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)

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

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

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Gaucher Disease (GD)

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

- Large spectrum of severity & symptoms

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

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Gaucher Disease (GD)

- Autosomal recessive
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✍ *At the clinical level…*

- 3 variants

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

Gaucher Disease (GD)

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✍ *At the clinical level…*

- 3 variants

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

Gaucher Disease (GD)

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

✍ *At the clinical level…*

- 3 variants

- Genotyope-Phenotype correlations

⇒ *only possible for a few mutations*

Gaucher Disease (GD)

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

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

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

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

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Gaucher Disease (GD)

- ✍ *"The prototype lysosomal disease…"*

(Zhao and Grabowski, 2002)

- Still…

  it does have some significant differences

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

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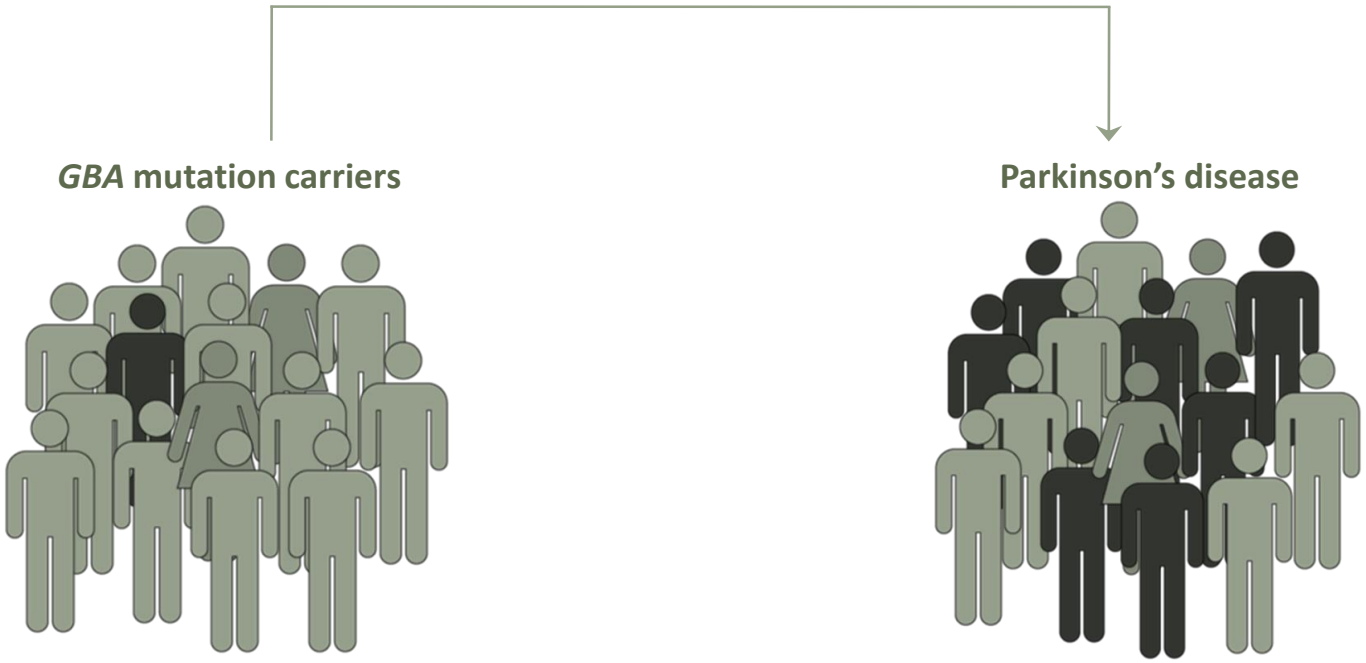
Gaucher Disease (GD)

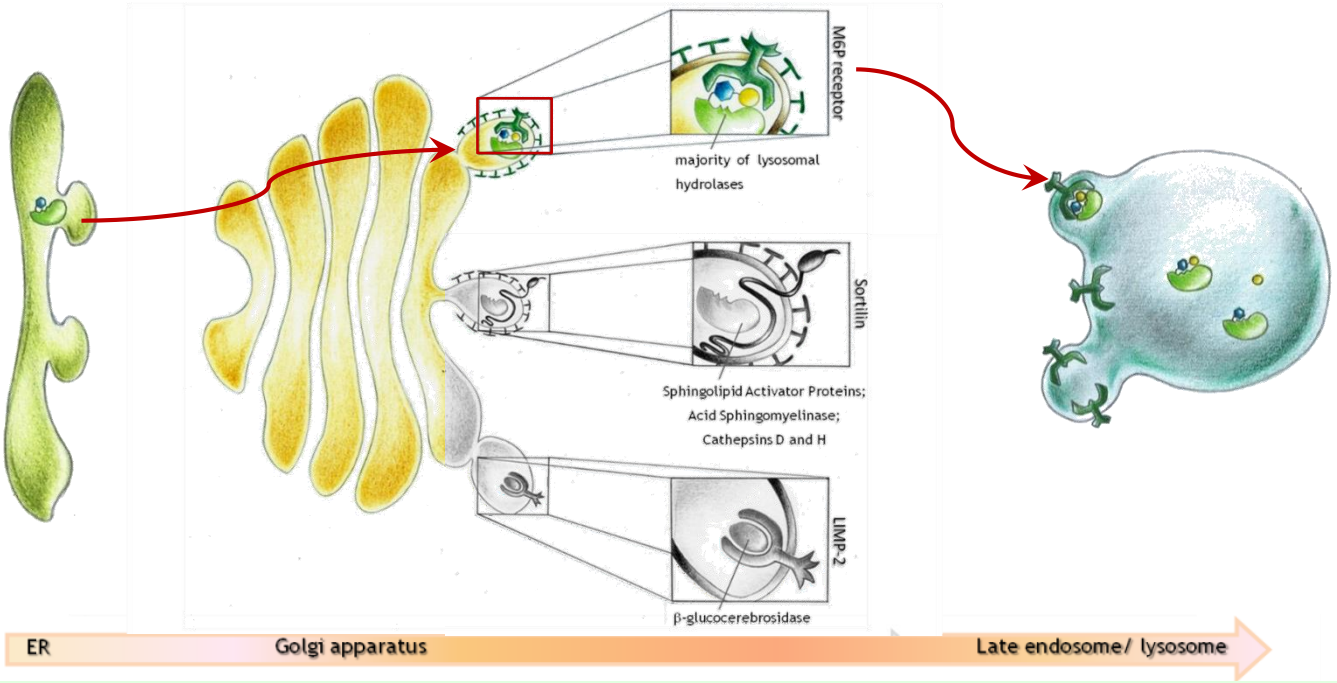
✍ *At the populational level…*



Gaucher Disease (GD)

✍ *At the molecular level…*

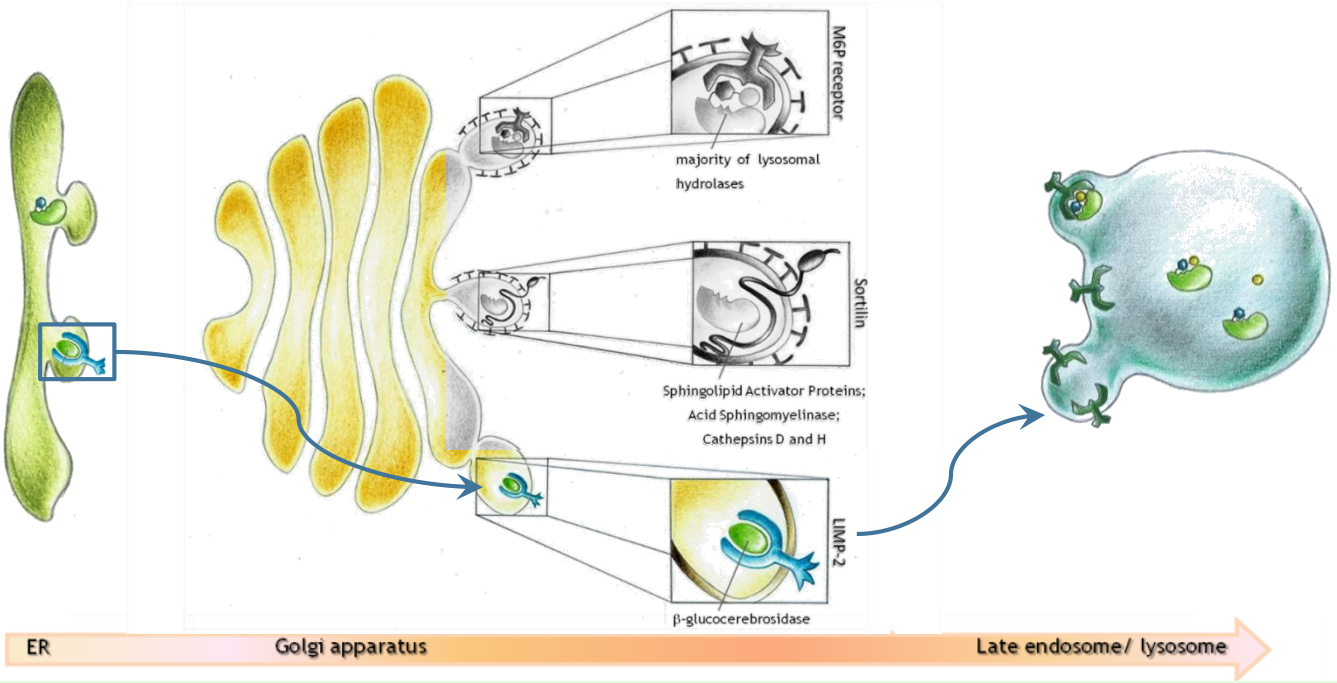
- **GCase**



Gaucher Disease (GD)

✍ *At the molecular level…*

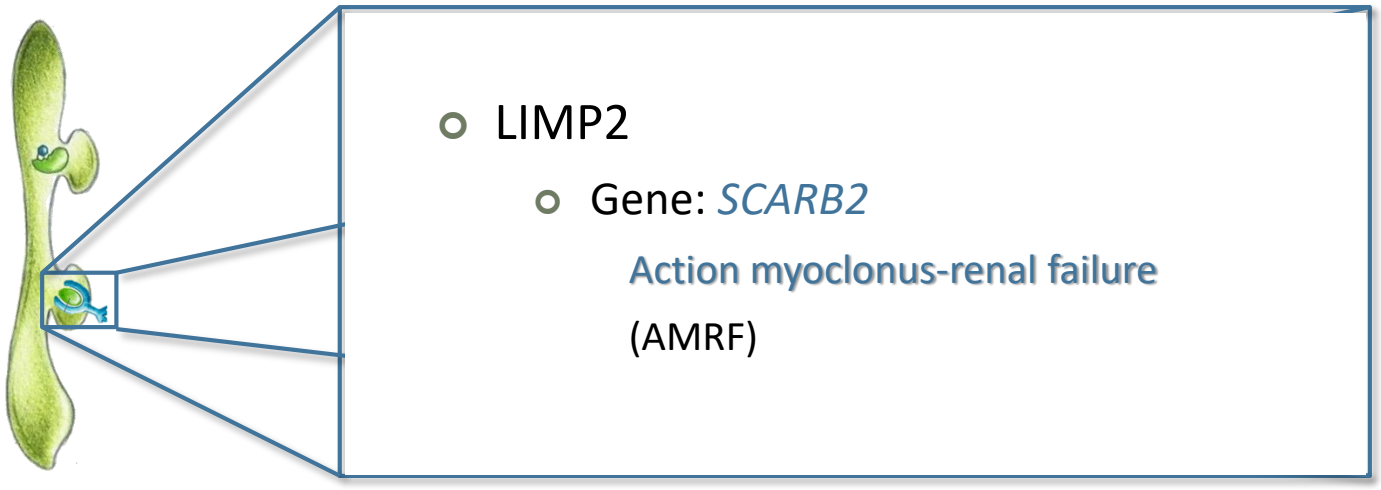
- **GCase**



Gaucher Disease (GD)

✍ *At the molecular level…*

- **GCase**



- LIMP2
  - Gene: *SCARB2*

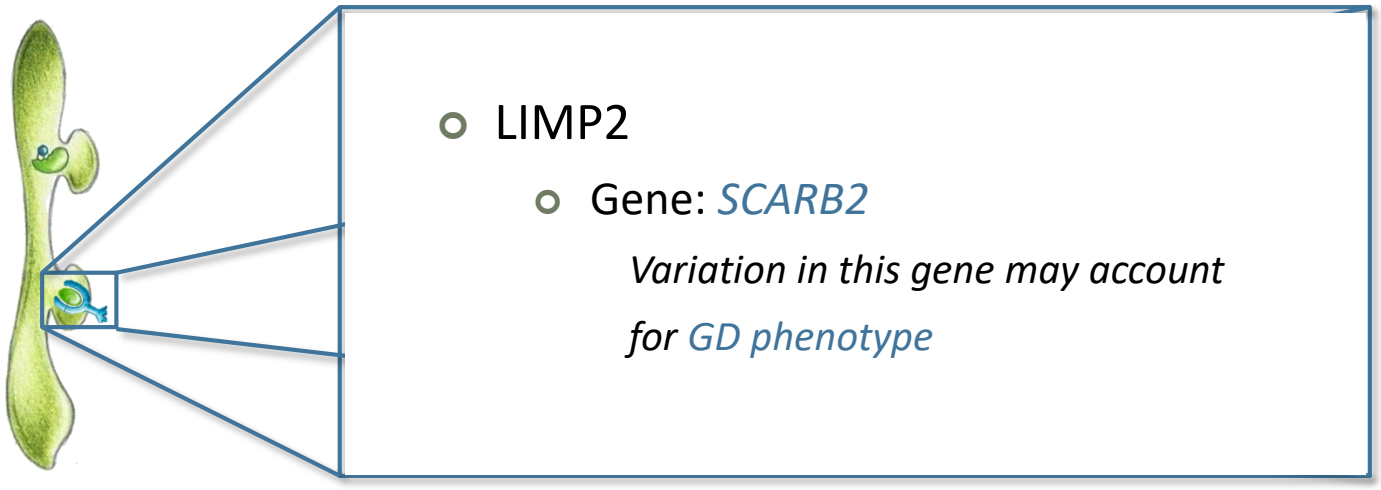
    Action myoclonus-renal failure

    (AMRF)

Gaucher Disease (GD)

✍ *At the molecular level…*

- **GCase**



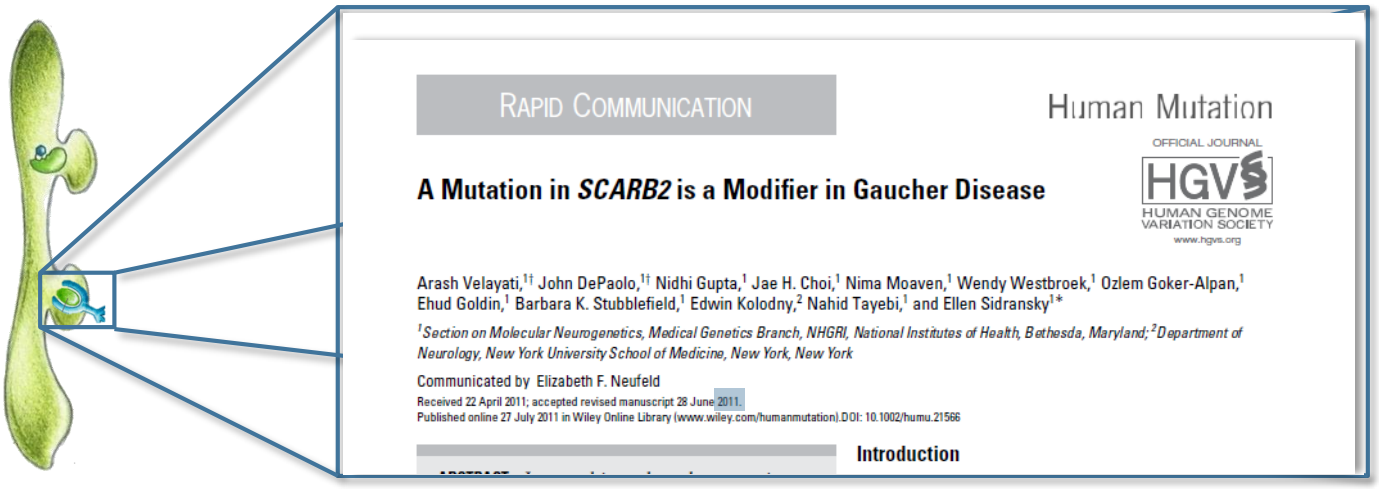
- LIMP2
  - Gene: *SCARB2*

    Variation in this gene may account for GD phenotype

Gaucher Disease (GD)

✍ *At the molecular level…*

- **GCase**



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]*

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Communicated by Elizabeth F. Neufeld

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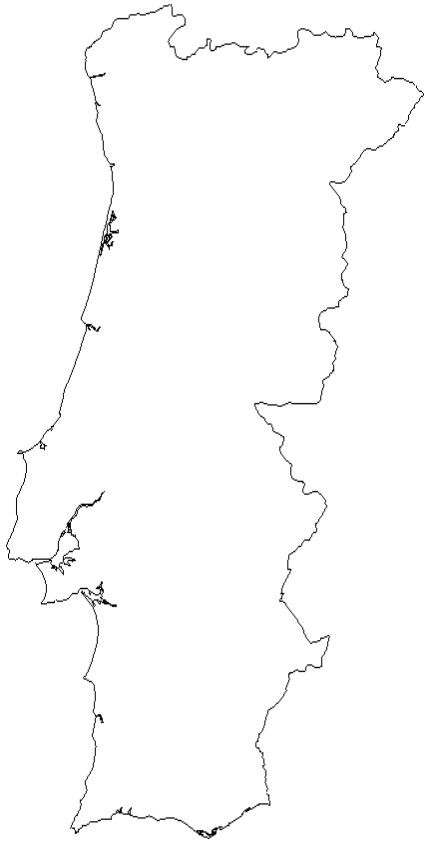
Introduction

Objective

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

in the Portuguese population

Sample Collection



- Portuguese GD cohort
  - 91 samples
    - Biochemically
    - molecularly

  characterized GD patients, diagnosed at CGMJM

  from ? to 2013

+

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

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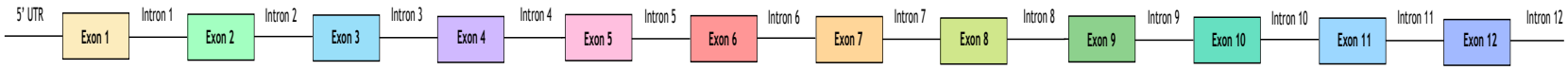
Genetic analysis

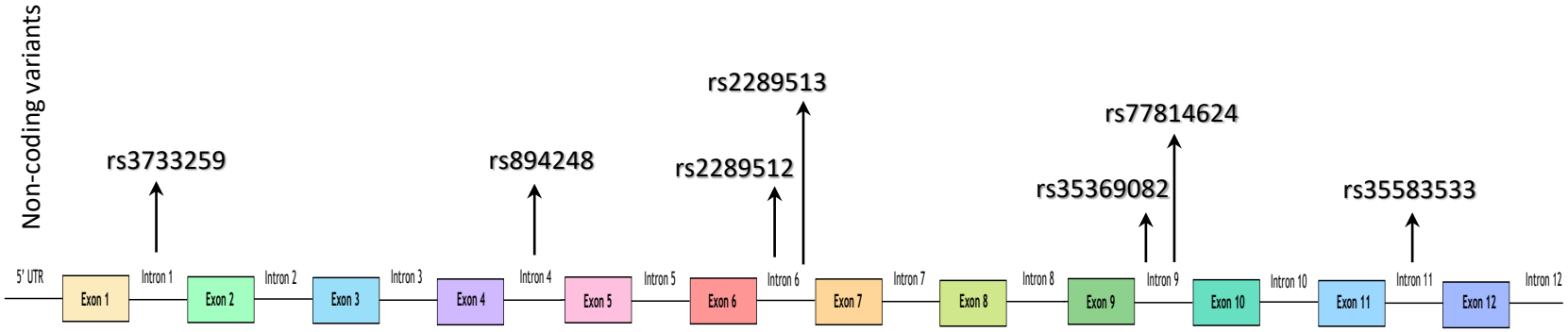
- DNA
  - Peripheral blood
  - Fibroblasts from patients' skin biopsies

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



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

Results



Registered polymorphisms
Also present in the controls

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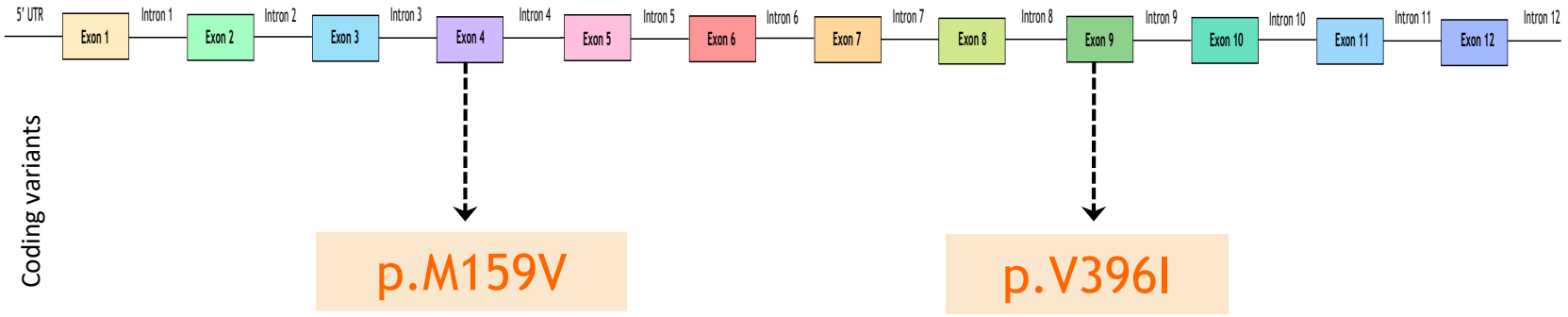
Results

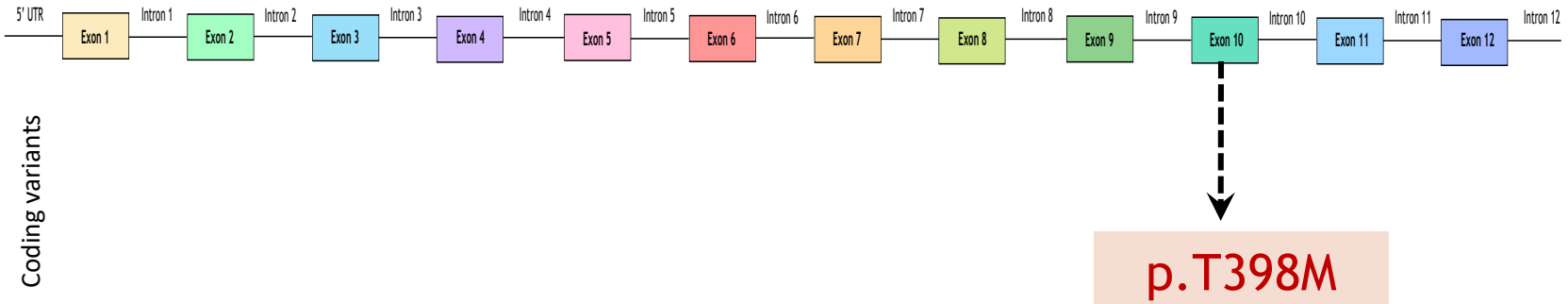
known polymorphic variations
high prevalence in the normal population



Results

Novel coding variant

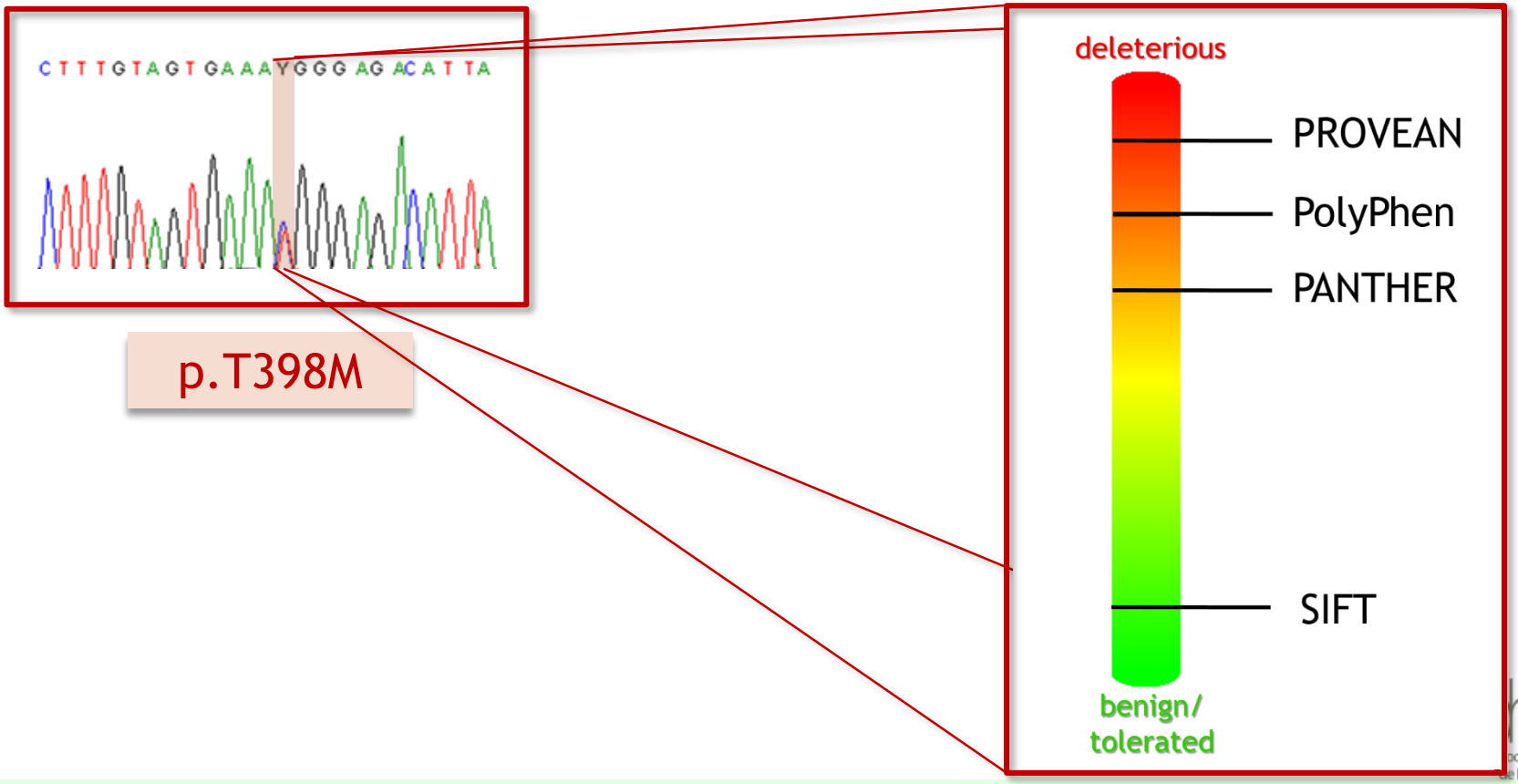
not detected in 50 controls



p.T398M

N= 1

In silico analyses



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;
  - bilateral convergent strabismus;
  - marked axial hypotonia

global psychomotor developmental delay

Reassessment of the clinical case

- 2nd child of young healthy unrelated parents

Cape Verdean origin

- Symptoms' onset: 7 months
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Neurological GD

Reassessment of the clinical case

- 2nd child of young healthy unrelated parents

Cape Verdean origin

SEVERE

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

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 / *GBA* genotype alone

- Still…

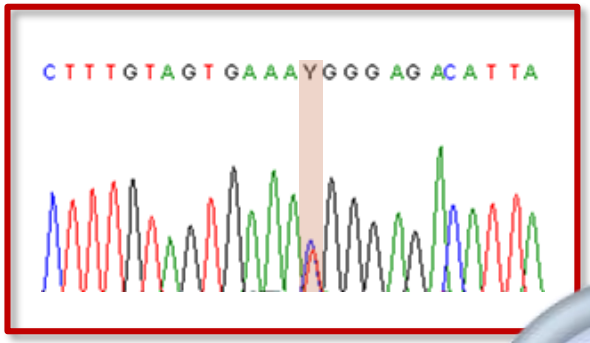
  therapeutic follow-up with assessment of chitotriosidase levels

  ⇓

  enzyme levels disparate from the ones expected for a GD patient under ERT

  low response to treatment?

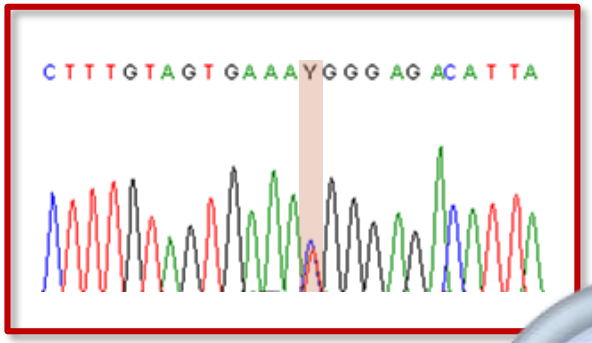
A LOOK FORWARD...



p.T398M

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

A LOOK FORWARD…



p.T398M

- **Functional** studies
  - Western Blot
  - 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 Bo

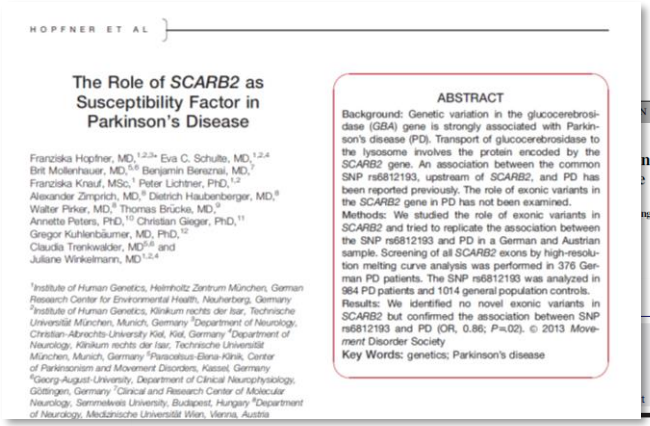
- *SCARB2* screening
- Portuguese cohort

is there an association?

A LOOK FORWARD…

Parkinson's disease
Dementia with Lewy Bodies

- *SCARB2* screening
- Portuguese cohort



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 Bleznak, MD,[7] Franziska Knauf, MSc,[1] Peter Lichtner, PhD,[1,2] Alexander Zimprich, MD,[8] Dietrich Haubenberger, MD,[8] Walter Pirker, MD,[9] 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]

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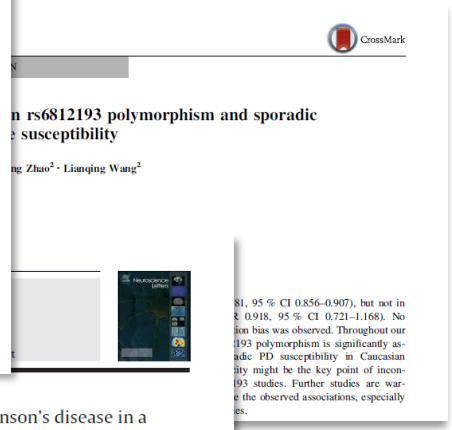
ABSTRACT

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

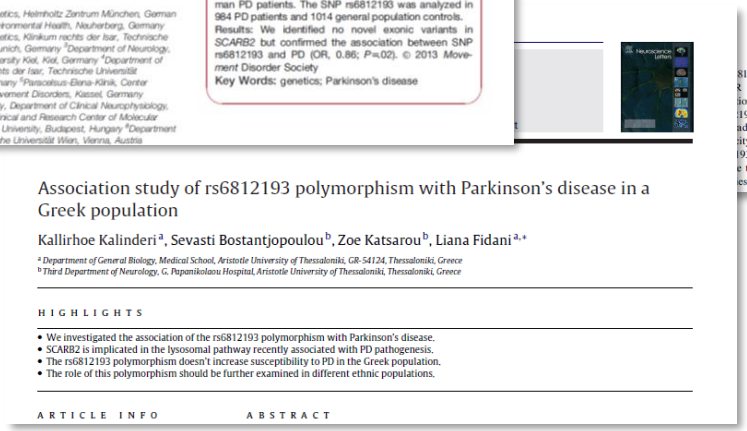


CrossMark

n rs6812193 polymorphism and sporadic
susceptibility

ng Zhao[2] · Lianqing Wang[2]

81, 95 % CI 0.856–0.907), but not in
8 0.918, 95 % CI 0.721–1.168). No
ion bias was observed. Throughout our
193 polymorphism is significantly as-
adic PD susceptibility in Caucasian
ity might be the key point of incon-
193 studies. Further studies are war-
e the observed associations, especially
es.



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

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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

Sociedade Portuguesa de Doenças Metabólicas

SCARB2 MUTATIONS IN GAUCHER DISEASE

SUMMARY

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

⇓

SCARB2 variability does not account much to the Portuguese GD phenotypic spectrum

✓ *Still,*

one novel variant here identified (p.T398M), deserves further attention and extra studies

✍ *Plenty of questions remain unanswered…*

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