METHOD FOR PREDICTING THE EARLY ONSET AND SEVERITY OF LEVODOPA INDUCED DYSKINESIA (LID) IN SUBJECTS DIAGNOSED OF PARKINSON'S DISEASE

Con el respaldo de ACCIÓ

Madrid, 14 de noviembre de 2017

1. THE TEAM AND THE INSTITUTIONS BEHIND

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IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer

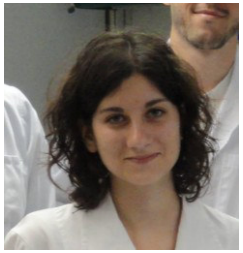
CLÍNIC BARCELONA Hospital Universitari

UNIVERSITAT DE BARCELONA

Dr. Rubén Fernández Santiago - geneticist

Dr. Mario Ezquerra Travalón - geneticist

Dr. Maria Josep Martí Domènech - neurologist



Núria Martín-Flores - biologist

Dr. Cristina Malagelada Grau - biochemist

2. THE PRODUCT

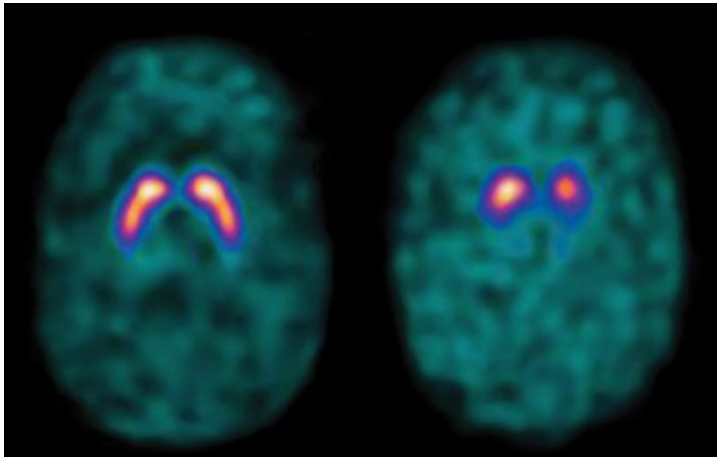
2.1. TARGET INDICATIONS

PARKINSON'S DISEASE (PD)

- UNKNOWN CAUSE: COMBINATION OF GENETIC (other family member with PD) AND ENVIRONMENTAL FACTORS (pesticides, well water, rural living etc…)

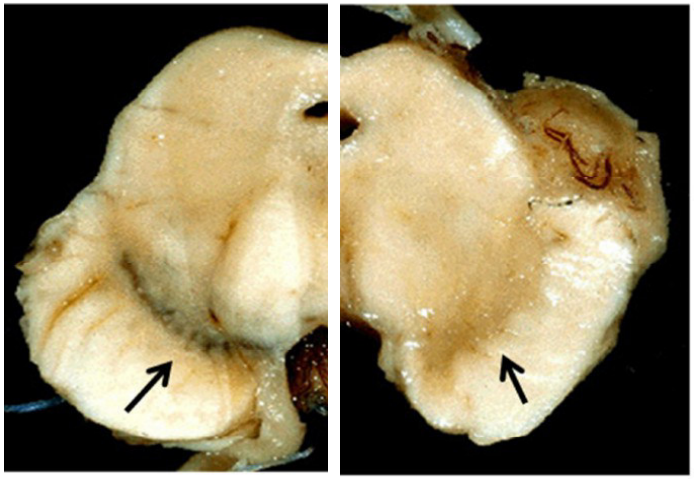
DaTScan diagnosis

Control PD



Post-mortem confirmation

Control PD



2.1. TARGET INDICATIONS

PARKINSON'S DISEASE (PD)

Epidemiology figures (estimations)

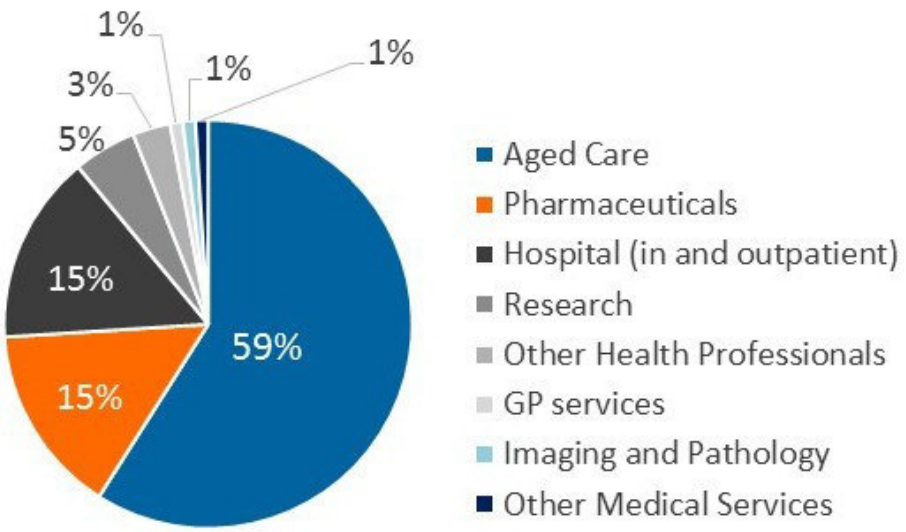
Incidence: 4.5 – 21 cases/100,000 population
Prevalence: 18 – 328 cases/100,000 population

Most studies yield prevalence of 120 cases per 100,000 population

►The annual European estimated cost of the disease is €13,9 billion[1], being health system costs 62% of the total

Source: Medscape (2017) http://bit.ly/17axmSp

Health System costs components (2011)



Source: internal

[1] Gustavsson, A. et al., Cost of disorders of the brain in Europe 2010 Eur Neuropsychopharmacol. 2011 Oct;21(10):718-79.

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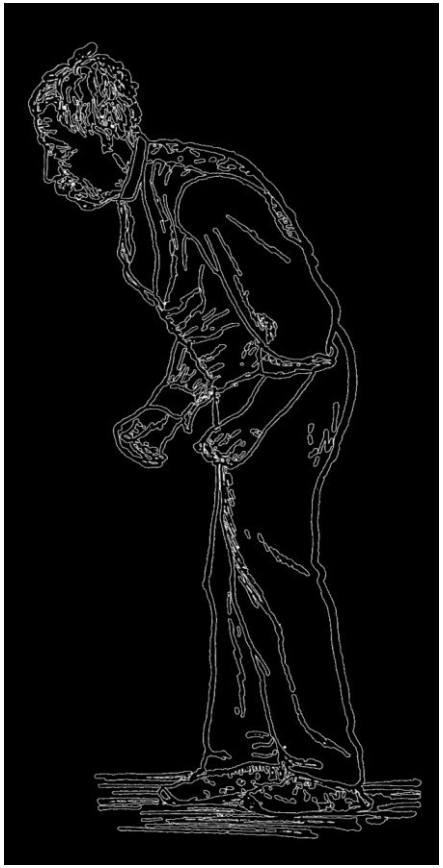
PARKINSON'S DISEASE (PD)



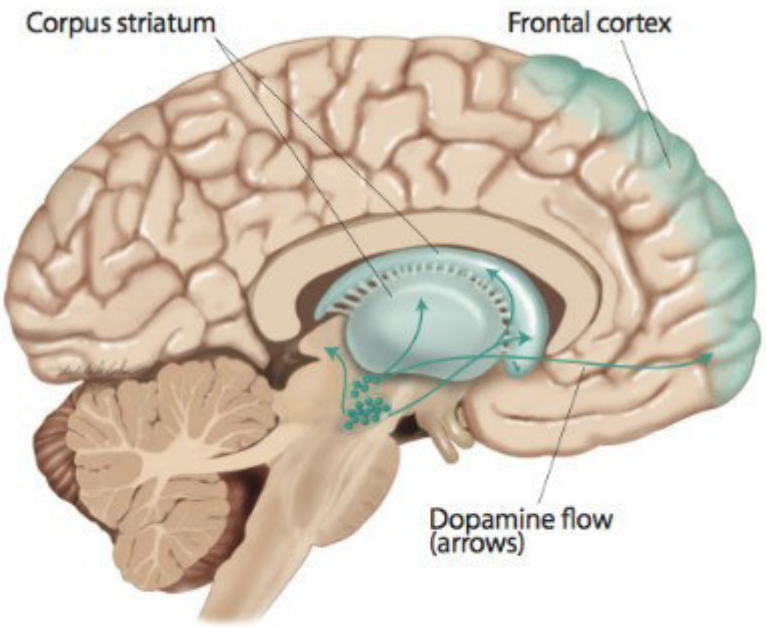
Motor symptoms

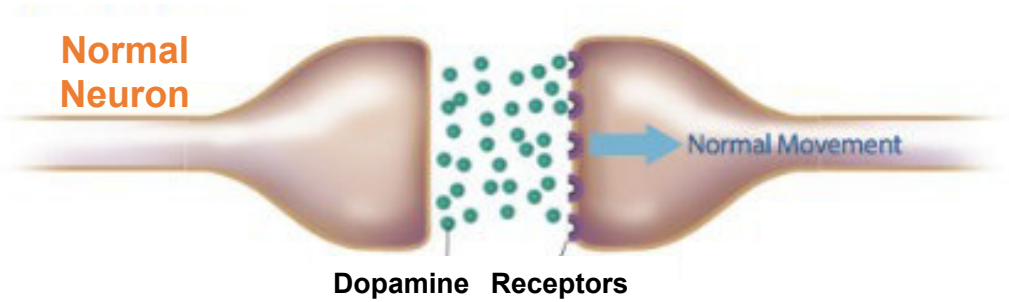
- Rigidity and tremor of extremities and head
- Slowness of movement (bradykinesia)
- Postural instability
- Loss of facial expression
- Slow, monotonous speech

Non-Motor symptoms

- Sleep disturbances
- Constipation
- Depression, fear and anxiety
- Cognitive decline (dementia)

2.1. TARGET INDICATIONS





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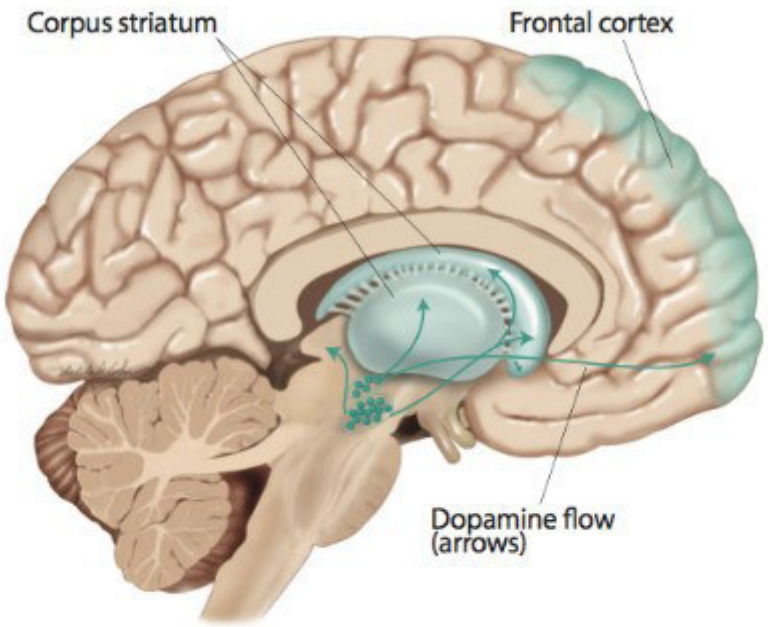
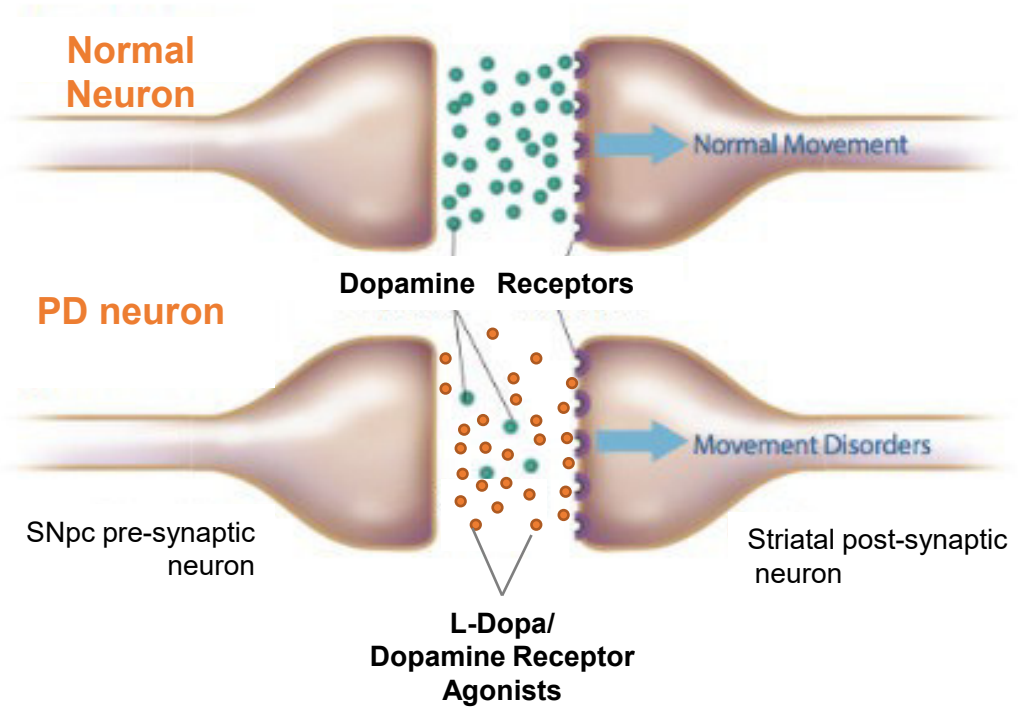
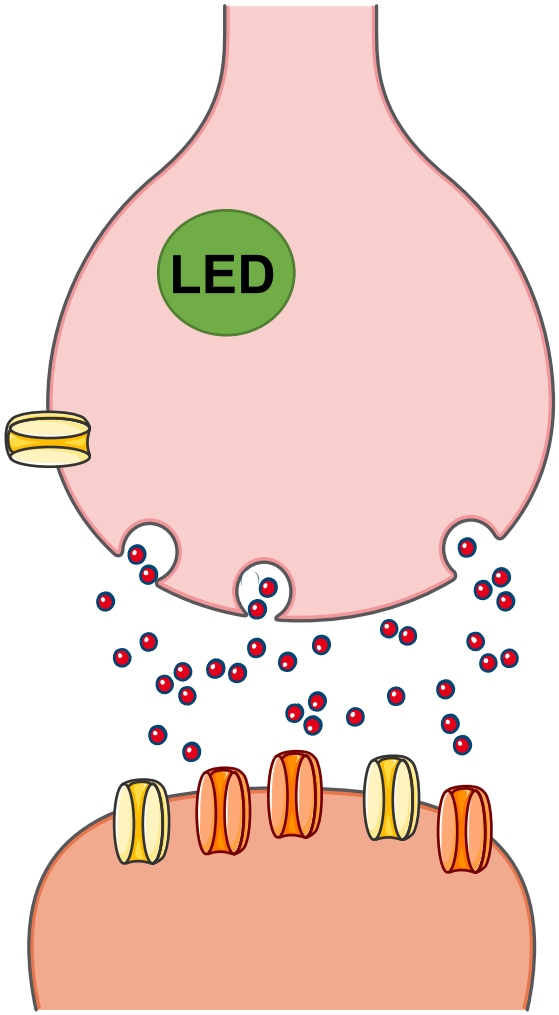




2.1. TARGET INDICATIONS: L-DOPA-INDUCED DYSKINESIA

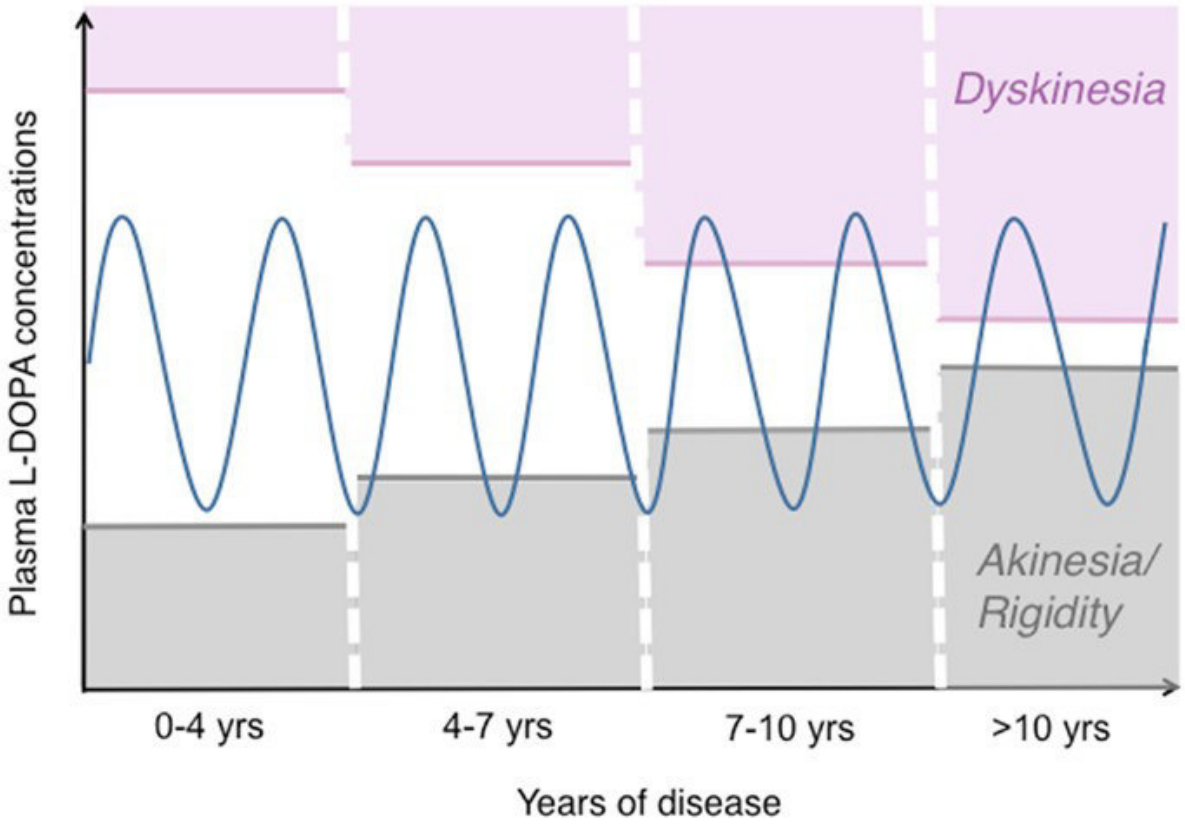
Nigral neurodegeneration
Early Stage



DYSKINESIA

2.1. TARGET INDICATIONS: L-DOPA-INDUCED DYSKINESIA

- Present in 50-80% of PD patients
- After 5-10 years of L-DOPA treatment



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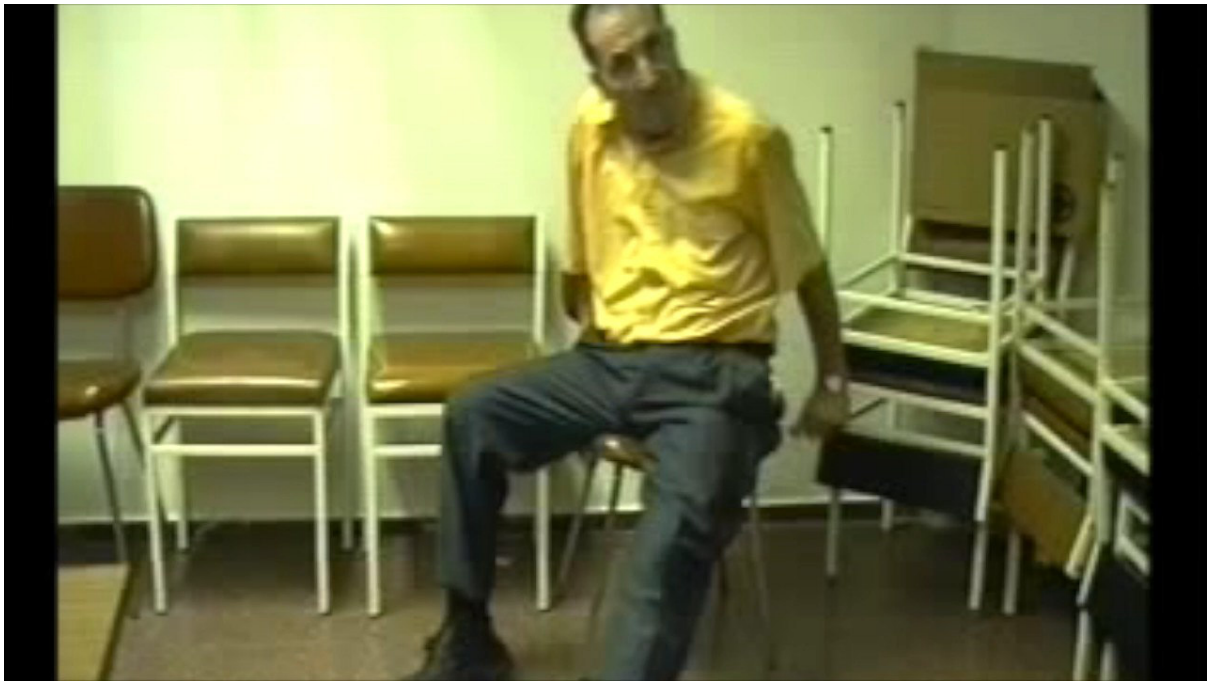
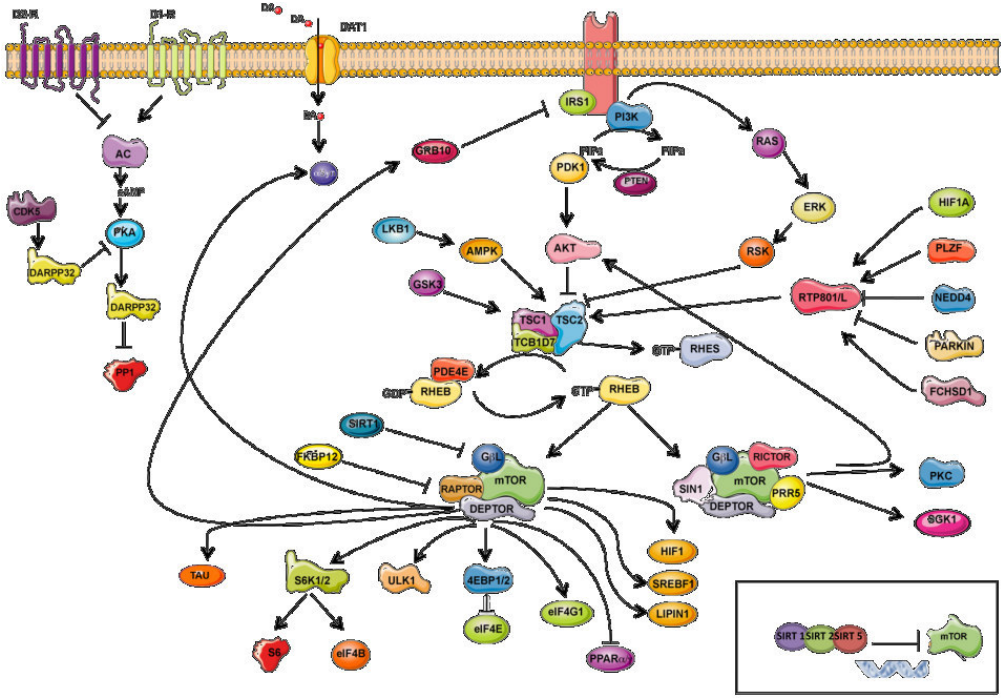


2.2 INNOVATIVE MECHANISM OF ACTION: THE MTOR PATHWAY



THE MTOR PATHWAY

NEURON SURVIVAL

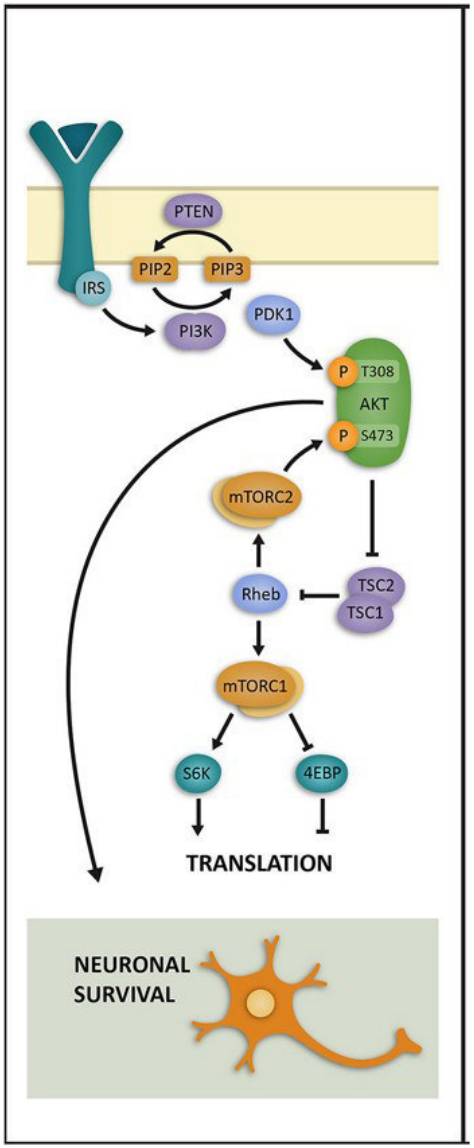
STRIATAL PLASTICITY

L-DOPA SUSCEPTIBILITY

DYSKINESIA

2.2 INNOVATIVE MECHANISM OF ACTION: THE MTOR PATHWAY

Physiological conditions



MTOR/AKT INACTIVATION in PD

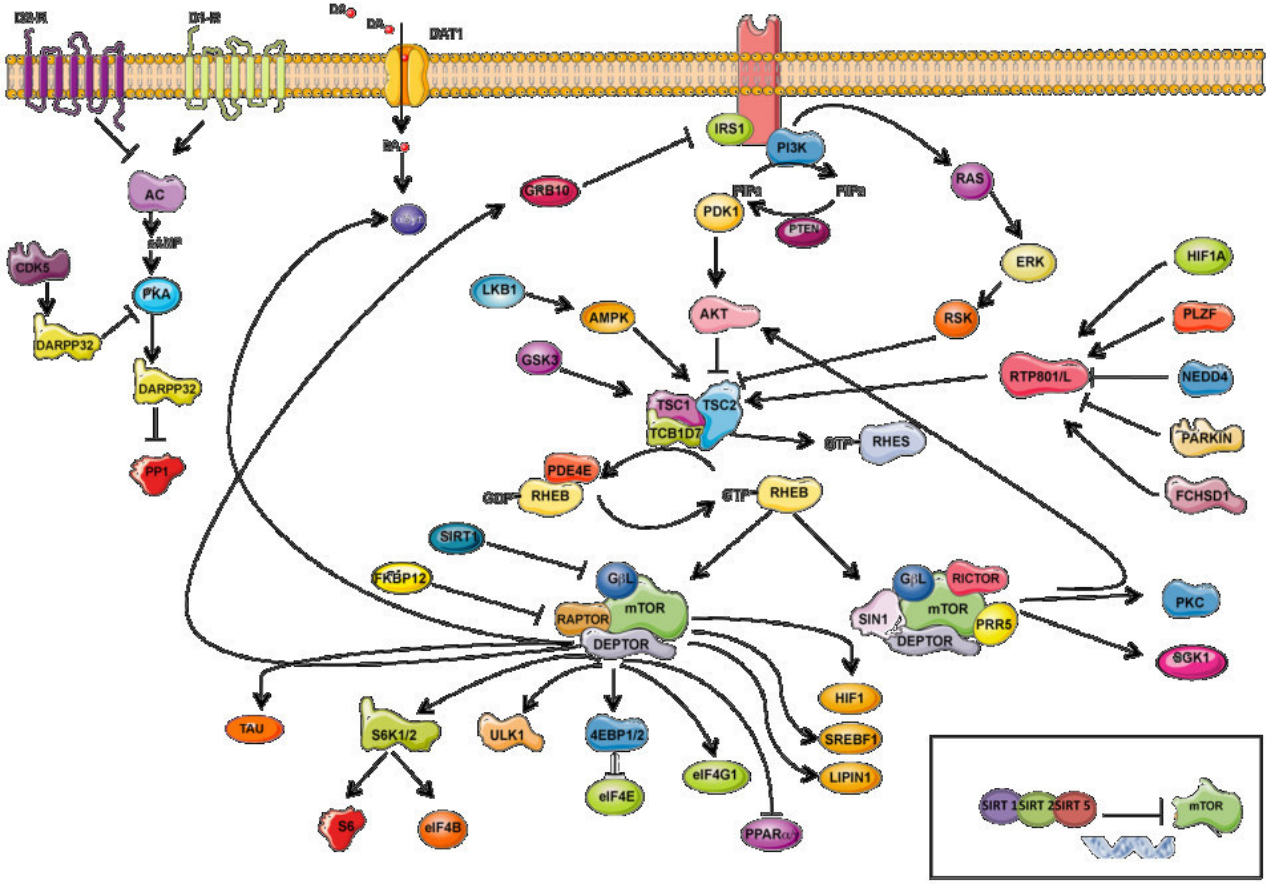
Malagelada C et al., 2006, 2008, 2010

MTOR INHIBITION IN STRIATUM PREVENTS LID IN L-DOPA-TREATED MICE AND RAT

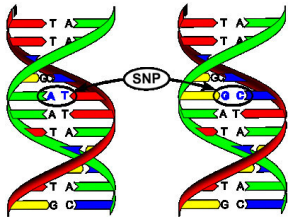
Decressac M et al., 2013
Subramaniam S et al., 2012
Santini E et al., 2009

2.2 INNOVATIVE MECHANISM OF ACTION: SNPs IN THE MTOR PATHWAY

RATIONALE: SNPs IN THE MTOR PATHWAY TO IDENTIFY HIGHLY SUSCEPTIBLE PD PATIENTS TO L-DOPA

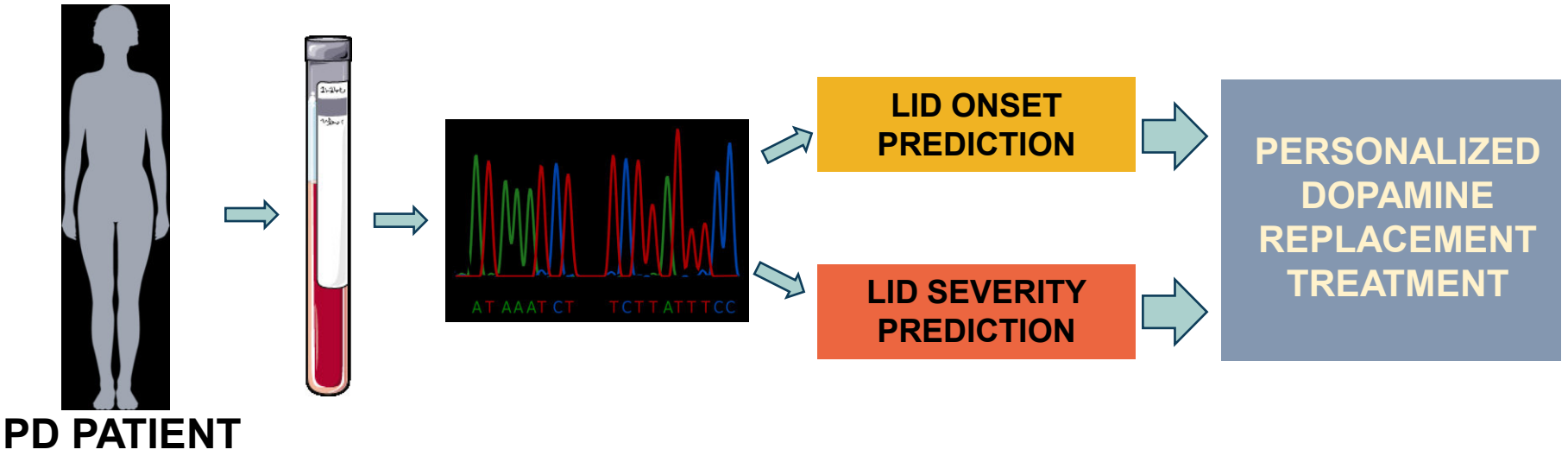


64 GENES
64 SNPs



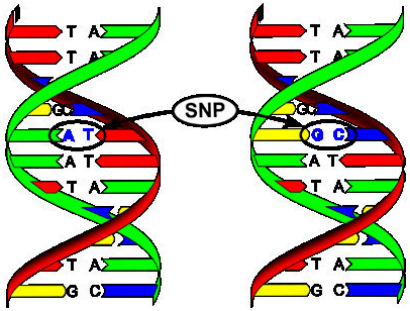
2.2. L-DOPA-INDUCED DYSKINESIA PREDICTOR

- A PREDICTOR FOR LID EARLY ONSET AND SEVERITY IN SUBJECTS DIAGNOSED OF PD BASED ON SNPs COMBINATIONS



2.2. PHARMACOGENETIC LID PREDICTOR

PROOF OF CONCEPT: population of 401 PD patients with recorded DA replacement therapy



SNPS: particular markers in specific genes

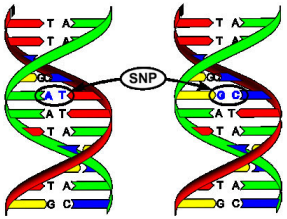
LID ONSET PREDICTION
rs1043098 E*IF4EBP2*, rs2043112 *RICTOR*, rs4790904 *PRKCA*

LID SEVERITY PREDICTION
rs1292034 *RPS6KB1*, rs12628 H*RAS*, rs6456121 *RPS6KA2* and rs456998 *FCHSD1*

Personalized dopamine replacement treatment

SPECIMENS TYPE	DNA (from blood or saliva samples)
INSTRUMENTATION REQUIRED	Thermocycler/PCR machine
TIME REQUIRED	2 hours
ESTIMATED PRICE	Less than 100 euros

2.2. PHARMACOGENETIC LID SEVERITY PREDICTOR



LID SEVERITY PREDICTION

rs1292034 *RPS6KB1*, rs12628 H*RAS*, rs6456121 *RPS6KA2* and rs456998 *FCHSD1*

Sensitivity	83,0%
Specificity	85,7%
Precision	86,1%
NPV	83,5%
Accuracy	84,2%

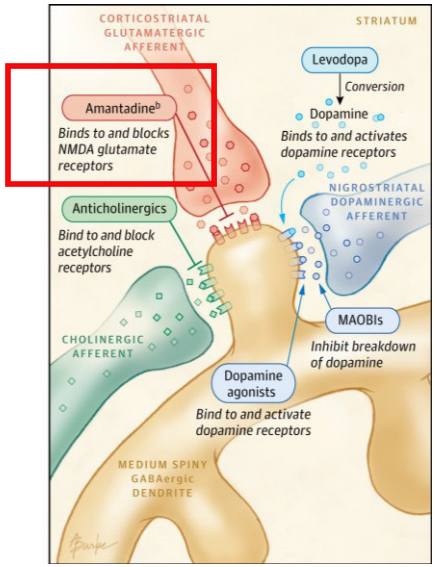
2.3. DIFFERENTIAL FEATURES FACING THE MARKET

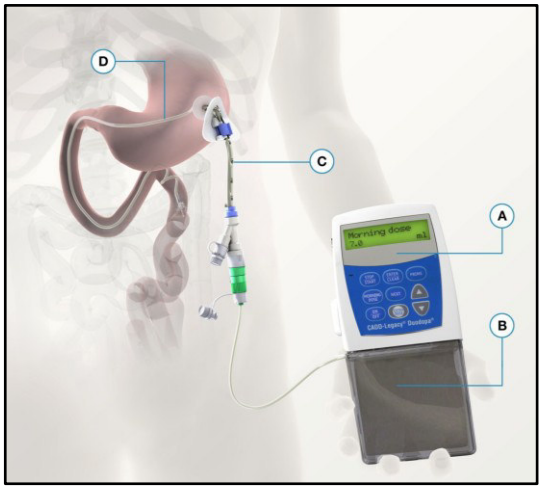
NO CURRENT PHARMACOGENETIC TEST IN THE MARKET TO PREDICT DYSKINESIA ONSET/SEVERITY

2.3. LID TREATMENTS SO FAR

PHARMACOLOGICAL THERAPY

- **Medication treatment:**
  - **Amantadine** is an NMDA receptor antagonist with a promising anti-dyskinetic effect. However, its sustained effect over time is still controversial.

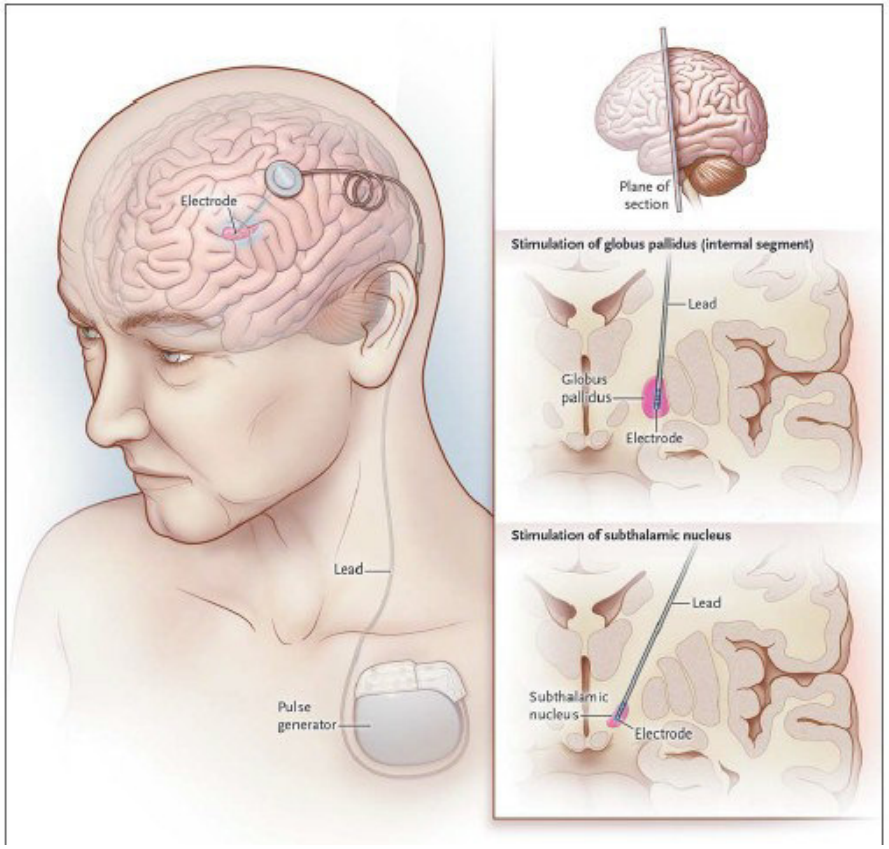




2.3. LID TREATMENTS SO FAR

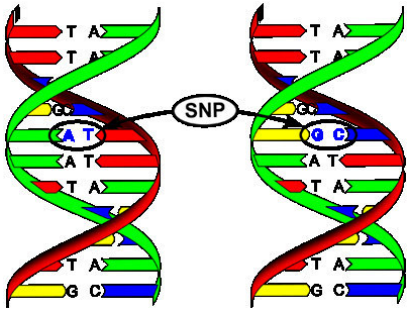
SURGERY

- **Surgical techniques:**
  DBS of GPi or STN are effective treatments but PD patients have to have specific criteria for the surgery. Side effects: infection, hematomas, executive alterations...



2.3. PHARMACOGENETIC LID PREDICTOR

THE ULTIMATE GOAL IS TO AVOID, OR AT LEAST, DELAY THE APPEARANCE AND THE SEVERITY OF LID IN NEWLY DIAGNOSED PATIENTS WITH PD.



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Personalized dopamine replacement treatment

2.4. CURRENT STATUS OF DEVELOPMENT

Market Assessment

INSIGHTS IN LIFE SCIENCES

Interviews to 3 first-class neurologists expert in PD

1. Head of the Department of Neurology at Virgen de las Nieves University Hospital (Spain):

"The test could be very useful in Clinical Trials of anti-dyskinetic drugs to stratify patients regarding LID risk."

2. Medical Director at Muhammad Ali Parkinson Center at Dignity Health St. Joseph's Hospital (USA)

"If the risk of developing LID is higher, then we are going to be more conscious in using L-DOPA, and more aggressive in using agonists instead of L-DOPA, and amantadine, and we are going to pay more attention to the patient to prevent them from really get out of hand"

"If it costs 100$ most people would pay for it (out of the pocket) to know if they are going to develop dyskinesia or not"

3. Consultant neurologist at NHS Greater Glasgow and Clyde (UK)

"The test could be useful to moderate the dose in those patients who request more medication"

2.4. LID PREDICTOR IMPLEMENTATION

Sent to Experts

Illustration of how the novel test for predicting LID might be used by the prescribers

Marketer provides the Hospital with the DNA extraction KITs and with educational material

Physician

1

Physician prescribes novel test for predicting LID. Sends sample to reference laboratory / Hospital laboratory

2

Saliva / swab sample or blood is received at the reference lab / Hospital lab, and DNA is extracted

DNA extraction

3

DNA is analyzed using PCR technology

Marketer provides the Laboratory with the oligo pool and plates for analysis

DNA Analysis

4

Test result is obtained and physician decides whether or not to change course of action with physician (Type of medication, dose, duration,...)

Test Result

5

Physician shares diagnostic

Patient

Parkinson's disease patients that might be treated with L-DOPA

*PCR: Polymerase Chain Reaction

2.4. CURRENT STATUS OF DEVELOPMENT

PHARMACOGENETIC TEST IMPLEMENTATION: CONVERSATIONS WITH THE CLINICAL BIOCHEMISTRY SERVICE IN THE HOSPITAL CLÍNIC TO RUN THE TESTS (FEASIBILITY, PRICE, DIAGNOSTICS)

2.4. IPR PROTECTION

European Patent Application Filed in EPO – 04/05/2017

1. **Title:**

   - ❑ Method for predicting early onset and severity of Levodopa Induced Dyskinesia (LID) in subjects diagnosed of Parkinson Disease (PD)

2. **Applicants:**

   - ❑ Universitat de Barcelona (UB)
   - ❑ Institut d'Investigacions Biomèdiques August Pi i Sunyer
   - ❑ Hospital Clínic de Barcelona

3. **Subject matter of protection**

   - ❑ The *in vitro* method based on specific SNP's identification
   - ❑ Its applications on selecting PD patients to receive a treatment different from levodopa or on better deciding levodopa dosage

2.4. PITFALLS AND RISKS

1. SNPS VALIDATION IS DIFFICULT IN POPULATIONS WITH VERY DIFFERENT GENETIC BACKGROUND

2. BUDGET MANAGERS IN HOSPITALS/INSURANCE COMPANIES NOT WILLING TO SPEND MONEY FOR THE TEST

3. THE TEST IS NOT A CURE BUT IS A METHOD TO PREVENT WORSENING CONDITIONS

4. NEUROLOGISTS COULD BE HESITANT TO CHANGE THE DOSAGE REGIME/OTHER DA AGONISTS BASED ON THE TEST RESULTS

3. PARTNERING OPPORTUNITIES

3. PARTNERING OPPORTUNITIES

- LICENSE AGREEMENT

- COLLABORATION TO VALIDATE TECHNOLOGY IN A SECOND POPULATION OF PD PATIENTS


ANY
QUESTIONS
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