CAUSES OF PD: THE ROLE OF GENETICS & ENVIRONMENT

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HOW DO WE GET TO CURES?
PARKINSON’S IS AN INCREASINGLY COMMON BRAIN DISEASE

Today one million people in the United States and more than five million worldwide live with Parkinson’s. Those numbers will only grow as our population ages.
MJFF IS THE WORLD’S LARGEST NONPROFIT FUNDER OF PD RESEARCH

Our Mission
To accelerate the development of improved therapies, and ultimately a cure, for people living with Parkinson’s disease today

Vital Stats
» Founded in 2000 by actor Michael J. Fox
» No chapters: team of 95 based in NYC
» 1,800 grassroots fundraisers reaching 120,000 supporters worldwide in 2014
» $527 million in research funded to date
» $67.5 million in research grants funded in 2014
» 1,750 research projects funded to date
» 35% of funded projects are outside of the United States
MJFF was founded by a person with Parkinson’s disease.

Assessing all potential projects through a patient-focused lens, everything we do is driven by the many unmet medical needs of Parkinson’s patients today.
MJFF has no endowment and deploys 89¢ of every dollar spent to research.
Our experts identify and manage the most compelling PD science, while our project managers apply business principles to ensure efficiency toward progress.
WHAT CAUSES PARKINSON’S DISEASE?
WHAT IS PARKINSON’S DISEASE?

- In Parkinson’s the brain cells that control movement deteriorate.
- We also see signs of disease in cells associated with non-motor symptoms.

Motor symptoms include:
- resting tremor
- slowness of movement
- rigidity
- balance and gait issues

Non-motor symptoms include:
- cognitive dysfunction
- depression and anxiety
- constipation and digestion issues
- sleep disorders
Scientists think that the cause of Parkinson’s falls on a continuum, with some due more to genetics, others from environmental factors and many a mix of the two.
WHAT ARE ENVIRONMENTAL FACTORS AND WHAT DO WE KNOW ABOUT THEM AND PD?

Most environmental factors don’t cause Parkinson’s on their own. Genetics make some more susceptible to disease with exposure.

Researchers are investigating the role of these factors:

» Certain chemicals in pesticides and solvents

» Head Injury

» High exposure to some metals

Environmental factors may be protective, too. Scientists are studying the potential of exercise and other drugs such as anti-inflammatory medication to prevent PD or slow progression.
MPTP has become a crucial preclinical model in which to test potential PD therapeutics.
ENVIRONMENTAL FACTORS: PESTICIDES

- Pesticides
- Weed killers
- Solvents
- Farming

In 2000, rotenone shown to cause PD symptoms in preclinical models
Scientists think that the cause of Parkinson’s falls on a continuum, with some due more to genetics, others from environmental factors and many a mix of the two.
Genes are like the instruction manual for the formation and activity of proteins. Genetic mutations can change the expression of proteins, which may play a role in disease.
GENETIC MUTATIONS ARE ASSOCIATED WITH VARIED DEGREES OF PD RISK

It is thought that genetics directly cause only about 10% of PD cases.

- There are different causes of Parkinson’s, including some genetic.

- Some genes may act alone to increase Parkinson’s risk.

- Some may act together or with other factors such as environmental exposures to cause PD.

- Different genetic mutations are associated with different degrees of PD risk.

- Certain mutations account for more cases of Parkinson’s in some groups.
SOME PARKINSON’S MUTATIONS ARE MORE PREVALENT IN CERTAIN GROUPS

1. *SNCA* (alpha-synuclein) mutations in a small number of European families
   a. Greater likelihood of disease and earlier onset

2. *LRRK2* mutations in people of Ashkenazi Jewish and Basque descent
   a. Estimates vary, but researchers believe there is a moderate likelihood of developing Parkinson’s disease

3. *GBA* mutations in people of Ashkenazi Jewish descent
   a. Lower likelihood of disease

However: Not everyone with mutations linked to Parkinson’s will develop the disease.

Researchers can learn about how Parkinson’s disease begins and progresses by observing people with these mutations.
CASE STUDY: ALPHA-SYNUCLEIN IS A MAJOR PLAYER IN PARKINSON’S

- In 1997 scientists discovered a rare mutation in the SNCA gene
- That gene makes the alpha-synuclein protein
- Alpha-synuclein is the main component of protein clumps that likely harm brain cells in all people with PD
- Testing drugs that target alpha-synuclein to prevent or break up the toxic protein clumps
- Measuring alpha-synuclein levels to find a test to diagnose and monitor PD progression

While not the direct cause of most Parkinson’s cases, genetic mutations linked to PD give scientists a starting point to better understand the disease.
LRRK2 MUTATIONS ARE ONE OF THE MOST COMMON GENETIC CAUSES OF PD

- In 2004, mutations in LRRK2 gene discovered to cause PD
- Mutations in LRRK2 account for 2% of PD cases

Drug companies are interested in developing inhibitors of LRRK2 activity
WHAT CAN WE LEARN FROM RARE GENETIC MUTATIONS THAT CAUSE PD?

» Rare mutations in genes such as SNCA, LRRK2 and GBA are linked to PD.
» We can follow these mutations to study what goes wrong in proteins in PD.
» People with non-genetic PD may have problems with those same proteins.
» And we can develop drugs that target those proteins and correct or counteract their abnormal behavior.
WHY DOES THE CAUSE OF PD MATTER?

New disease targets point scientists to where to intervene to stop or prevent the disease.

Strategies from existing clues already in development:
» Targeting alpha-synuclein and LRRK2
» Following epidemiological clues from other studies (e.g., nicotine, caffeine)
» Repurposing drugs approved for other diseases (e.g., isradipine, exenatide)

Strategies to uncover new targets:
» Using advanced genetic sequencing technologies to find new genetic targets
» Exploring pathways known to play a role in Parkinson’s
MANY QUESTIONS REMAIN AROUND THE GENETICS OF PARKINSON’S

- Do genetics contribute to rate of progression or the “type” of Parkinson’s one has?

- What keeps some people with Parkinson’s risk mutations from developing PD?

- Researchers are investigating these connections.

- Genetic factors that lead to slower progression or protect from PD onset may point scientists to new drug targets and treatments.
MJFF employs various mechanisms and a customized approach to carry out our strategy across all states of PD progression.
HOW CLOSE ARE WE TO A THERAPY THAT WILL SLOW THE DISEASE?

Three vaccines against toxic clumps of alpha-synuclein are in clinical trials. A similar approach in Alzheimer’s reported positive impact on disease biology.

» **AFFiRiS**: Austrian biotech testing vaccine in only Austria currently

» **Prothena**: San Francisco biotech testing antibody in the U.S.

» **Biogen**: Boston biotech testing antibody in control volunteers in the U.S.

» Handful of companies with compounds against alpha-synuclein expect to move into clinical trials this year.

» **Neuropore**: San Diego biotech testing alpha-synuclein stabilizer to prevent clumping

Scientists are also working toward treatments against other proteins that may play a role in Parkinson’s, such as LRRK2 and GCase.
AS MORE DRUGS MAKE IT TO TRIALS, NEED FOR PD BIOMARKERS GROWS

Parkinson’s Progression Markers Initiative

» Three study arms with different cohorts:
  – Recently diagnosed PD and controls: Completed enrollment in 2014
  – Risk factors of smell loss and RBD: Completed enrollment in 2015
  – People with genetic mutations, with or without PD: Recruiting

» Studying alpha-synuclein levels in spinal fluid and blood

» Learning more about how biology correlates to clinical experience

Researchers are also working toward an imaging agent to measure alpha-synuclein levels in the brain.
WHERE IS THE FIELD IN MANAGEMENT OF MOTOR SYMPTOMS?

Two recently approved medications and more in development are helping avoid motor fluctuations and side effects.

Approved in Early 2015

» Rytary: extended-release levodopa/carbidopa

» Duopa: gel formulation of levodopa/carbidopa infused directly into small intestine

In Late-Stage Development

» CVT-301: inhaled formulation of levodopa in Phase III testing

» APL-130277: thin-film, under-the-tongue strip for rescue from “off” in Phase III

» DBS for Gait Freezing: targeting different brain area in clinical trials
WHAT PROJECTS ARE IN THE PIPELINE TO TREAT NON-MOTOR SYMPTOMS?

- **Northera**: approved in 2014 for orthostatic hypotension
- **Nuplazid**: Parkinson’s psychosis drug close to FDA approval
- **SYN-120**: drug in Phase II testing for cognitive dysfunction
- **NH004**: thin-film strip of drug in Phase II testing for drooling
- **Telehealth Depression Study**: cognitive behavioral therapy provided over the telephone
GET INVOLVED IN GENETICS RESEARCH

• Learn more about how PPMI is enrolling people with a LRRK2 or GBA mutation and people of Ashkenazi Jewish, North African Berber or Basque ancestry.

• Join the 23andMe Parkinson’s Community. People diagnosed with Parkinson's can receive a 23andMe kit at no cost.

“We can all play a role in making the cure a reality” – Jon Gilman
HOW CAN YOU SPEED RESEARCH?

Fox Insight: Virtual Research Hub
- Collects data from surveys and online profile
- Aggregates data from mobile applications and wearable devices
- Study Parkinson’s variability and trends
- Prioritize most pressing patient needs

Fox Trial Finder
- Matches people with clinical studies looking for volunteers.
- More than 48,000 registered & over 400 studies listed

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