^{1,2,3,4,11,*}



A lesion model of envy and Schadenfreude: legal, deservingness and moral dimensions as revealed by neurodegeneration

Hernando Santamaría-García,^{1,2,3,4,5} Sandra Baez,^{3,4,5,6} Pablo Reyes,^{1,2} José A. Santamaría-García,⁶ José M. Santacruz-Escudero,^{1,2,7} Diana Matallana,^{1,2} Analía Arévalo,⁸ Mariano Sigman,⁹ Adolfo M. García^{1,4,12} and Agustín Ibáñez^{1,4,11,12,13}

SCIENTIFIC REPORTS

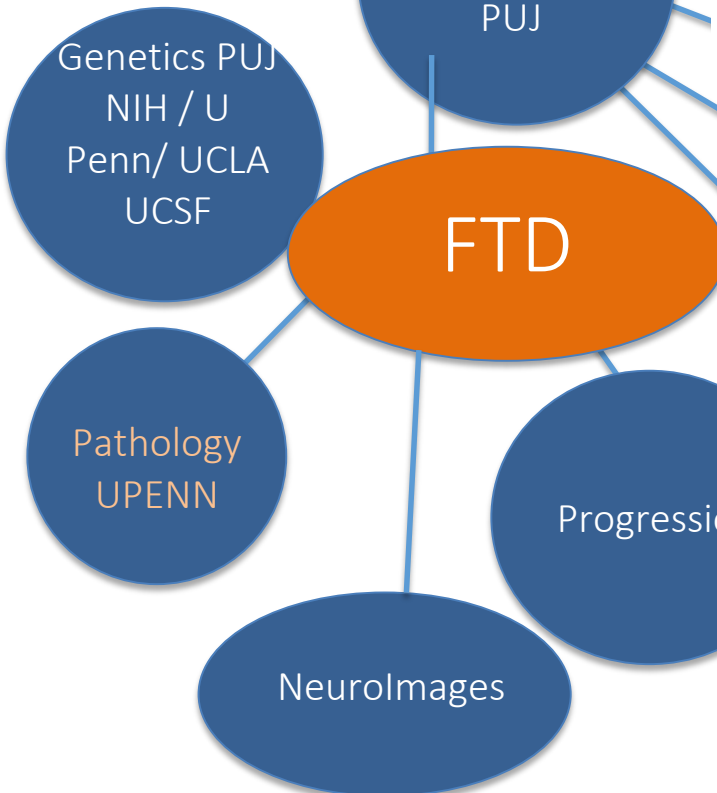
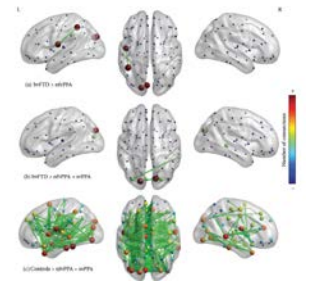
Empathy for others' suffering and its mediators in mental health professionals

Hernando Santamaría-García^{1,2,3,4,5}, Sandra Baez^{3,4,5,6}, Adolfo M. García^{5,6,7}, Daniel Flichtentrei⁸, María Prats⁹, Ricardo Mastanduno⁹, Mariano Sigman⁹, Diana Matallana^{1,10}, Marcelo Cetekovich^{5,6} & Agustín Ibáñez^{5,6,11,12,13}

Comparing Moral Judgments of Patients With Frontotemporal Dementia and Frontal Stroke

Sandra Baez, MS; Blas Couto, MD, PhD; Teresa Torralba, PsyD; Luciano A. Sposato, MD, MBA; David Huepe, PhD; Patricia Montañes, PhD; Pablo Reyes, MS; Diana Matallana, PhD; Nora S. Vigliecca, PhD; Andrea Slachevsky, PhD; Facundo Manes, MD, MS; Agustín Ibáñez, PhD

IMPORTANCE Several clinical reports have stated that patients with prefrontal lesions or



Journal List • Scientific Reports • PMC6060104



Sci Rep. 2018; 8: 11181.
 Published online 2018 Jul 25. doi: 10.1038/s41598-018-29538-9
 PMCID: PMC6060104
 PMID: 30046142

Weighted Symbolic Dependence Metric (wSDM) for fMRI resting-state connectivity: A multicentric validation for frontotemporal dementia

Sebastian Moguliner,^{1,2,3} Adolfo M. García,^{1,4,5} Ezequiel Mikulan,^{1,4} Eugenia Hesse,^{1,4,13} Indira García-Cordero,^{1,4} Margherita Melloni,^{1,4} Sabrina Cervetto,^{1,6} Cecilia Serrano,⁷ Eduar Herrera,^{1,4,8} Pablo Reyes,⁹ Diana Matallana,⁹ Facundo Manes,^{1,4,10} Agustín Ibáñez,^{1,4,10,11,12} and Lucas Sedeño^{10,14}

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From 2007– 2008

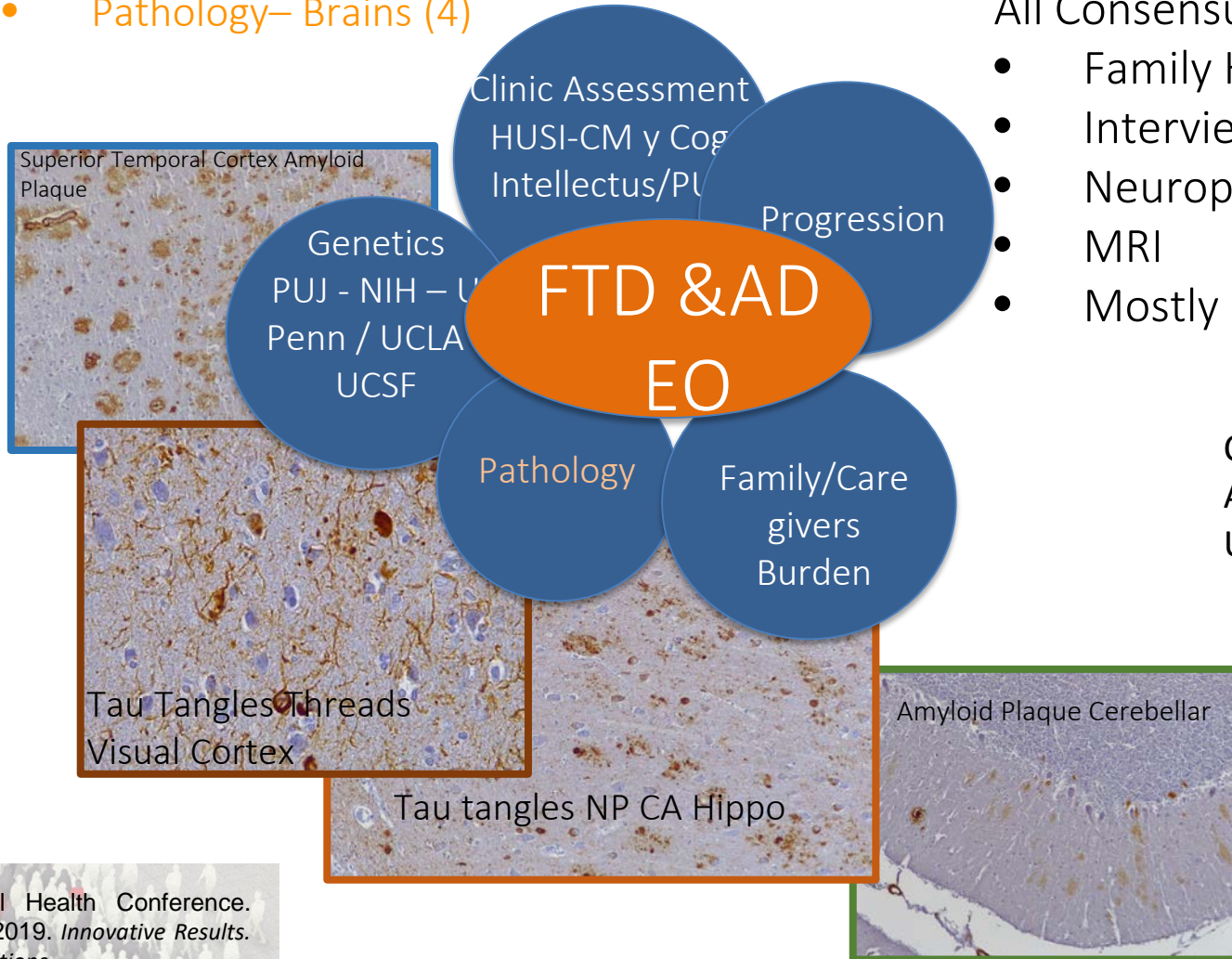
Early Onset -EO- / Young Onset

2007 – 2018

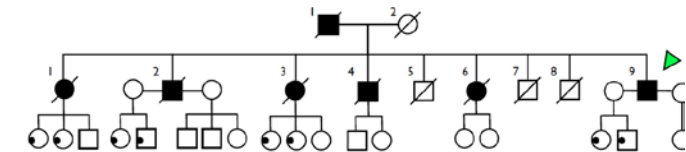
- Genetics/ Genetic Counseling
- 245 Pacientes Probable DFT
- Pathology– Brains (4)

All Patients from 2011-2019.
All Consensus MC (HUSI + FSFB)

- Family History
- Interviews and Family care
- Neuropsychology Assessment
- MRI
- Mostly all (-) to A280



Colombian Familial Dementia with Frontotemporal Features Associated with a Presenilin-1 Mutation. Irwin D., Raskovsky K., UPENN / Matallana D, Cano C., et. al. (Identified in 2001)

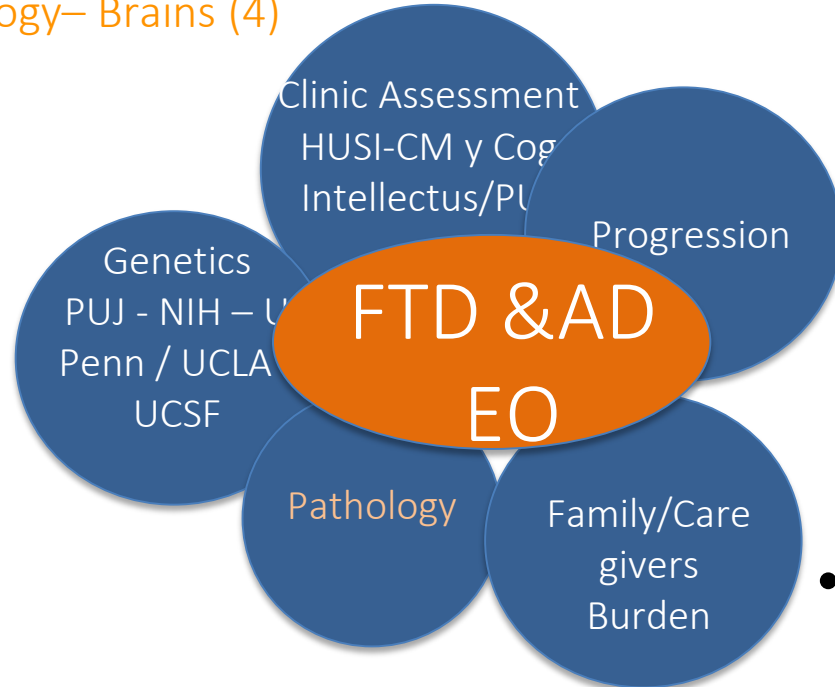


From 2007– 2008

Early Onset -EO- / Young Onset

2007 – 2018

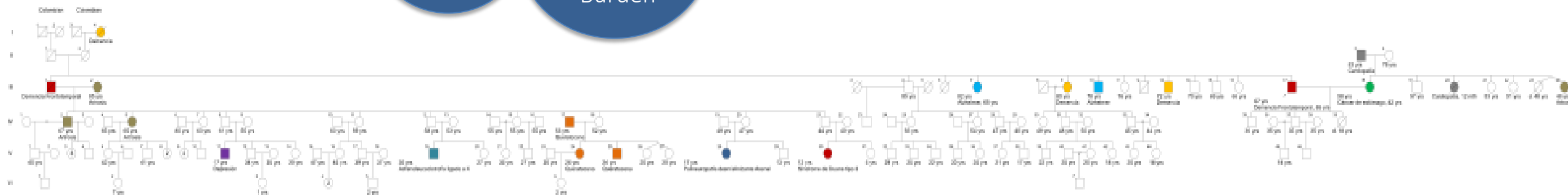
- Genetics/ Genetic Counseling
- 245 Pacientes Probable DFT
- Pathology– Brains (4)



Patients from 2018-2019.
Waiting to be assessed:
By Consensus MC (HUSI + FSFB)

- MRI
 - Genetics
- 189

- Genetics Taken of this Family : 47 Subjects (April 2019)



LEGENDA
 ■ Síndrome Frontotemporal
 ■ Demencia
 ■ Síndrome de Huntington
 ■ Corea de Huntington
 ■ Alzheimer
 ■ Esquizofrenia
 ■ Síndrome de Tourette
 ■ Síndrome de Gilles de la Tourette
 ■ Síndrome de Tourette
 ■ Síndrome de Tourette
 ■ Síndrome de Tourette

NOTAS
 ■ Síndrome de Huntington
 ■ Síndrome de Huntington

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New Directions Based on our samples:

- Contact Families of patients
- Motoneuron Disease
- Amyotrophic Lateral Sclerosis (ALS)
- Contact patients and Families of c9orf72
- Study Family and Subjects pre-symptomatic
- Search MAPT y PGN Families
- Aranzazu Families: Late Onset BD. 4 generations; severe progression of Earle and late onset (Agudelo F., Uribe JM, Jordan MI)

Genetics Biomarkers

Nik Spencer/Nature

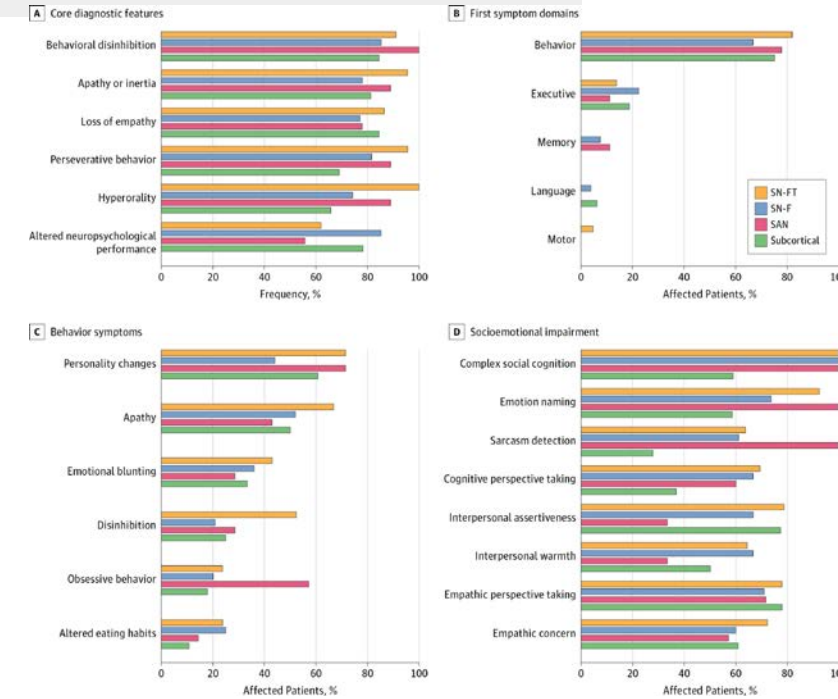
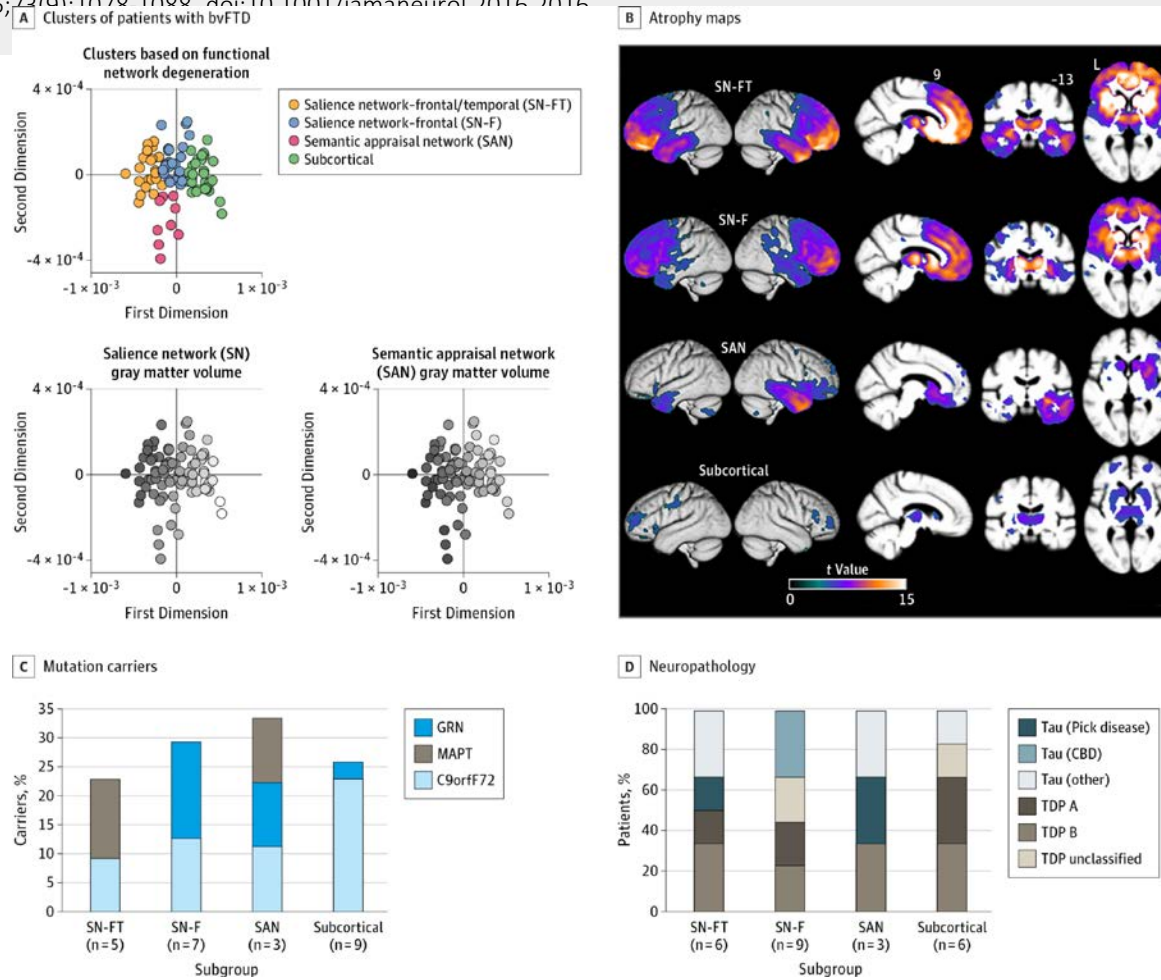
Ready To:

From: Distinct Subtypes of Behavioral Variant Frontotemporal Dementia Based on Patterns of Network Degeneration

JAMA Neurol. 2016;73(9):1078-1088. doi:10.1001/jamaneurol.2016.2016

functional
salience
network SN

semantic
appraisal
network SAN



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Total patients evaluated with genetics

Total	DFT	325
Controls		100
AD and Other Dementia		30

DNA Genetic study: 245 possible DFT
(U Penn - UCLA-UCSF)

40 U Penn. 7 Possible pathogenic

Table 1. Mutations found in the South-American FTD series.

Patient	Phenotype	Family history	Variant	gnomAD frequency*	SIFT	Polyphen	CADD	ACMG-AMP classification
BOG0315	bvFTD	-	<i>C9orf72</i> Repeat expansion	Pathogenic
BOG0034	bvFTD	+	<i>GRN</i> c.C328T;p.R110X	3.99E-06	.	.	27.0	Pathogenic
BOG0309	svPPA	+	<i>TARDBP</i> c.A1147G;p.I383V	1.91E-05	T	B	18.6	Likely pathogenic
BOG0003	svPPA	-	<i>TARDBP</i> c.A1147G;p.I383V	1.91E-05	T	B	18.6	Likely pathogenic

* Overall gnomAD frequencies as these variants were not found among the Latino individuals included in this database. Phenotype - bvFTD: behavioral variant frontotemporal dementia, svPPA: semantic variant primary progressive aphasia. Family history -+: at least one first-degree relative diagnosed with some type of dementia, -: apparently sporadic. SIFT predictions -T: Tolerated, D: Deleterious. Polyphen predictions - D: Probably Damaging, P: Possibly Damaging, B: Benign.

Argentina
INCyT/INECO: Ibáñez A.

UCSF / UCLA Genetic later study
Miller B. Coppola G.

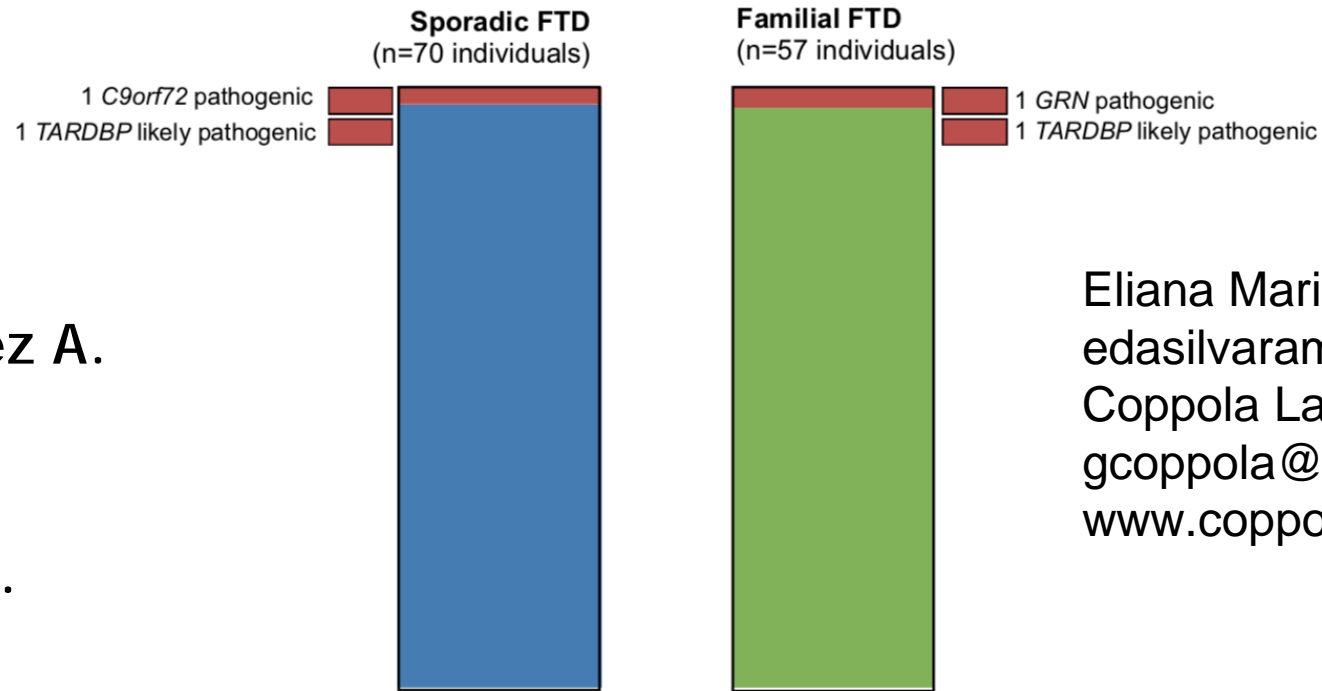
Eliana Marisa Ramos, PhD
edasilvaramos@mednet.ucla.edu
Coppola Lab (UCLA)
gcoppola@ucla.edu
www.coppolalab.ucla.edu



Early onset dementia: an experience towards the future.



b)

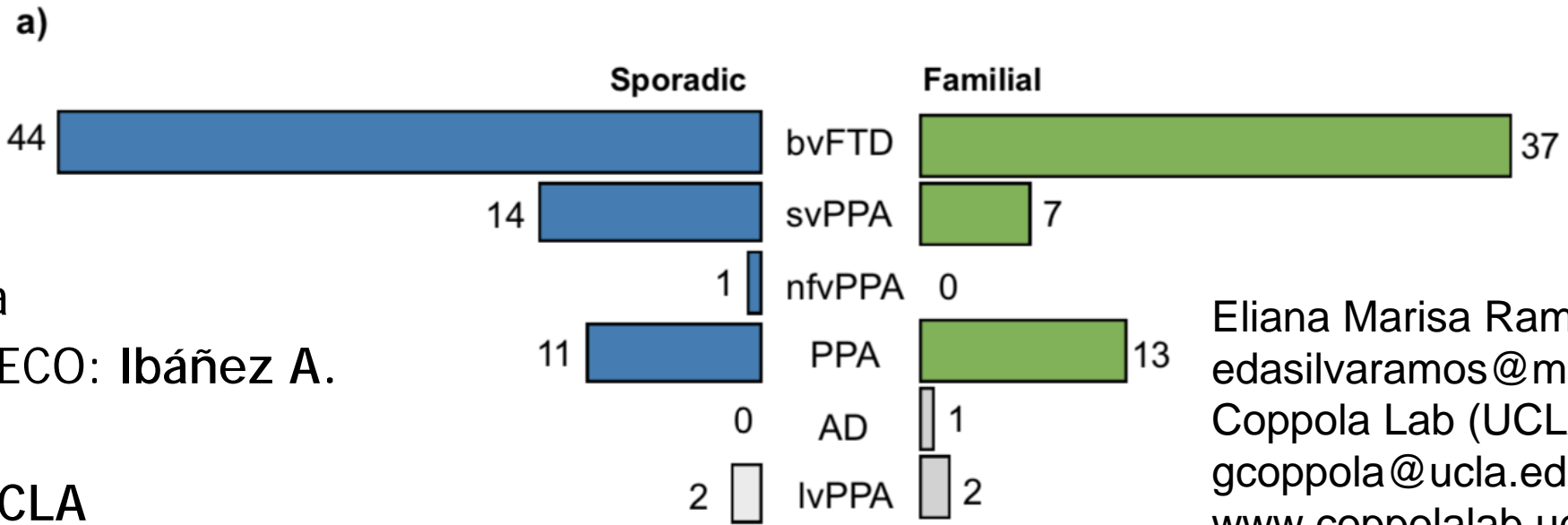


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Figure 2. Clinical and genetic characteristics of the cases included in the South American series. a) Clinical diagnoses among 72 sporadic patients with dementia (left) and 60 individuals with family history (right). Six additional cases (not shown here) had no information available regarding family history. **b)** Carriers of (likely) pathogenic variants in the main FTD genes (red) among 70 sporadic cases (blue, left) and in 57 familial cases (green, right) diagnosed with FTD-spectrum phenotypes. (AD: Alzheimer's disease dementia; FTD: frontotemporal dementia; bvFTD: behavioral variant FTD; lvPPA: logopenic variant primary progressive aphasia (PPA); nfvPPA: non-fluent variant PPA; svPPA: semantic variant PPA)



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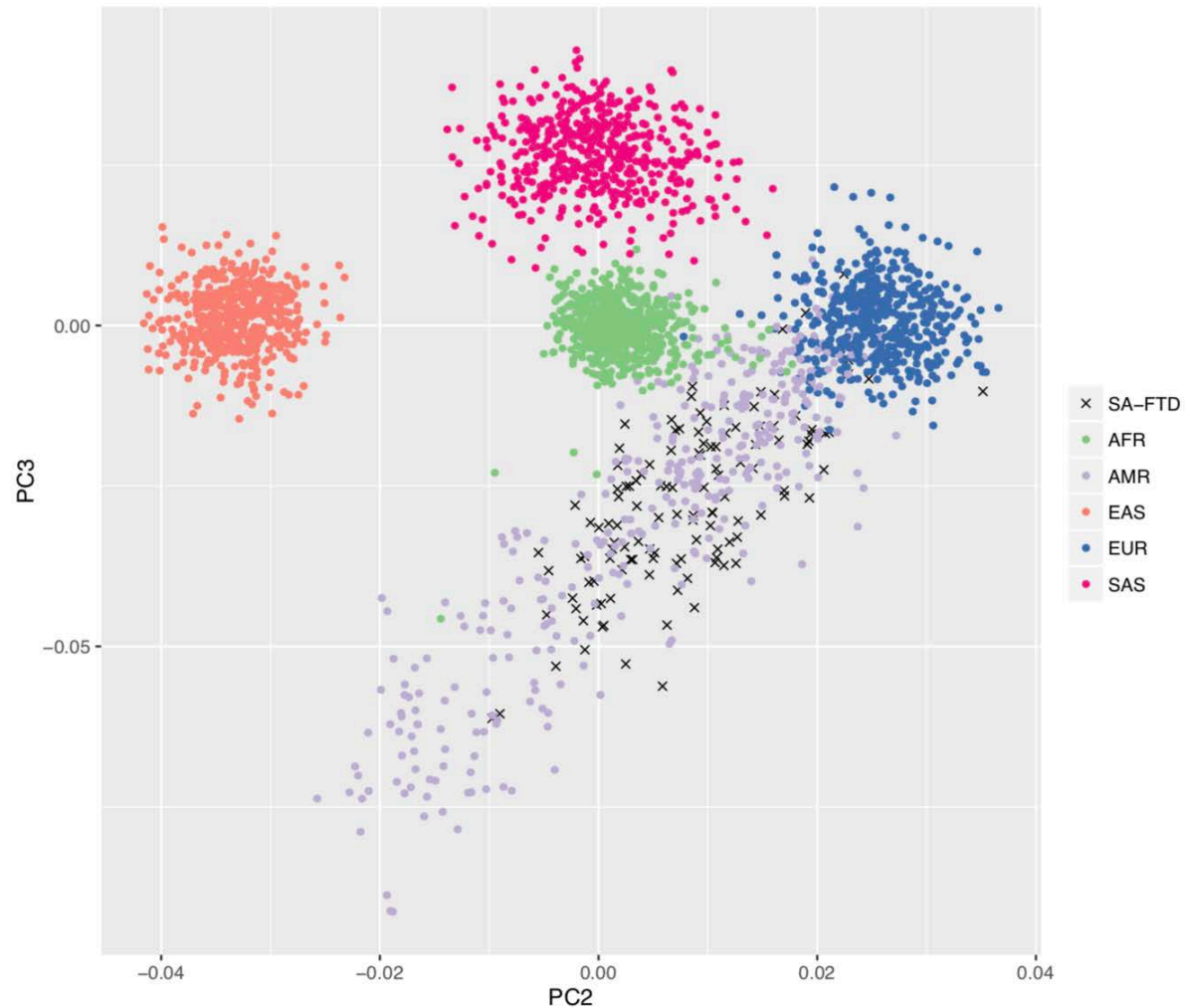


Figure 1. Ancestry estimation. PCA for the cohort and reference groups are plotted along principal components (PCs) 2 and 3. Colored dots represent the five continental groups from 1000 Genomes Project used as reference (AFR: African, AMR: Admixed American, EAS: East Asian, EUR: European, SAS: South Asian), while the black + represent the South American FTD (SA-FTD) series screened in this study.



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Thanks

GRACIAS

To Our Patients, Families and
Caregivers.

To our Human resources:
Researchers, Doctors, Clinicians,
Students, Hospital and University
professors.

And... Present and Future
Academic Partners



FTD Patient
with Artistic
Emergence at
Dementia onset.