Mitochondrial dysfunction in the pathogenesis of Parkinsons disease: elucidating disease mechanisms and identifying therapeutic targets

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Principal Investigators

Charalampos Tzoulis

Institution

University of Bergen

Contact information of lead PI
Country

Norway

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Mitochondrial dysfunction in the pathogenesis of Parkinsons disease: elucidating disease mechanisms and identifying therapeutic targets

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RCN

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01/04/2015

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3.0

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract

Parkinsons disease (PD) is one of the most common neurodegenerative disorders with an increasing prevalence and a world-wide socioeconomic impact. The need for understanding and treating this debilitating disorder has never been more urgent.
We will elucidate the complex genetic aetiology and molecular pathogenesis of PD through mitochondrial dysfunction. I suggest that neurodegeneration in PD is driven by mitochondrial dysfunction resulting from a two-hit pathogenic process at the level of two genomes.
Combinations of inherited genetic defects in nuclear-encoded mitochondrial genes acting on susceptible mitochondrial DNA (mtDNA) backgrounds disrupt normal mitochondrial function and lead to increased somatic mitochondrial mutagenesis in neurons. This causes a gradual build-up of mtDNA damage leading to respiratory dysfunction and neuronal death.
The studies are based on unique patient materials. ParkVest is one of the best characterized PD cohorts word-wide. It comprises 200 Norwegian patients with PD who have been prospectively followed-up since 2004. Patient brains are systematically collected post-mortem. The Italian sample comprises ~2,000 PD patients and as many healthy controls.
Initially we will define the complete exome in the ParkVest cohort using a combination of Next Generation Sequencing and chip-based arrays. Exome data will be processed by an innovative, pathway-targeted analysis focussing on groups of nuclear-encoded mitochondrial genes and mtDNA sequences. Top genetic hits will be replicated by targeted resequencing in the large Italian cohort. Subsequently, we will study the brains of the ParkVest patients and translate the genetic findings into biological mechanisms at the level of the neuron.
By combining high sample quality, large size and innovative genetic and molecular analyses these studies will elucidate part of the missing heritability in PD and identify novel pathomechanisms explaining neurodegeneration at the molecular level.

Lay Summary
Further information available at:

Types:
Investments > €500k

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Norway

Diseases:
Parkinson's disease & PD-related disorders

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