The Libyan International Medical University

Faculty of Basic Medical Science

Genetic basis of Parkinson's disease

Aynoor Bader El Tajouri

Supervised by: Dr. Amal Alnaili

Assisted by: Dr. Nawar Montaser

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Abstract

Parkinson's disease (PD) is a chronic progressive disease of the nervous system affecting ones movement. It is the second most common neurodegenerative disorder after Alzheimer's disease. PD is characterized by cardinal features of rigidity, bradykinesia, tremor and postural instability. The causes of the disease are mostly unknown and usually sporadic, however there have been studies showing a 10-15% association with a genetic predisposition, as well as a number of environmental factors, such as exposure to toxins 'herbicides and pesticides'. This report will summarize the most common identified molecular genetics of PD and its familial forms.

Introduction

Research on Parkinson's disease has proved that the main cause behind the disease and its main symptoms, are the degradation of dopaminergic neurons which produce dopamine in the substantia nigra. This is the region of the brain which is a part of the basal ganglia, a collection of brain regions controlling movement through connections with the motor cortex.[2] Degeneration of these neurons could result from a range of point mutations and duplications in genes such as the alpha-synuclein (*SNCA*) gene, leucine-rich repeat kinase 2 (*LRRK2*) gene, *Parkin*, *PINK1*, *DJ-1* and *ATP13A2*. Other uncommon variants which have been identified in recent studies are the polymorphisms in the *SNCA* and heterozygous mutations in the beta-glucocerebrosidase (*GBA*) gene.[6]

Materials and Methods

A research defined publications of interest as articles reporting patient series or cases characterized genetic status and Parkinson's disease. I have searched in the Nature Briefing database using the following search terms: Parkinson disease, genotype or genetic heterogeneity or genetic variability or mutation. The search was set to include full text articles but excluded conference abstracts, editorials and notes. In order to get more information the research has been repeated in PubMed with identical search terms. The searches have identified 54 articles out of which some were excluded. The remaining articles were 35.

Discussion and Results

Over recent years, many variants in a growing number of genes involved in the pathogenesis of Parkinson's disease have been identified. There are eighteen specific chromosomal regions (locus) called *PARK* are numbered in chronological order such as; *PARK1*, *PARK2*, etc. (Table 1) *PARK4*, was

designated a chromosomal region associated with PD, but was later found to be identical with *PARK1*. Six out of these chromosomal regions have identified mutations that cause monogenic PD, meaning a mutation in a single gene is able to cause the phenotype.[6] These are mutations in alpha-synuclein gene *SNCA* (*PARK1/4*) and *LRRK2* (*PARK8*) which are found to be autosomal-dominant, and mutations in *Parkin* (*PARK2*), *PINK1* (*PARK6*), *DJ-1* (*PARK7*), and *ATP13A2* (*PARK9*) have an autosomal recessive (AR) mode of inheritance.[9]

Manifestations

Parkinson's disease is characterized by a set of symptoms; Tremor often on one hand or involving both hands, later on leading to stiffness. Over time, PD may cause movement to slow (bradykinesia), making simple tasks difficult and time-consuming. As well as muscle stiffness which can be painful and accompanied by impaired posture and loss of automatic movements, including blinking as well as speech changes, either speaking softly, quickly or slur.[1]

Pathophysiology

Parkinson's disease is due to certain nerve cells (neurons) in the brain gradually breaking down (undergoing apoptosis). These neurons produce a chemical messenger in your brain called dopamine. When dopamine levels decrease, it causes abnormal brain activity and this is what produces most of the symptoms associated with the disease. This loss of dopaminergic (DA) neurons of the substantia nigra pars compacta (SNpc) is a hallmark pathologic feature of PD, and essential for its diagnosis.[2][6] Postmortem studies have shown that even mildly affected PD patients have lost about 60% of their DA neurons, as well as dysfunction of the remaining neurons, resulting in approximately 80% loss of DA in the corpus striatum. The remaining DA terminals increase the amount of

neurotransmitter synthesized and delivered to the extracellular fluid. Once released, a portion of the DA appears to diffuse out of the synapse and into the extracellular space, where its actions are prolonged due to the relative absence of high-affinity DA uptake sites. The increased synthesis and release of DA may increase reactive metabolites formed from DA and thus contribute to the progression of the disease. Neurologic deficits emerge when the availability of DA falls below the level required for rapid compensation.[1] Although there are several groups of dopaminergic neurons in the central nervous system (CNS), it is the loss of DA cells in the SNpc that is believed to account for all of the motor manifestations of PD. Some central dopaminergic systems, such as the ventral tegmental area and hypothalamic systems, are relatively spared, and descending spinal dopaminergic systems are spared entirely. Although some DA neurons are spared in PD, it is also the case that neuron loss is not restricted to the dopaminergic neurons. Other catecholamine cell groups including the locus coeruleus are involved, as well as serotoninergic neurons of the raphe nuclei.[6]

Genetics

It can be caused by rare familial genetic mutations, but in most cases it is likely to result from an interaction between multiple genetic and environmental risk factors, which is why it is known to be multifactorial, resulting from several genes, environmental exposures and gene-environment interactions.[5]

Twin studies which took place in the early 1980s demonstrated a low rate of occurrence of the disease among identical twins [reviewed by Duvoisin]. However other studies done in recent years have identified specific disease-causing mutations, most investigates genes are the alpha-synuclein and parkin.[7]

Alpha-synuclein

Disease causing gene locus mapped to 4q21q23 region by Polymeropoulos et al, they identified a base pair change from G to A at position 209, which resulted in an Ala to Thr substitution at position 53 in alpha-synuclein. The second disease-causing mutation, is an Ala to Pro substitution at position 30. Alpha-synuclein has also been discovered in Lewy bodies of sporadic PD cases. The discovery of these mutations in alpha-synuclein suggests a pathogenic mechanism linked to protein aggregation as it has been found in Alzheimer plaques along with the act that a central portion of alpha-synuclein was found to have the capacity to self-aggregate.[4] Alpha-Synuclein messenger RNA (mRNA) is expressed in forebrain structures, such as hippocampus and cortex, but also in a few specific midbrain-brainstem nuclei such as, the dorsal motor nuclei, which are involved in PD. Vila and co-workers while working with a model of chronic MPTP toxicity have identified the possibility in which alpha-synuclein plays a role in a plasticity response, and that alpha-synuclein mRNA in substantia nigra is up-regulated during the first 4 postnatal weeks, a period of differentiation in DA neurons. They have found that alpha-synuclein mRNA levels are decreased or non-existing in the SNpc of patients with sporadic PD. [8][11]

Parkin

This has been found to be the most common form of autosomal recessive PD. Parkin is the component of ubiquitin-proteasome system and binds to membrane of the damaged mitochondria. This phenotype is characterized by early onset of of motor syndrome with dystonia.[5]

Mutations in the parkin gene were first identified in Japanese families, in study done by researchers Ishikawa and Tsuji which has taken 17 patients from the age 9 to 43 years. It is shown to be inherited in an autosomal-recessive pattern, and occurs at an early age. It was found to map to the chromosome 6q25.2-27 region, and a marker for this region is D6S305, was found to be deleted in one of the patients. Screening of complementary DNA (cDNA) which was also deleted in this patient, led to the identification of a sequence encoding 465 amino acid protein. Deletion mutations were identified in four other affected patients in three independent families, confirming the pathogenic significance.[6] A 4.5-kb mRNA transcript was identified in many human tissues, including brain. In brain, it is expressed in various regions, including the substantia nigra. Another molecular genetic analysis of 34 affected individuals from 18 unrelated Japanese families revealed four additional deletional mutations, making it a total of six identified mutations. The deletions affected exon 3, exon 4, and exons 3 to 4, and a 1–base pair (bp) deletion in exon 5 resulted in a frame shift. On the other hand molecular analysis of European families, revealed that in addition to deletion mutations, a variety of point mutations resulting in truncation or missense could also cause the phenotype.[10] Mutations in parkin may cause idiopathic PD. Lucking et al have found that among 73 families with early onset (45 years) of parkinsonism and affected family members, 49% had parkin mutations. Patients without affected family members, 18% had mutations. The majority (77%) of these were younger than 20 years of age. In all, 19 different rearrangements of exons mutations were identified, including multiplications as well as deletions, and there were 16 different point mutations. Parkin has been localized at substantia nigra and locus coeruleus, and at the cellular level to the cytoplasm. Parkin has been shown to play a role in protein degradation as an ubiquitin-protein ligase. These findings

suggest that abnormal accumulation of proteins or abnormal regulation of the half-life of normal cellular proteins may play a role in cell death. [11]

Symbol	Gene locus	Disorder	Inheritance	Gene
PARK1	4q21-22	EOPD	AD	*SNCA*
PARK2	6q25.2–q27	EOPD	AR	*Parkin*
PARK3	2p13	Classical PD	AD	Unknown
PARK4	4q21–q23	EOPD	AD	*SNCA*
PARK5	4p13	Classical PD	AD	*UCHL1*
PARK6	1p35–p36	EOPD	AR	*PINK1*
PARK7	1p36	EOPD	AR	*DJ-1*
PARK8	12q12	Classical PD	AD	*LRRK2*
PARK9	1p36	Kufor-Rakeb syndrome; atypical PD with dementia, spasticity, and supranuclear gaze palsy	AR	*ATP13A2*
PARK10	1p32	Classical PD	Risk factor	Unknown
PARK11	2q36-27	Late-onset PD	AD	Unknown; not *GIGYF2*

PARK12	Xq21–q25	Classical PD	Risk factor	Unknown
PARK13	2p12	Classical PD	AD or risk factor	*HTRA2*
PARK14	22q13.1	Early-onset dystonia-parkinsonism	AR	*PLA2G6*
PARK15	22q12–q13	Early-onset parkinsonian-pyramidal syndrome	AR	*FBX07*
PARK16	1q32	Classical PD	Risk factor	Unknown
PARK17	16q11.2	Classical PD	AD	*VPS35*
PARK18	3q27.1	Classical PD	AD	*EIF4G1*

AD, autosomal dominant; AR, autosomal recessive.

Table-1 *PARK* designated PD-related loci

GBA

This gene encodes the lysosomal enzyme β-glucocerebrosidase which has an important role in glycolipid metabolism. Therefore the loss-of-function mutations in β-glucocerebrosidase will lead to an accumulation of glucocerebroside resulting in symptoms known as Gaucher disease, involving the liver, blood, bone marrow, spleen, lungs, and the nervous system. Gaucher disease is inherited autosomal recessive, there has been about 300 missense, nonsense, and frame-shift disease-causing mutations which been identified by Hruska et al. in 2008. Mutations in *GBA* have been found to increase the risk of developing PD and are found in up to 14% of autopsy-proven diagnoses of PD and both homozygous and heterozygous *GBA* mutations appear to predispose to classical Parkinsonism. Relatives of patients with Gaucher disease carrying heterozygous *GBA* mutations are at risk of PD.[3] Heterozygous *GBA* mutations are associated with a severe phenotype and fast progression of both motor and non-motor symptoms.[10]

In 2009, 16 centers from Europe, America, and Asia carried out by Sidransky et al. analysed selected *GBA* mutations in >5000 (14% of which are Ashkenazi Jews) PD patients and healthy controls without family history of PD and sequenced the entire coding region in a subset of subjects. Mutant *GBA* alleles were found in 19.6% of Ashkenazi Jews and in 6.9% of non-Ashkenazi Jewish patients. The percentage of mutations were five times higher in patients in comparison to controls. Age at onset was found to be lower among subjects with *GBA* mutations than in those without *GBA* mutations. [3]

Future work

Genetic forms of PD are rare, however they play a major importance in the understanding of the pathophysiology of idiopathic PD. It enables the identification of individuals who are at risk before occurrence, as well as the premotor phases of the disease.[7] All genetic forms are easily tested for, however, there are no causative treatment approaches available after 15 years of genetic research. Future work will enable the development of improved human cellular models in order for drug screening and regenerative medicine, generation of animal models that replicate the clinical and pathological findings in humans and the development of cause-directed therapies.[8]

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