Sociedade Portuguesa de Doenças Metabólicas
15th International Symposium
14th-15th March, 2019

SCARB2 MUTATIONS AS MODIFIERS IN GAUCHER DISEASE:

the wrong enzyme at the wrong place?

COUTINHO MF[1], LACERDA L[2], GASPAR A[3], PINTO E[2], RIBEIRO I[2], LARANJEIRA F[2], RIBEIRO H[2], SILVA E[2], FERREIRA C[2], PRATA MJ[4,5], ALVES S[1]

Gaucher Disease (GD)

- Autosomal recessive
- Lysosomal Storage Disorder
  - Deficient enzyme: **β-glucocerebrosidase (Gcase)**
  - Gene: *GBA* (1q21)

Original illustration by Marcos Bernardino for Cristiana Petriz´s "*Gigi e a Doença de Gaucher*", 2010

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  - **Atypical form:**
  - Deficient enzyme: Saposin C
  - Gene: *PSAP* (10q21-q22)

Original illustration by Marcos Bernardino for Cristiana Petriz´s "*Gigi e a Doença de Gaucher*", 2010

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Gaucher Disease (GD)

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- Large spectrum of severity & symptoms

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- 3 variants

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- 3 variants

based on the presence

abscence

& progressivity

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based on the presence / abscence *& progressivity* | of neuronopathic disease

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GD type 1

2

3

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GD type 1	**Non-Neurological**
2	
3	

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GD type 1	Non-Neurological
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3	

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- Genotyope-Phenotype correlations

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- Genotyope-Phenotype correlations

⇒ *only possible for a few mutations*

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- One of the **most frequent** LSD

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- One of the **most frequent** LSD
- Available **ERT**

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Gaucher Disease (GD)

- ✍ *"The prototype lysosomal disease…"*

(Zhao and Grabowski, 2002)

Original illustration by Marcos Bernardino for Cristiana Petriz´s "*Gigi e a Doença de Gaucher*", 2010

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- 1st described

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- 1st described
- 1st drug approved

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Gaucher Disease (GD)

- ✍ *"The prototype lysosomal disease…"*

(Zhao and Grabowski, 2002)

- 1st described
- 1st drug approved
- > nr therapeutic approaches

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Gaucher Disease (GD)

- ✍ *"The prototype lysosomal disease…"*

(Zhao and Grabowski, 2002)

- Still…

  it does have some significant differences

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Gaucher Disease (GD)

✍ *At the populational level…*

- **Surprising link to common disorders**

Gaucher Disease (GD)

✍ *At the populational level…*

***GBA* mutation carriers**

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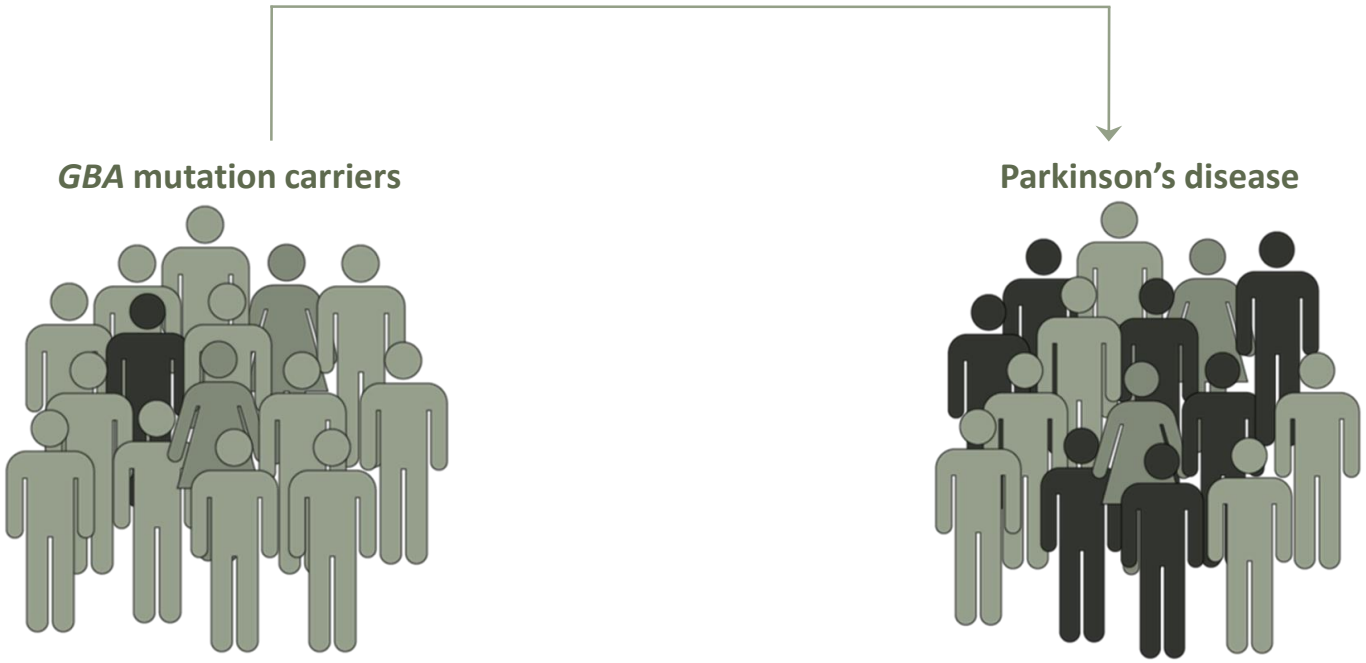
Gaucher Disease (GD)

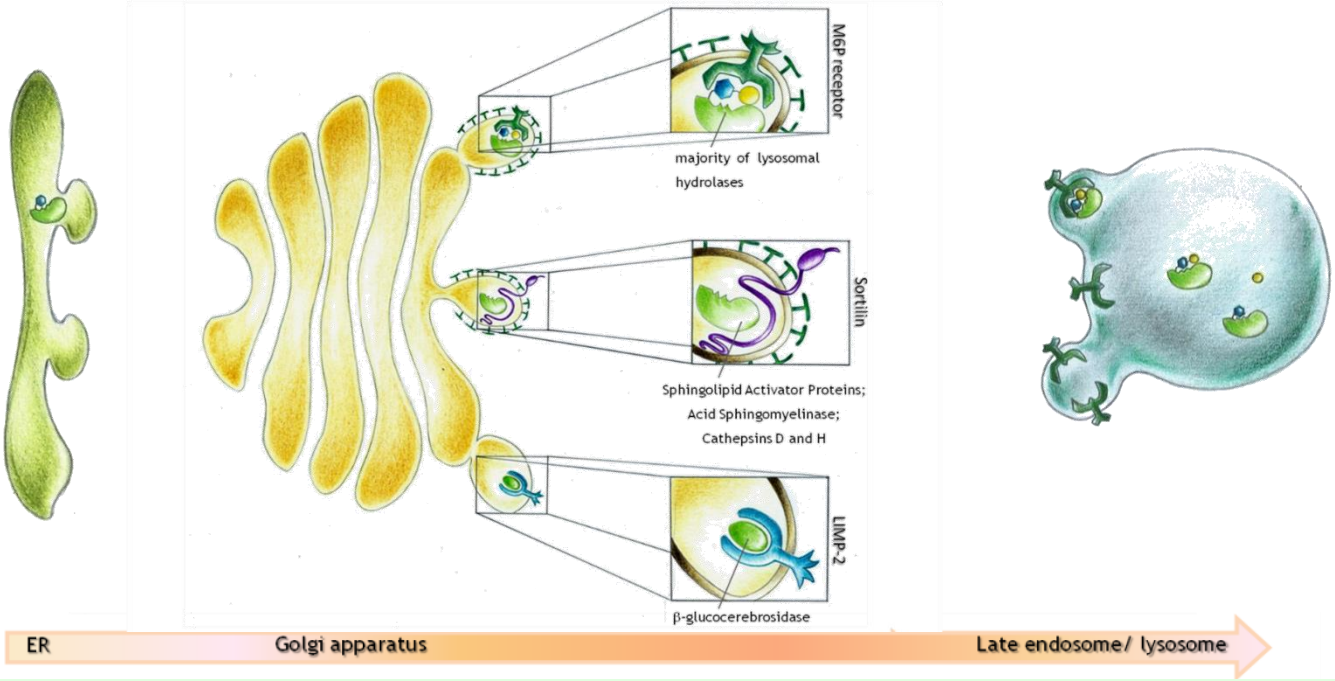
✍ *At the populational level…*



Gaucher Disease (GD)

✍ *At the molecular level…*

- **GCase**



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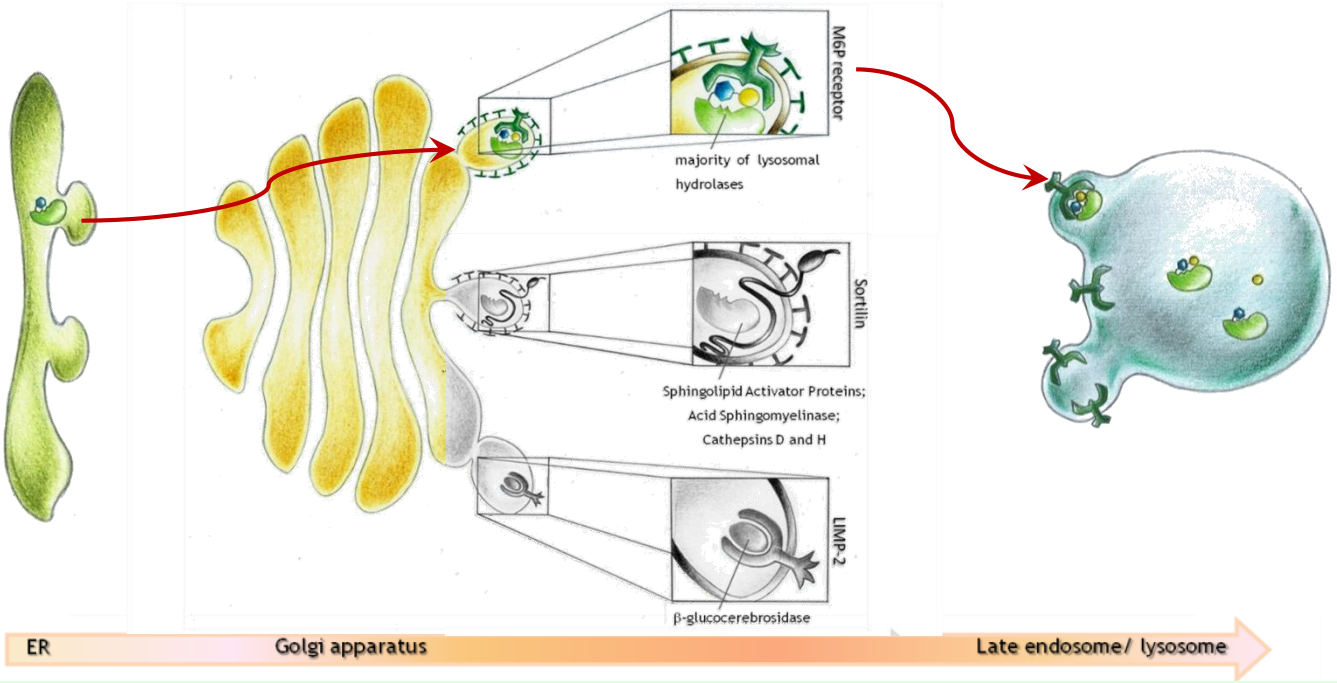

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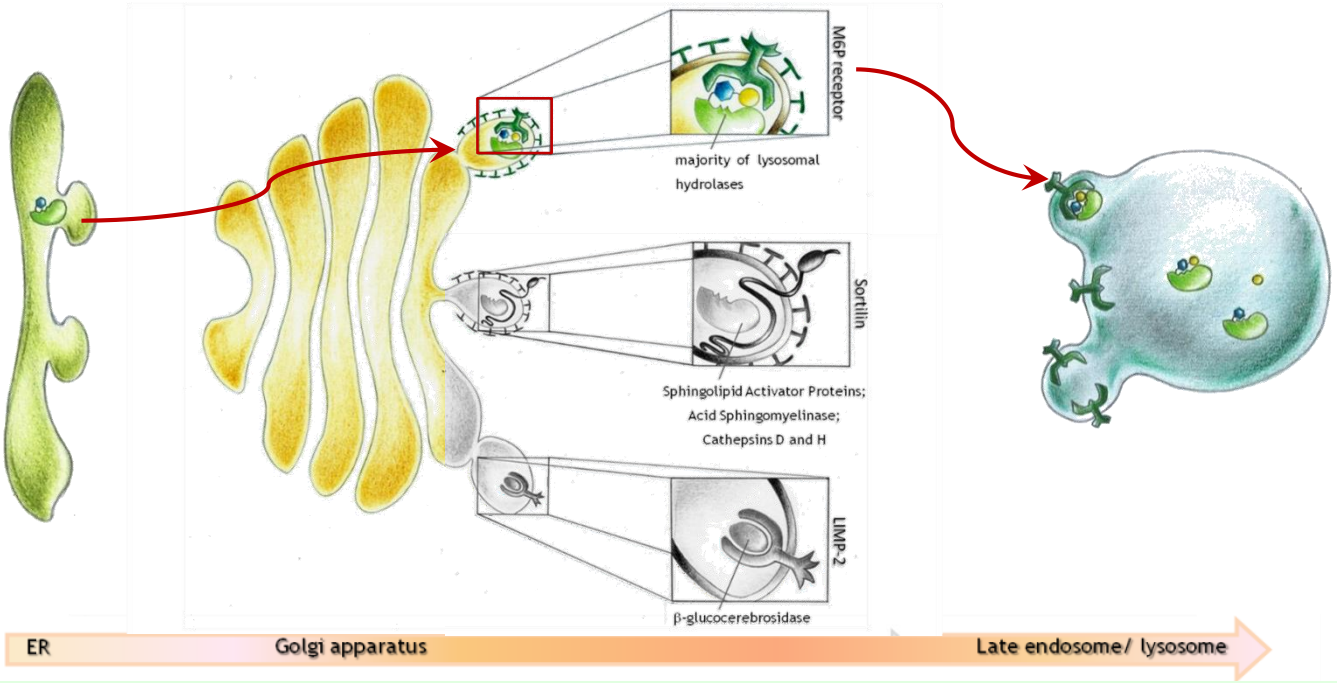

Gaucher Disease (GD)

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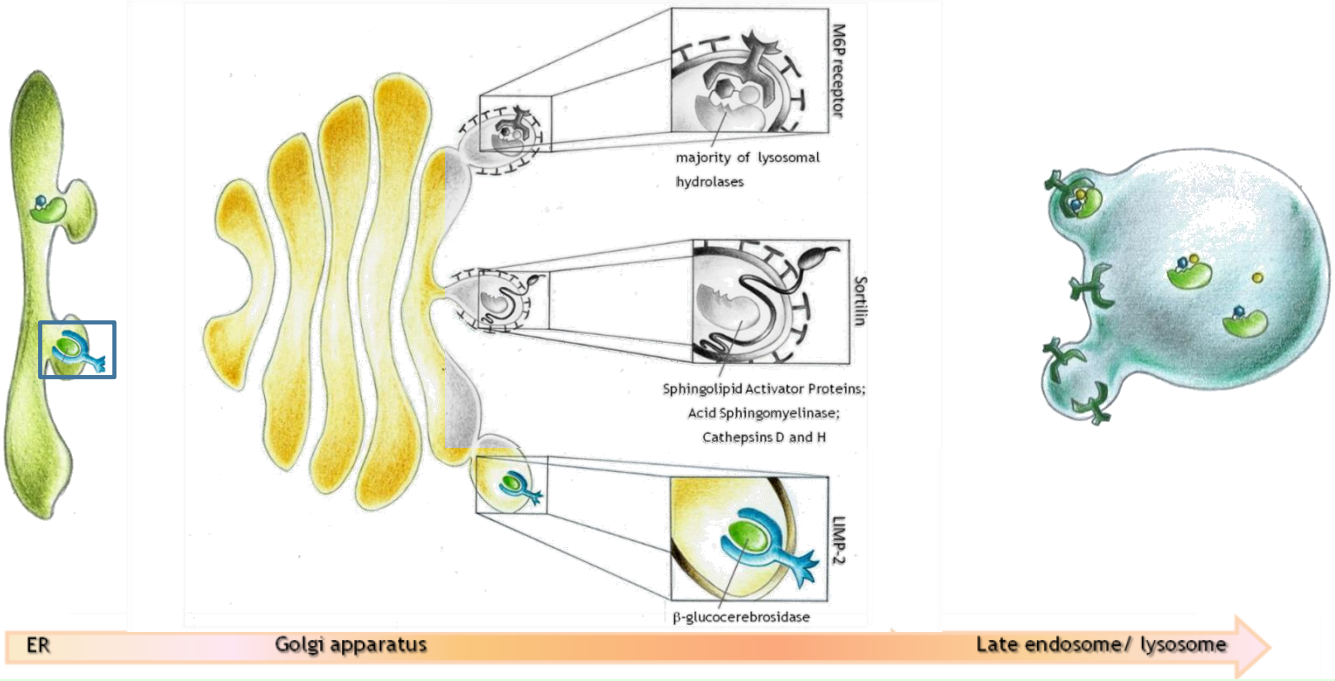

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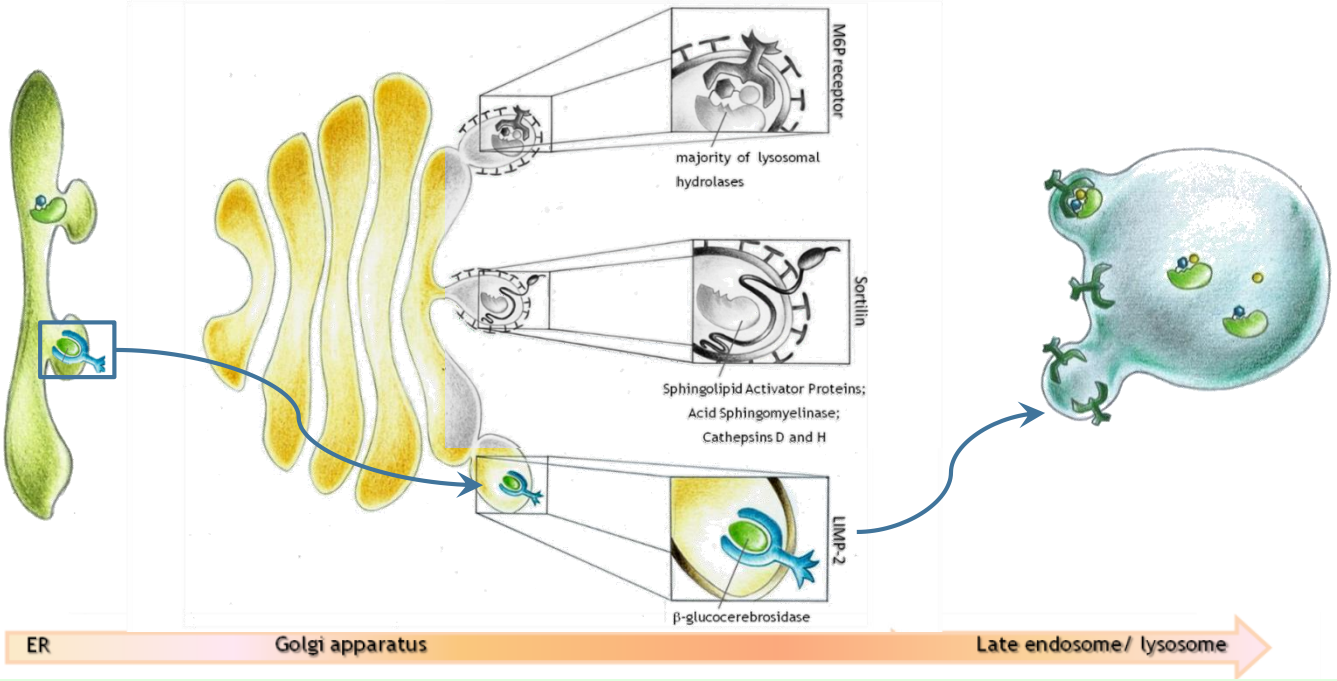

Gaucher Disease (GD)

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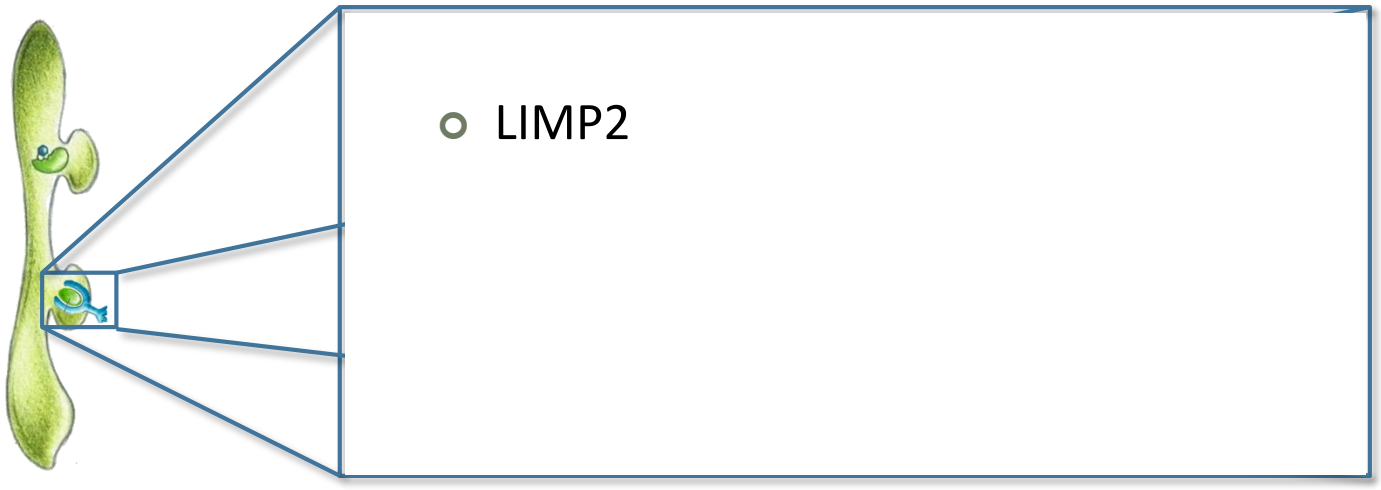

- LIMP2

Gaucher Disease (GD)

✍ *At the molecular level…*

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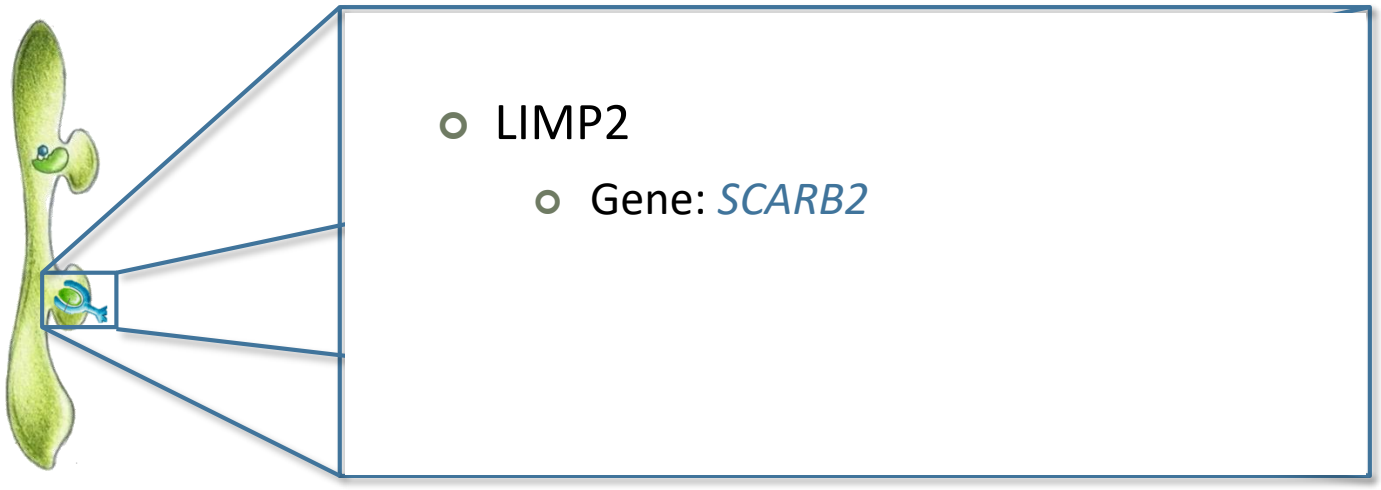

- LIMP2
  - Gene: *SCARB2*

Gaucher Disease (GD)

✍ *At the molecular level…*

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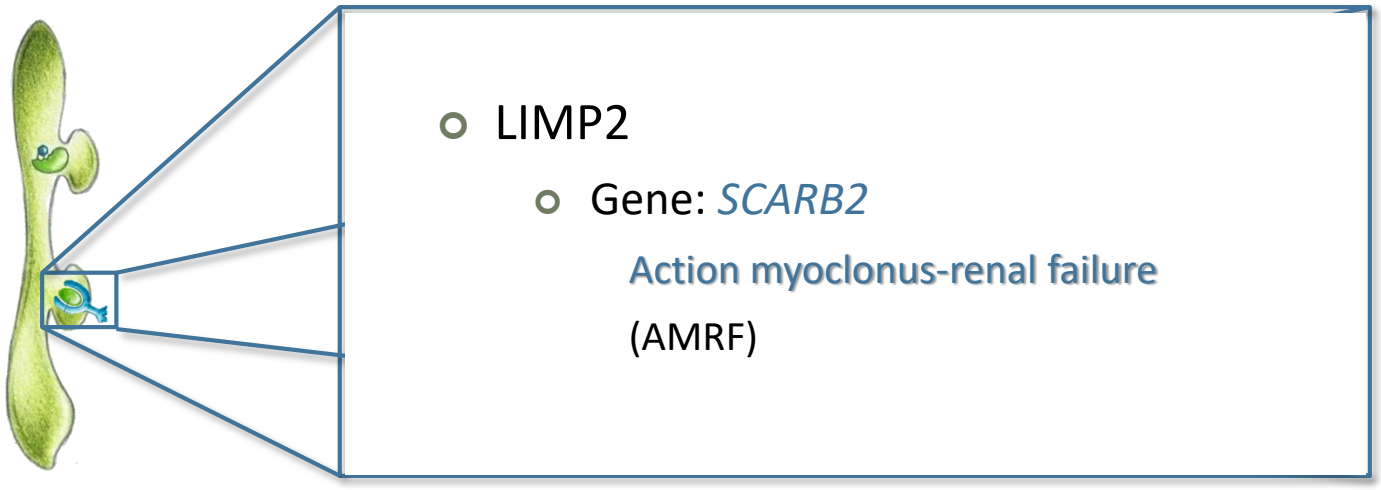

- LIMP2
  - Gene: *SCARB2*

    Action myoclonus-renal failure

    (AMRF)

Gaucher Disease (GD)

✍ *At the molecular level…*

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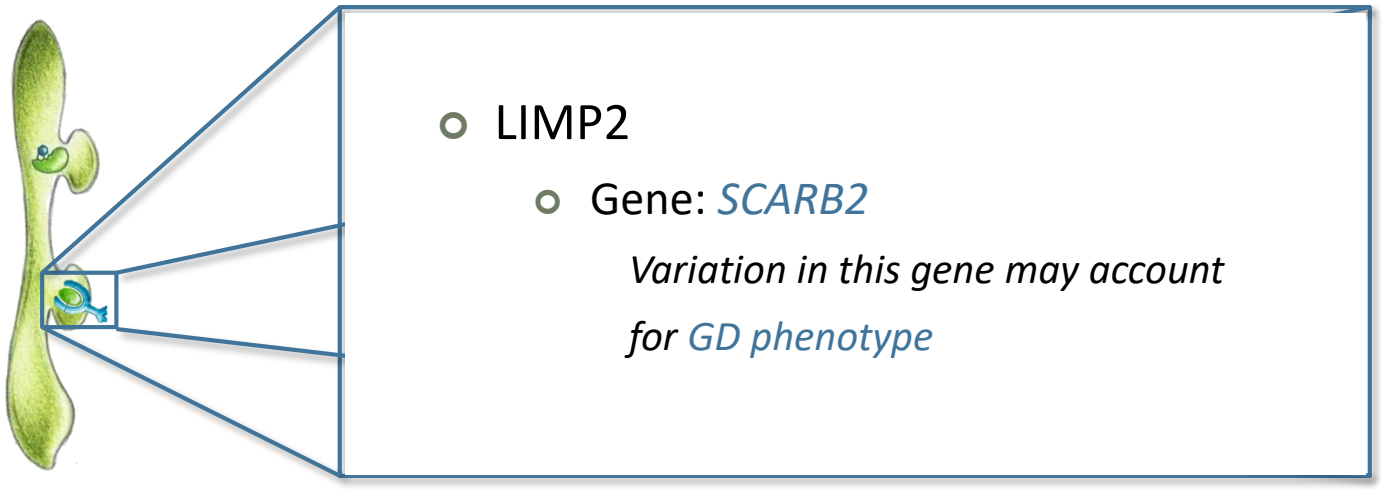

- LIMP2
  - Gene: *SCARB2*

    Variation in this gene may account for GD phenotype

Gaucher Disease (GD)

✍ *At the molecular level…*

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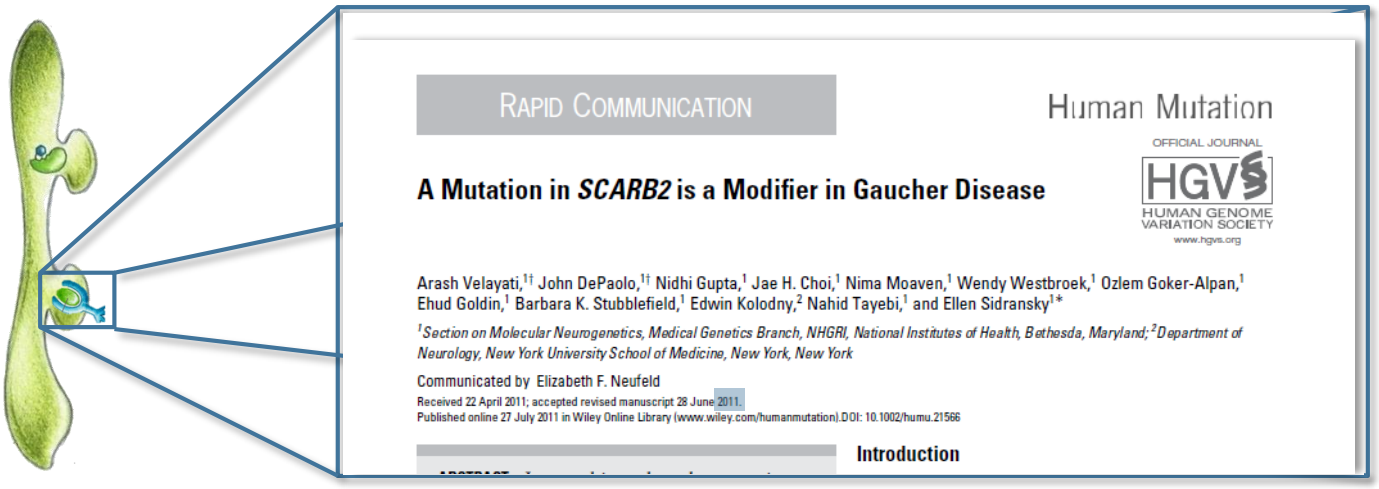

RAPID COMMUNICATION

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

A Mutation in *SCARB2* is a Modifier in Gaucher Disease

Arash Velayati,[1†] John DePaolo,[1†] Nidhi Gupta,[1] Jae H. Choi,[1] Nima Moaven,[1] Wendy Westbroek,[1] Ozlem Goker-Alpan,[1] Ehud Goldin,[1] Barbara K. Stubblefield,[1] Edwin Kolodny,[2] Nahid Tayebi,[1] and Ellen Sidransky[1]*

[1]*Section on Molecular Neurogenetics, Medical Genetics Branch, NHGRI, National Institutes of Health, Bethesda, Maryland;* [2]*Department of Neurology, New York University School of Medicine, New York, New York*

Communicated by Elizabeth F. Neufeld

Received 22 April 2011; accepted revised manuscript 28 June 2011.
Published online 27 July 2011 in Wiley Online Library (www.wiley.com/humanmutation).DOI: 10.1002/humu.21566

Introduction

Objective

Understand the role of variations in *SCARB2* in the broad phenotype spectrum observed for GD patients

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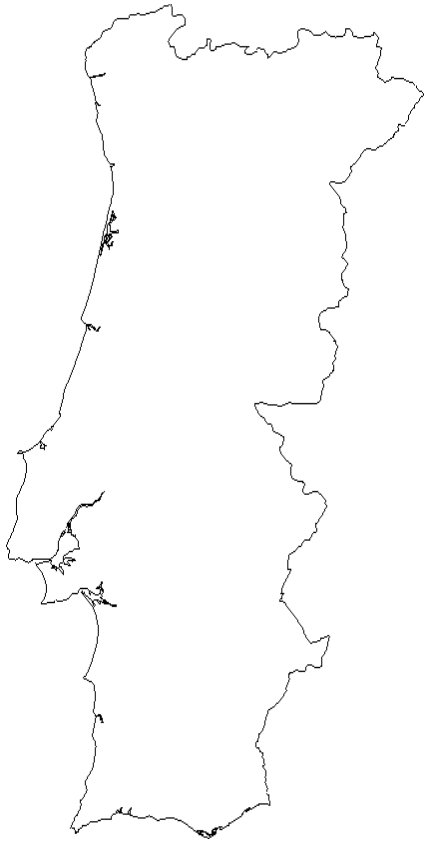
Understand the role of variations in *SCARB2* in the broad phenotype spectrum observed for GD patients

in Portugal

Sample Collection



- Portuguese GD population
  - 91 samples

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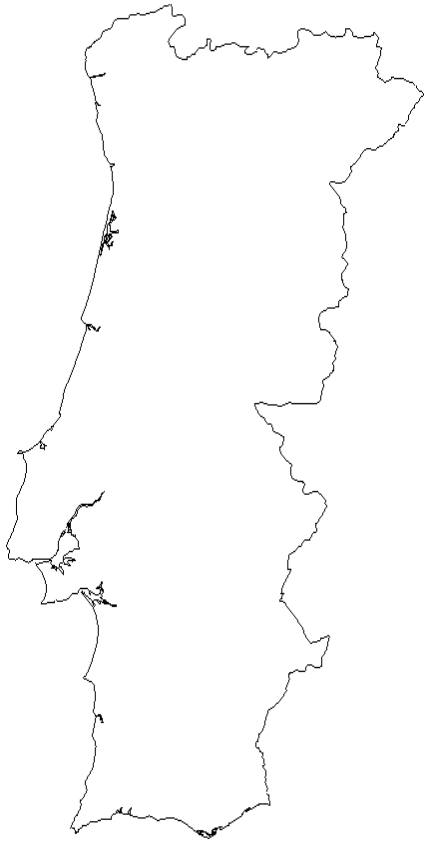
Sample Collection



- Portuguese GD population
  - 91 samples
    - Biochemically
    - molecularly

characterized GD patients, diagnosed at CGMJM

until 2013

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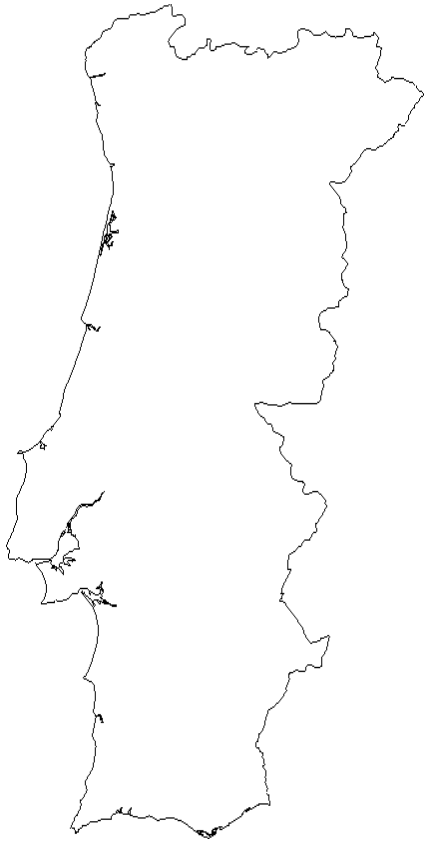
Sample Collection



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- Controls
  - 50 samples

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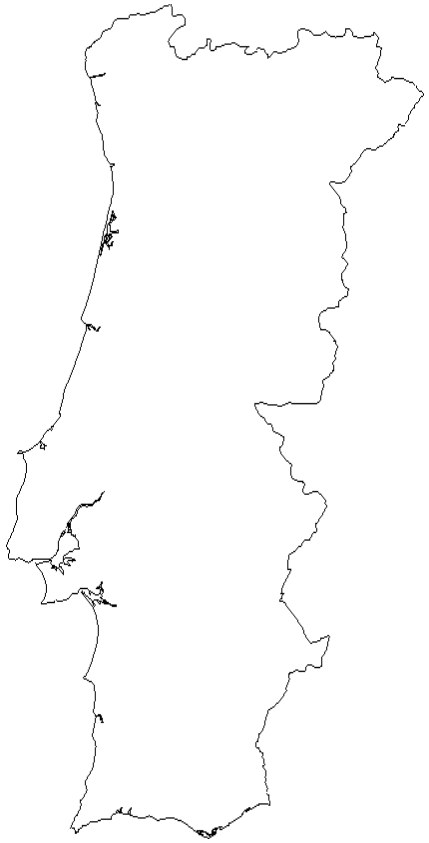

- Portuguese GD population
  - 91 samples
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    characterized GD patients, diagnosed at CGMJM

    until 2013

+

- Controls
  - 50 samples
    - *screening of the novel variants*

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Genetic analysis

- DNA
  - Peripheral blood
  - Fibroblasts from patients' skin biopsies

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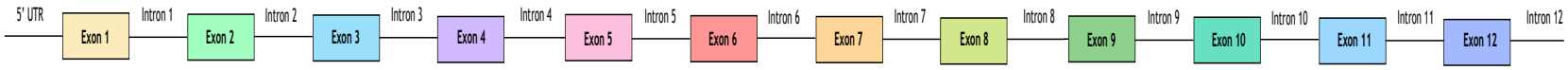
- Sanger sequencing
  - 12 *SCARB2* exons + intronic bounderies



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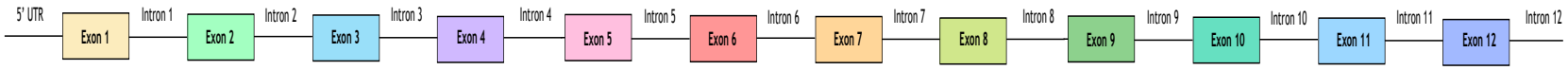
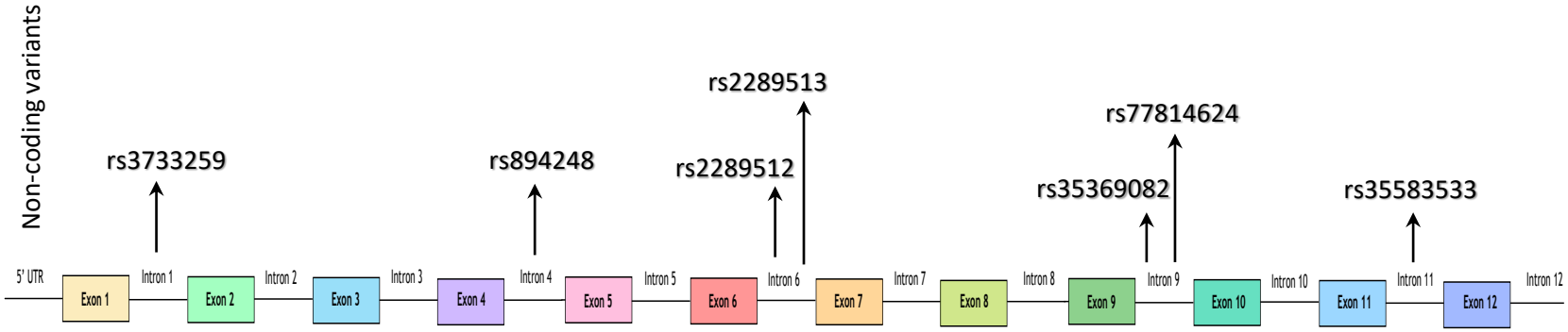


- *In silico* analyses
  - Evaluation of the deleterious potential of the novel variant(s)

Results



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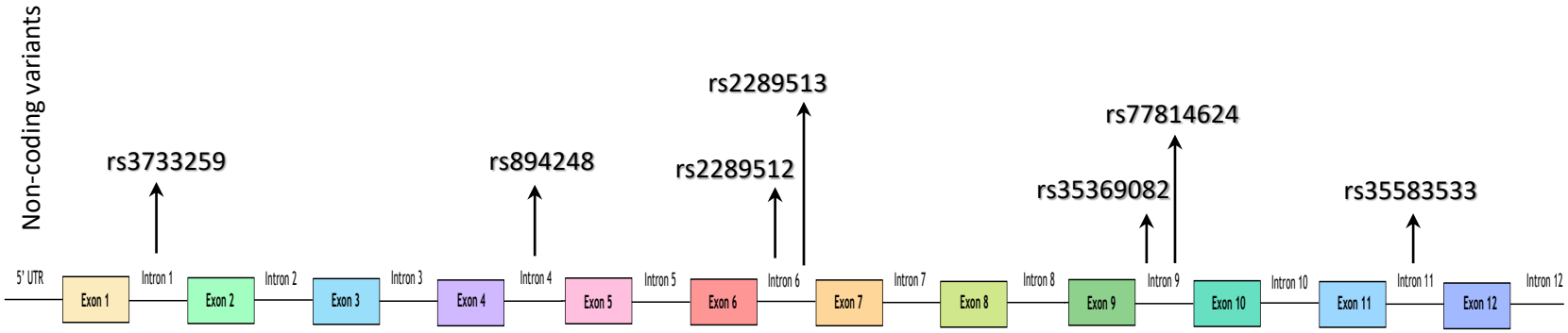
Results



Registered polymorphisms
Also present in the controls

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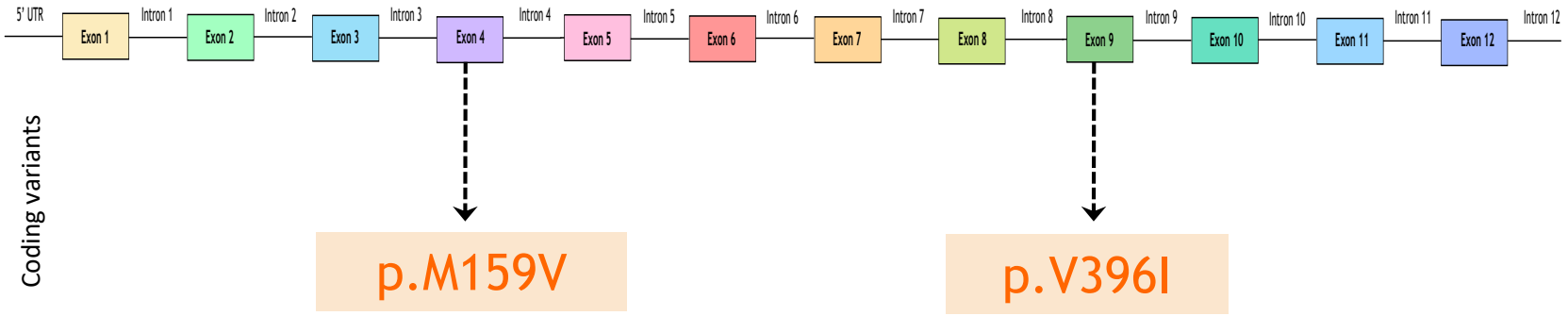
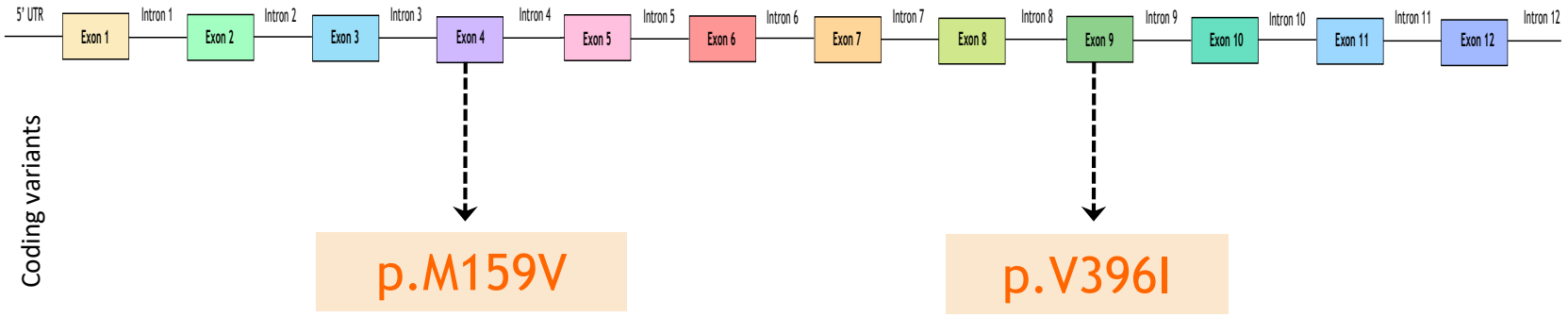
Results



Results

known polymorphic variations
high prevalence in the normal population



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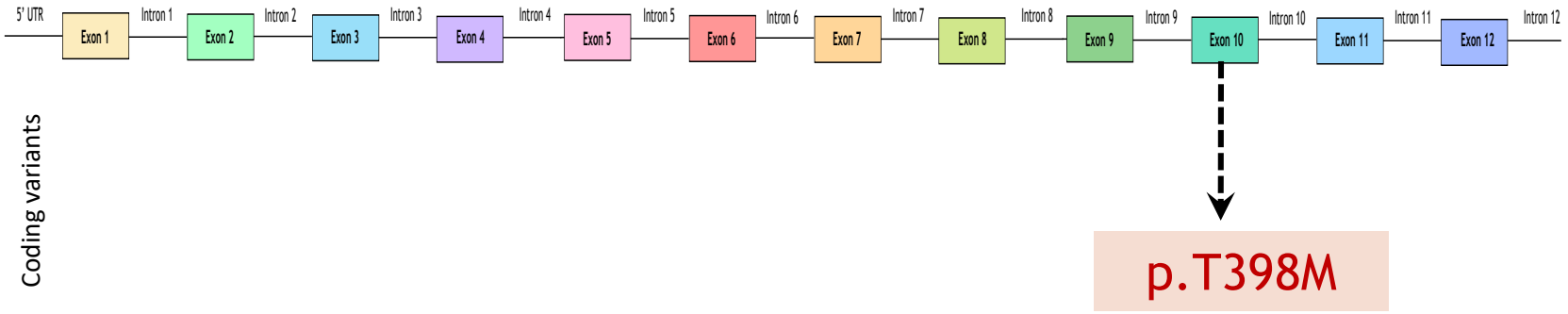
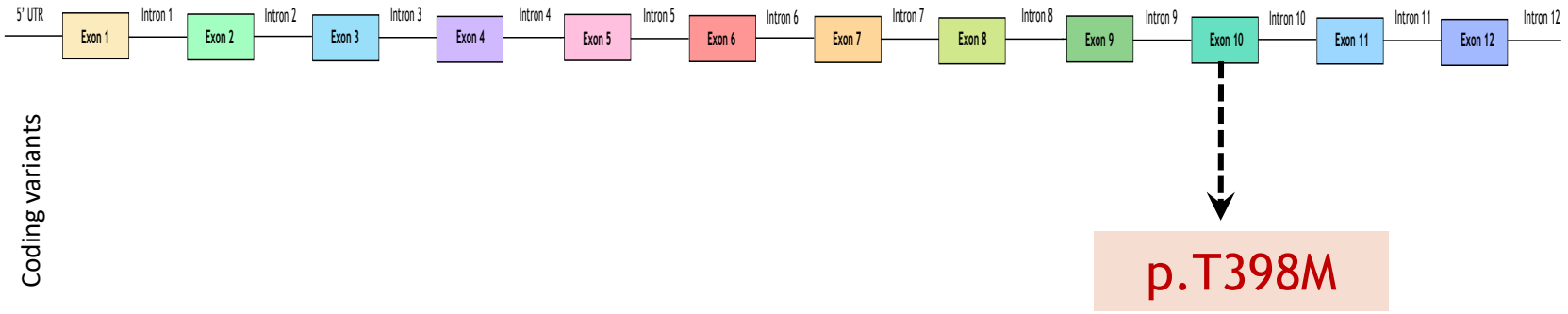


Results

Novel coding variant
not detected in 50 controls



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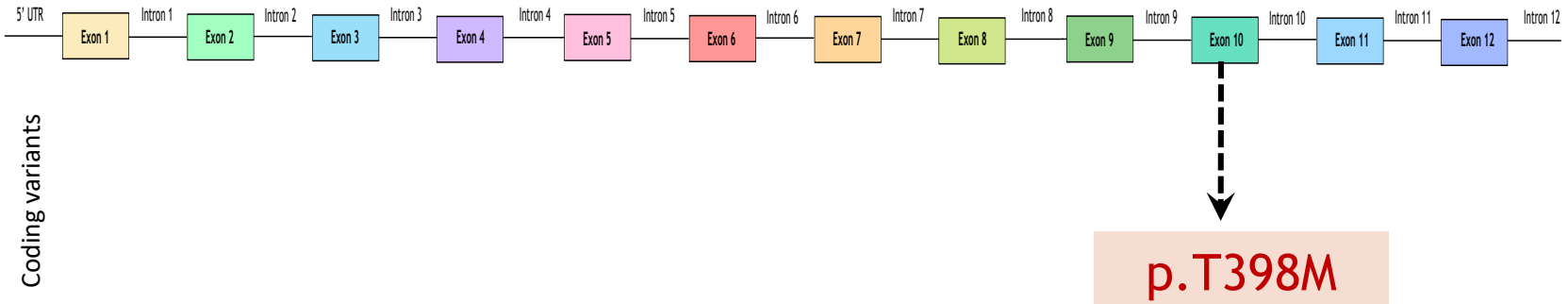
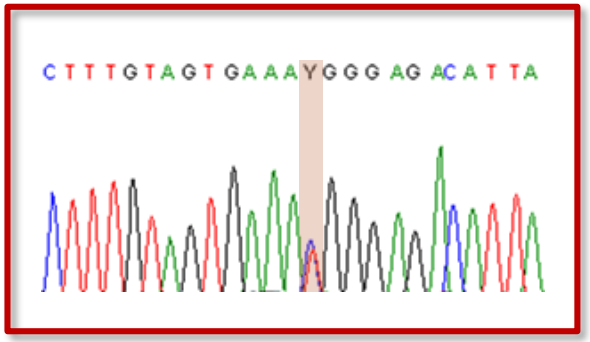


p.T398M

N= 1

In silico analyses



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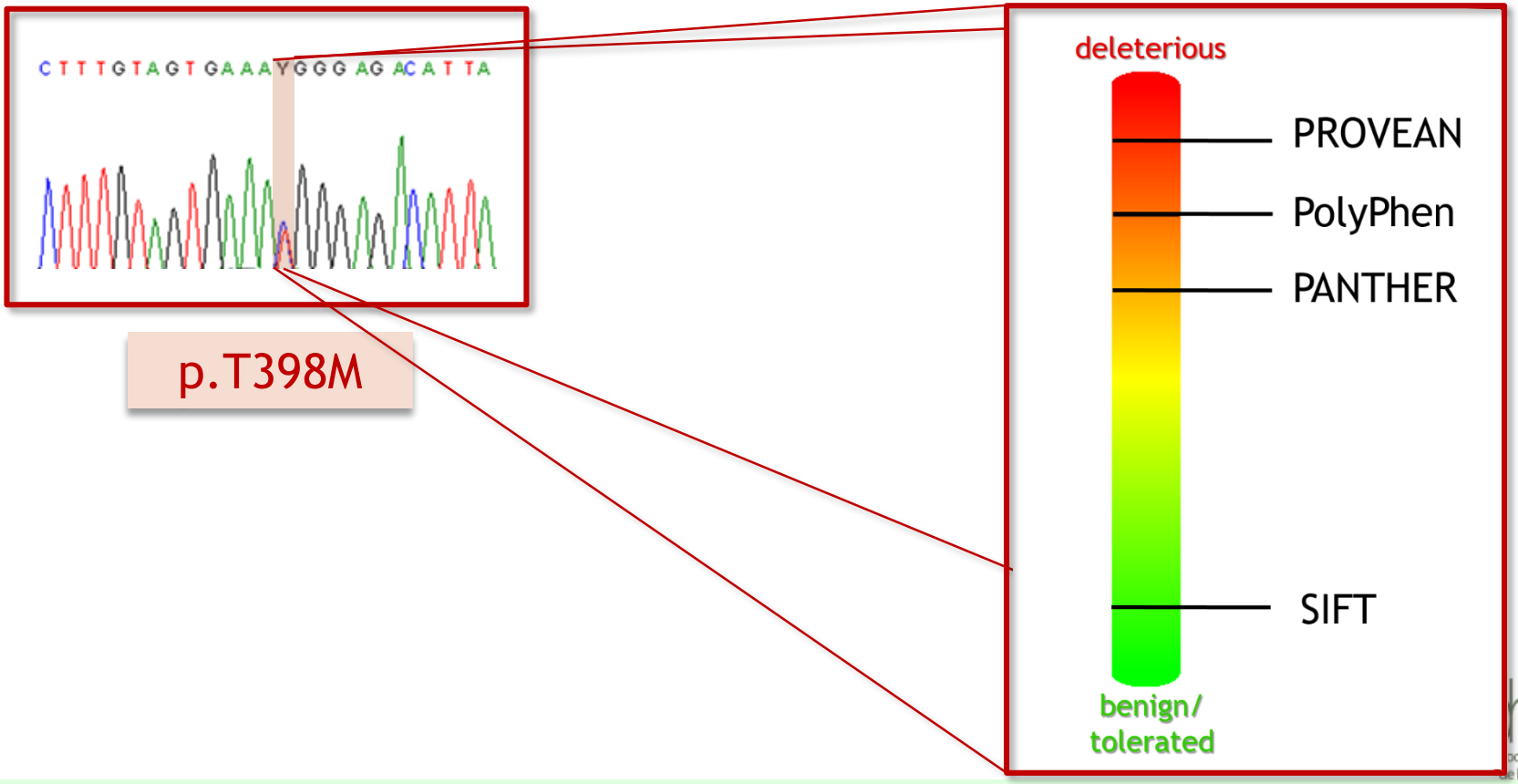

Reassessment of the clinical case

- 2nd child of young healthy unrelated parents

Cape Verdean origin

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- Symptoms' onset: 7 months

Reassessment of the clinical case

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Cape Verdean origin

- Symptoms' onset: 7 months
- Multi-symptomatic clinical presentation
  - abdominal distension;
  - diarrhea;
  - anorexia;
  - feeding difficulties;
  - rough coughing;
  - progressive weight loss.

Reassessment of the clinical case

- 2nd child of young healthy unrelated parents

Cape Verdean origin

- Symptoms' onset: 7 months
- Disease progression:
  - severe anemia;
  - poor facial mimic;
  - stridor;
  - thrombocytopenia;
  - cardiomegaly;
  - marked splenomegaly;
  - interstitial lung disease with multiple recurrent infections;

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global psychomotor developmental delay

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Neurological GD

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Cape Verdean origin

SEVERE

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Neurological GD

Reassessment of the *GBA* genotype

- 2nd child of young healthy unrelated parents

Cape Verdean origin

- Genotype: **L444P/L444P**

Reassessment of the *GBA* genotype

- 2nd child of young healthy unrelated parents

Cape Verdean origin

- Genotype: **L444P/L444P**

- Common mutation
- Known genotype-phenotype correlation

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Cape Verdean origin

- Genotype: **L444P/L444P**

- Common mutation
- Known genotype-phenotype correlation

⇓

Neurological GD

Reassessment of the *GBA* genotype

- 2nd child of young parents
  - healthy
  - unrelated

Cape Verdean origin

- Genotype: **L444P/L444P**

- Common mutation
- Known genotype-phenotype correlation

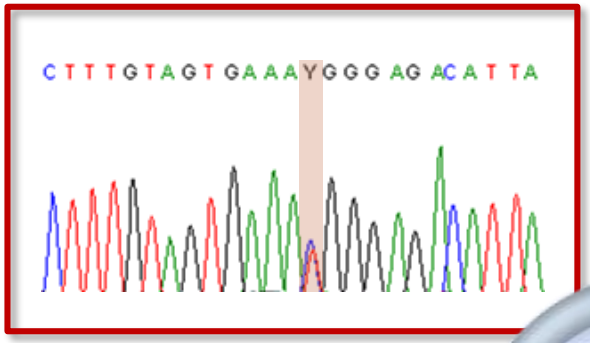
⇓

Neurological GD

p.T398M: GD modulator?

- No conclusions can be drawn by the analysis of the phenotype | alone
  GBA genotype |

A LOOK FORWARD...



p.T398M

- **Functional** studies

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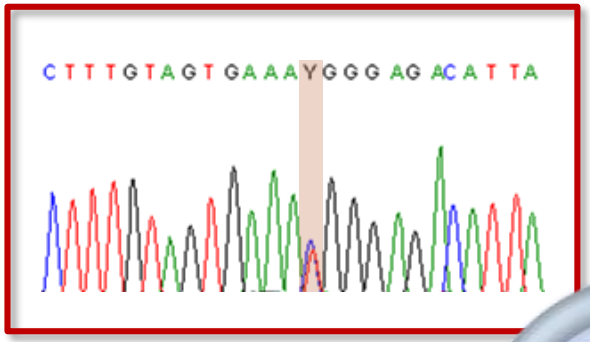
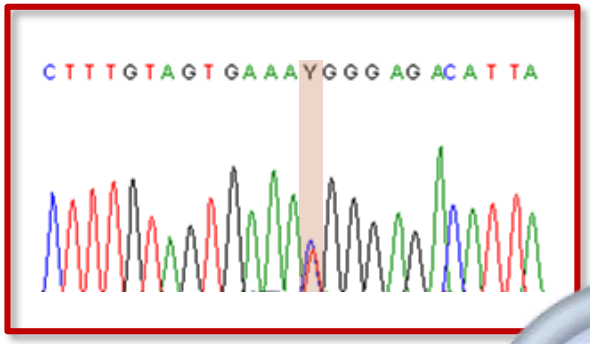
A LOOK FORWARD...



p.T398M

- **Functional** studies
  - Western Blot
  - Real time PCR
  - Immunofluorescence
  - GCase activity assay

A LOOK FORWARD…



p.T398M

- **Functional** studies
  - Western Blot
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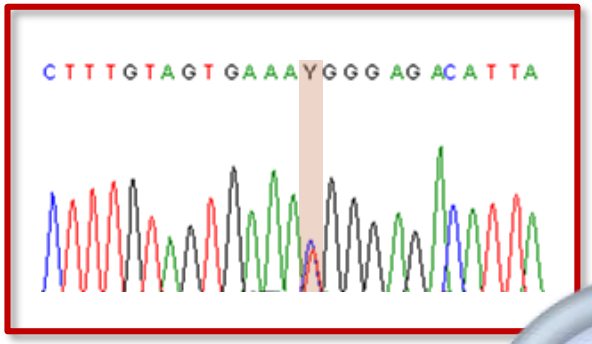
~~dysfunction~~ or

reduction of LIMP-2 levels

A LOOK FORWARD…



p.T398M

- **Functional** studies
  - Western Blot
  - Real time PCR
  - Immunofluorescence
  - GCase activity assay

Lower receptor density

⇓

key factor for recombinant GCase uptake

reduction of LIMP-2 levels

(Desnick and Schuchman, 2012)

A LOOK FORWARD…

Parkinson's disease
Dementia with Lewy Bodies

A LOOK FORWARD…

Parkinson's disease
Dementia with Lewy Bo

- *SCARB2* screening
- Portuguese population

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Parkinson's disease
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is there an association?

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Neurol Sci (2015) 36:1479–1481
DOI 10.1007/s10072-015-2186-1

BRIEF COMMUNICATION

Association between rs6812193 polymorphism and sporadic Parkinson's disease susceptibility

Qiang Huo[1,3] · Tao Li[1] · Peiqing Zhao[2] · Lianqing Wang[2]

Received: 8 December 2014 / Accepted: 19 March 2015 / Published online: 29 March 2015

Abstract Recently, the association of a single nucleotide polymorphism rs6812193 C/T with sporadic Parkinson's disease (PD) susceptibility has been widely evaluated, but the results remained inconsistent. This association should be clarified because of the importance of it on human health and quality of life. We performed a comprehensive meta-analysis to evaluate the association between the rs6812193 polymorphism and sporadic PD. PubMed was used to retrieve articles published up to June 2014 for all population (OR 0.881, 95 % CI 0.856–0.907), but not in Asian samples (OR 0.918, 95 % CI 0.721–1.168). No evidence of publication bias was observed. Throughout our analysis, the rs6812193 polymorphism is significantly associated with sporadic PD susceptibility in Caucasian samples, and ethnicity might be the key point of inconsistency in rs6812193 studies. Further studies are warranted to re-examine the observed associations, especially in different ethnicities.

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A LOOK FORWARD…

Parkinson's disease
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Neuroscience Letters 541 (2013) 190–192

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

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Association study of rs6812193 polymorphism with Parkinson's disease in a Greek population

Kallirhoe Kalinderi[a], Sevasti Bostantjopoulou[b], Zoe Katsarou[b], Liana Fidani[a,*]

[a] Department of General Biology, Medical School, Aristotle University of Thessaloniki, GR-54124, Thessaloniki, Greece
[b] Third Department of Neurology, G. Papanikolaou Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

HIGHLIGHTS

- We investigated the association of the rs6812193 polymorphism with Parkinson's disease.
- SCARB2 is implicated in the lysosomal pathway recently associated with PD pathogenesis.
- The rs6812193 polymorphism doesn't increase susceptibility to PD in the Greek population.
- The role of this polymorphism should be further examined in different ethnic populations.

ARTICLE INFO ABSTRACT

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Parkinson's disease
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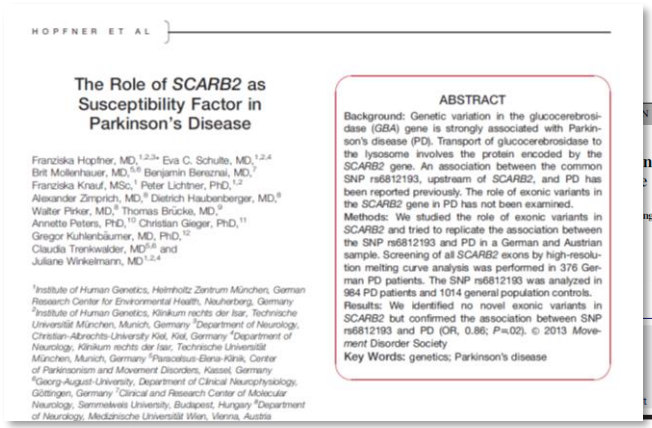


HOPFNER ET AL

The Role of *SCARB2* as Susceptibility Factor in Parkinson's Disease

Franziska Hopfner, MD,[1,2,3*] Eva C. Schulte, MD,[1,2,4] Brit Mollenhauer, MD,[5,6] Benjamin Bereznai, MD,[7] Franziska Knauf, MSc,[1] Peter Lichtner, PhD,[1,2] Alexander Zimprich, MD,[8] Dietrich Haubenberger, MD,[8] Walter Pirker, MD,[8] Thomas Brücke, MD,[9] Annette Peters, PhD,[10] Christian Gieger, PhD,[11] Gregor Kuhlenbäumer, MD, PhD,[12] Claudia Trenkwalder, MD[5,6] and Juliane Winkelmann, MD[1,2,4]

[1]Institute of Human Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany [2]Institute of Human Genetics, Klinikum rechts der Isar, Technische Universität München, Munich, Germany [3]Department of Neurology, Christian-Albrechts-University Kiel, Kiel, Germany [4]Department of Neurology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany [5]Paracelsus-Elena-Klinik, Center of Parkinsonism and Movement Disorders, Kassel, Germany [6]Georg-August-University, Department of Clinical Neurophysiology, Göttingen, Germany [7]Clinical and Research Center of Molecular Neurology, Semmelweis University, Budapest, Hungary [8]Department of Neurology, Medizinische Universität Wien, Vienna, Austria

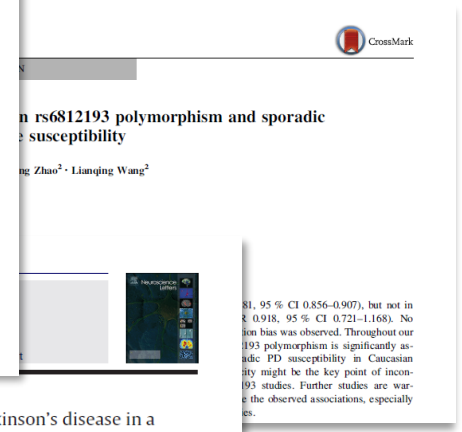
ABSTRACT

Background: Genetic variation in the glucocerebrosidase (*GBA*) gene is strongly associated with Parkinson's disease (PD). Transport of glucocerebrosidase to the lysosome involves the protein encoded by the *SCARB2* gene. An association between the common SNP rs6812193, upstream of *SCARB2*, and PD has been reported previously. The role of exonic variants in the *SCARB2* gene in PD has not been examined.

Methods: We studied the role of exonic variants in *SCARB2* and tried to replicate the association between the SNP rs6812193 and PD in a German and Austrian sample. Screening of all *SCARB2* exons by high-resolution melting curve analysis was performed in 376 German PD patients. The SNP rs6812193 was analyzed in 984 PD patients and 1014 general population controls.

Results: We identified no novel exonic variants in *SCARB2* but confirmed the association between SNP rs6812193 and PD (OR, 0.86; *P*=.02). © 2013 *Movement* Disorder Society

Key Words: genetics; Parkinson's disease



CrossMark

n rs6812193 polymorphism and sporadic susceptibility

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Sociedade Portuguesa de Doenças Metabólicas

SCARB2 MUTATIONS IN GAUCHER DISEASE

SUMMARY

- ✓ 1st time a whole **GD population** is screened for *SCARB2* mutations;

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✍ *Plenty of questions remain unanswered…*

Acknowledgments

Dr. Sandra Alves

Prof. Mª João Prata

UID-SA, DHG, INSA

Biochemical Genetics Unit, CGMJM, CHP

FCT
Fundação para a Ciência e a Tecnologia
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