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THE ROLE OF PARK GENES FAMILY IN PARKINSON DISEASE

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Parkinson Disease (PD) is a neurodegenerative disease associated with degeneration of dopaminergic neurons in the basal ganglia. Parkinson disease is the second most common neurodegenerative disorder, after Alzheimer disease (rev. in Chai and Lim, 2013). The analysis of prevalence studies showed that there were 5 mln PD patients in 2005, and there is expected increase to 9.3 mln by 2030 (Dorsay et al., 2005). The main clinical indicators of PD are bradykinesia, postural instability, muscle rigidity and resting tremor, good L-dope response and asymmetrical clinical manifestation. There are two types of the pathology such as sporadic and familial forms of PD. 95% of all cases rare sporadic, which means there are no causes that promote the disease development. This review article aims to focus on PARK family of genes that are associated with Parkinson Disease development. It describes possible underlying mechanisms and clinical manifestations of the genetically predetermined Parkinson Disease form. To the present, there are huge amount of genes-candidates for PD but this review focuses on genes that showed significant association on Genome Wide Association Studies of PD genes as well as to describe briefly the clinical manifestations of different familial PD forms.

Keywords: genetics, familial Parkinson Disease, clinical manifestations.

РОЛЬ СЕМЕЙСТВА ПАРК-ГЕНОВ В БОЛЕЗНИ ПАРКИНСОНА

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Болезнь Паркинсона (БП) является нейродегенеративным заболеванием, связанным с дегенерацией дофаминергических нейронов в базальных ганглиях. Болезнь Паркинсона является вторым наиболее распространенным нейродегенеративным расстройством, после болезни Альцгеймера (ред. Chai and Lim, 2013). Анализ исследований по распространённости показал, что в 2005 году было 5 млн пациентов с БП, и, как ожидается, эти цифры вырастут до 9,3 млн к 2030 году (Dorsay др., 2005). Основными клиническими проявлениями являются брадикинезия, постуральная нестабильность, мышечная ригидность и тремор покоя, хороший ответ L-допу и асимметричные клиническим проявлением самой болезни. Существуют две формы патологии, такие как спорадическая и семейная форма БП. 95% всех случаев имеют спорадический характер, что означает, что нет причины, которые способствуют развитию болезни. Целью данной обзорной статьи является описание генов группы PARK, которые связаны с развитием болезни Паркинсона. Кроме того, она описывает возможные патологические механизмы и клинические проявления генетически заданной формы болезни Паркинсона. В данном обзоре, описываются только те гены, которые характеризовались значимостью по результатам анализа Genome Wide Association (Всемирной ассоциации исследований генома), а также данный обзор описание клинических проявлений различных семейных форм БП.

Ключевые слова: генетика, наследственные формы Болезни Паркинсона, клиника.

ПАРКИНСОН АУРУЫНДАҒЫ ПАРК-ГЕНДЕР ТОБЫНЫҢ РӨЛІ

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Паркинсон ауруы базальды ганглиядағы дофаминергиялық нейрондардың дегенерациясымен байланысты болатын нейродегенеративті ауру болып табылады. Паркинсон ауруы Альцгеймер ауруынан кейінгі екінші орындағы ең көптаралған нейродегенеративті бұзылыстарға жатады (ред. Chai and Lim, 2013). Аурудың таралуы бойынша зерттеу нәтижелері көрсеткендей, 2005 жылы Паркинсон ауруымен ауыратын науқастар саны 5 млн болған, ал 2030 жылы бұл көрсеткіш 9,3 млн – ға өседі деп күтілуде (Dorsay др., 2005). Басты клиникалық көріністеріне брадикинезия, постуральды тұрақсыздық, бұлшық еттің тырысуы, тыныштық тағыдіріл, L-допаға жауап және бұл аурудың ассиметриялық клиникалық көріністері жатады. ПА екі патологиялық түрі кездеседі: спорадиялық және отбасылық. ПА 95% спорадиялық түрі кездеседі, яғни бұл аурудың дамуына ешқандай себептің жоқтығын көрсетеді. Осы шолулық мақаланың мақсаты Паркинсон ауруының дамуымен байланысы PARK тобының гендерін сипаттау болып табылады. Содан басқа, ол ПА генетикалық түрінің патологиялық механизмін және клиникалық көріністерін сипаттайды. Бұл шолуда тек Genome Wide Association (Геномды зерттеудің бүкіл әлемдік ассоциациясы) сараптамасының нәтижелері көрсеткендей маңызды деген сипаты бар гендер ғана баяндалған, сонымен бірге ПА әртүрлі отбасылық формаларының клиникалық көріністерін сипаттайды.

Негізгі сөздері: генетика, Паркинсон ауруының тұқымқуалаушылық түрі, клиника.

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Introduction

Parkinson Disease (PD) is a neurodegenerative disease associated with degeneration of dopaminergic neurons in the basal ganglia. Parkinson disease is the second most common neurodegenerative disorder, after Alzheimer disease (rev. in Chai and Lim, 2013). The main clinical indicators of PD are bradykinesia, postural instability, muscle rigidity and resting tremor, good L-dope response and asymmetrical clinical manifestation. On the other hand, the conditions that represent one or more cardinal features but do not fulfill the criteria for PD diagnosis are defined as Parkinsonism. Patients with parkinsonism are believed to be less L-dope responsive, they have additional clinical bouquet such as cognitive impairment, motor neuron disease and dystonia. The gender-adjusted and age- associated Parkinson Disease incidence rate shows males have slightly higher prevalence than females, particularly, 19:100,000 and 9.9:100,000 respectively. The analysis of prevalence studies showed that there were 5 mln PD patients in 2005, and there is expected increase to 9.3 mln by 2030 (Dorsay et al., 2005). Clinical symptoms appear when up to 80% of dopaminergic neurons degenerate in the basal ganglia but what makes these cells most vulnerable is not well-understood. Nowadays, several theories are implicated in the selective degeneration of dopaminergic neurons in PD, particularly, impaired functioning of the ubiquitin-proteasome system might lead to aggregation and accumulation of toxic oligomeric proteins that interfere with neuronal physiology and thereby promote the death (Cookson et al., 2005). Dopaminergic neurons have elevated level of the oxidative stress because of dopamine biosynthesis. Some research shows that mitochondrial dysfunctioning can contribute by

increasing further the free radical geeration. Some environmental factors such as 1-methyl-4-phenylpyridinium (MPP+) and paraquat are known to lead to mitochondrial dysfunctioning and thereby promote the disease pathogenesis (Schulz and Falkenburger, 2004). There are two types of the pathology such as sporadic and familial forms of PD. 95% of all cases rare sporadic, which means there are no causes that promote the disease development. Some research suggests that exposure to different environmental factors can promote the disease development; however, large epidemiological studies suggested that exposure to environmental factors only are not obligatory lead to PD development[rev. in Chai and Lim, 2012) Genetic research suggests that PD has different inheritance patterns such as Mendelian form where mutation of a single gene leads to PD development, so called autosomal dominant, autosomal recessive, or, extremely rare, X-linked manner of inheritance (rev. in Chai and Lim, 2013, Pankratz et al., 2003). So, for instance, latest genetic research discovered mutations in at least five distinct genes (a-synuclein, parkin, DJ-1, PINK1, and LRRK2) and several autosomal recessive genes that are linked with the familial PD form. On the other hand, there is unknown trigger that induces the pathological mechanism although research suggests that there is a link between genes- risk factors and clinical symptoms (Cruts at el., 2012). For example, an elegant work of Lin and colleagues showed that there might be a physiological interplay between α-synuclein overexpression and LRRK2 –induced protein hyperphosphorylation which in turn may lead to the neuronal degeneration (Lin et al., 2009). This review aims to focus on genes that showed significant results on Genome Wide Association Studies of PD genes as well as to describe briefly the clinical manifestations of different familialPD forms.

Heritable Causes.PARK family of genes.

PARK1-PARK4-linked (α-synucleinopathy) autosomal dominant forms. Neuropathologically the brains of the patients with Parkinson Disease's show deposits of filamentous protein aggregates, so called Lewy Bodies, Lewy neuritis as well as intraneuronalinclusions. These aggregates are found in dopaminergic neurons of SN and other brain regions such as cortex and magnocellular basal forebrain nuclei. Lewy bodies are predominantly composed of hyper-phosphorylated α-synuclein protein fibrils (Masliah et al., 2000, Schell et al., 2009). Although the exact physiological mechanisms leading to the hyperphosphorylation of α-synuclein are under investigation, recent research suggest that hyperphosphorylation can occur due to overexpression, particularly, due to duplication (Chartier-Harlin et al., 2004) or triplication of the α-synuclein gene locus (Singleton et., 2003). Moreover, mutations in the α-synuclein gene itself can also promote PD development, so for instance, the first pathogenic point mutation in α-synuclein (p.A53T) substitution was discovered in 1997 (Polymeropoulos et al., 1997; that was followed by the further identification of mutations such as p.A30P (Kruger et al., 2001) and p.E46K (Zarranz et al., 2004), moreover, there is increasing amount of pathogenic mutations are being identified (Ross et al., 2009). This autosomal dominant form of PD accounts for less than 1% of familial PD cases. It should be noted that although α-synuclein aggregation and fibrillation are thought to lead to neuronal dysfunction, the exact mechanism of how ubiquitously expressed α-synuclein mutations promote selective dopaminergic degeneration is not clear.

Clinical manifestations of the PARK1-PARK4 form. The patients typically have early-onset and rapidly progressive for of the disease; they have moderate L-dopa response, particularly at the initial stages. The patients with duplication or triplication of α-synuclein gene more frequently show myoclonus, severe insomnia, constipations and cognitive impairment, dysautonomia, psychiatric symptoms such as depression and hallucinations (Lesage et al., 2013)

PARK-2 autosomal recessive form of PD. PARK-2 gene encodes the protein called parkin or E3 ubiquitin protein ligase, protein that is widely expressed in the brain; however, its precise function is unknown.Some research suggests that parkin is one of components of the multiprotein E3 ubiquitin ligase complex, so-called ubiquitin-proteasome system that mediates the targeting of proteins for degradation. However, the exact mechanism of how the loss of function of the parkin results in dopaminergic neurons degeneration is not clear. The current idea is that E3 ubiquitin ligase complex participates in the degeneration of toxic proteins, for example, synphilin-1, CDC-rel1, cyclin E, p38 tRNA synthase, Pael-R, synaptotagmin XI, sp22, CASK and PICK1 so that due to loss of function of the parkin, there might be an accumulation of toxic

substances and thereby an increased free radicals generation which in turn leads to the cell death (Kilarski et al., 2012, Djarmati et al., 2004, Chung et al., 2001). The PARK-2 represents most common autosomal recessive form, so it account for 50 % of autosomal recessive form as well as 10-20 % of autosomal dominant of familial PD cases (Shyu et al., 2005).

Clinical manifestations of the PARK-2 form. The patients have early-onset and slowly progressive form with motor fluctuations; they have good L-dopa response. Most of the patients have leg dystonia at the very beginning of the disease. The patients suffer from hyperreflexia, peripheral neuropathy as well as they develop dysautonomia and psychiatric symptoms such as depression, anxiety and psychosis as the disease progresses (Takahashi et al., 1994).

PARK-6 autosomal recessive form of PD. This form represents rare form and it accounts for 2-8 % of the familial form. PARK-6 form is linked to the PINK-1 gene mutations. PINK-1 gene encodes phosphatase and tensin homolog-induced putative kinase 1 (PINK-1) that is involved in neuroprotection against mitochondrial dysfunctioning as well as proteasome-induced apoptosis (Valente et al., 2001, Poole et al., 2006, Kumazawa et al., 2008)

Clinical manifestations of the PARK-6 PD form. The patients have early-onset, slow disease progression and good L-dopa response but the dyskinesia and motor fluctuations are very common in these patients. They also manifest psychiatric symptoms such as depression, anxiety, orthostatic hypotension and cognitive impairment as the disease progresses (Albanese et al., 2005, Hatano et al., 2004).

PARK-7 autosomal recessive form of PD. To the present time, 1-2% of the familial PD forms are associated with more than 25 pathogenic mutations in DJ-1 gene. DJ-1 encodes highly expressed protein DJ-1 in glia and neurons which is involved in modulation of transcription, chaperon-like functions, peroxiredoxin as well as mitochondrial complex stabilizing component (Parsanedjad et al.,). Some data suggests that DJ-1 loss of function is associated with higher sensitivity to oxidative stress caused by toxic substances such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrindine (MPP+) (Kim et al., 2005).

Clinical manifestations of the PARK-7 form. The patients have early-onset, slow disease progression and good L-dope response. At the very beginning patients have blepharospam, leg dystonia and psychiatric symptoms (van Duijnwt al., 2001).

PARK-8 autosomal dominant form of PD. To the time being, this form represents the most common of familial PD and thereby accounts for up to 34 % of the familial form as well as 1-2 % of the sporadic form (Cruts et al., 2012). As the research shows so far more than 127 LRRK (Leucine-Rich Repeat Kinase) gene mutations are known with only 7 being associated with PD (Chai and Lim, 2013). The exact function of the LRRK is not well-established but research shows that it is involved in lysosomal and autophagy pathways (Dodson et al., 2014), call signaling and synaptic glutamate transmission (Beccano-Kelly et al., 2014), cytoskeletal dynamics (Bretscher A, et al., 2002). The aberrant phosphorylation can lead to toxic protein aggregation leading to neuronal cell death.

Clinical manifestations of the PARK-8 PD form. The patients typically have late-onset, slow disease progression and good L-dope response. During the disease course, the patients suffer from insomnia, dysautonomia; anosmia, psychiatric symptoms such as anxiety, depression and hallucinations as well as they experience cognitive decline (Healy et al., 2008).

PARK-15 autosomal recessive form of PD. This form represents FBXO7 (The F box, named after cyclin F-7) gene encodes a member of the F-box family of proteins that participate in ubiquitin-proteosome protein-degradation pathway (Shojaee et al., 2008).

Clinical manifestations of PARK-15 PD form. The patients have early-onset, progressive form and good L-dopa response. The patients had equinovarus deformity since childhood; they had motor fluctuations and spasticity predominantly in lower limbs and severe dementia as the disease progresses (Shojaee et al., 2008, Di Fonzo et al., 2009)

PARK-17 autosomal dominant form of PD. This form represents extremely rare forms of PD, particularly, 0,3 % of sporadic and 2 % of familial PD cases. PARK-17 form is associated with mutations in VPS35 (vacuolar protein sorting protein-35) that is involved in transportation of different proteins between endosomes and Golgi network (Zimprich et al., 2011).

Clinical manifestations of the PARK-17 PD form. The patients usually have late-onset, slow-disease progression, resting tremor-dominant PD and good L-Dopa response, cognitive deficits and

psychiatric symptoms as the disease progresses (Wider et al., 2008).

PARK-18 autosomal dominant forms of PD. This form represents extremely rare forms of PD with 0,2% of familial PD cases. PARK-18 PD form is associated with mutations in EIF4G1 (eukaryotic translation initiation factor 4 gamma,1) gene that is ubiquitously expressed in CNS. EIF4G1 protein is involved in growth control, stress response and bioenergetics (Chartier-Harlin et al., 2011).

Clinical manifestations of the PARK-18 PD form. The patients usually have late-onset, with asymmetric resting tremor or akineticrigidity that progressively mixes during the disease course and good L-DOPA response, some patients also develop psychiatric symptoms and cognitive decline (Chartier-Harlin et al., 2011).

Table 1.

Short overview of the genes that play role in PD.

Inheritance mode	Gene	Locus name	Chromosomal location	Product (Protein) name	% of PD attribute	L-DOPA response-veness	Age of onset
Autosomal dominant	SNCA	PARK1-PARK4 [4,27,33,34]	4q21	α-synuclein	Less 1% familial PD	Good	30-60 years
	PARK8	LRRK2 [7,17,39]	12q12	LRRK2	1%-2% sporadic/ 34% familial PD	Good	50-70 years
	PARK18	EIF4G1 [3]	3q27.1	EIF4G1	0.2% familial PD	Good	50-60 years
	PARK17	VPS-35 [35,40]	16q12	VPS-35	0.3% sporadic and 2% familial PD	Good	40-60 years
Autosomal recessive	PRKN	PARK2 [4,18,22]	6q25.2-q27	Parkin, E3 ubiquitin ligase	10-20% sporadic PD/ 5% familial PD	Good	Childhood -30
	PARK6	PINK [13,19]	1p36	PINK-1	2-8% familial PD	Good	30-40 years
	PARK7	DJ – 1 [14,32]	1p36.23	DJ-1	1-2% familial PD	Good	20-30 years
	PARK15	FBX07 [10,30]	22q12.3	PARK-FBX07	Rare	Good	Childhood -30

Conclusion.

This review aimed to overview some genetics of PD; however, from the overwhelming amount of literature it is seen that PD is a complex pathogenic pathway where a tapestry of different events rather than just a single pathogenic pathway promotes the disease progression. These include the ubiquitin-proteasome and autophagy pathways, so genetically linked aberrations might promote protein misfolding leading to toxic aggregations, particularly, α-synuclein composed Lewy Bodies, PARK-2,6,8,15 and 17 forms of PD), mitochondrial-related redox pathways, particularly, PARK-2, 6,7 AND 18 and probablyLRRK2-related cases) and pathways involving aberrant protein phosphorylation (e.g. in LRRK2-related cases). It is beyond doubts that new pathways and genes that are involved in endosome and lipid metabolisms will appear in the future, but it is crucial to realize that all pathways often act in a vicious cycle and they promote one each other and that each of PD-linked gene products affects multiple pathways. For instance, parkin is involved in several processes such as protein and mitochondrial homeostasis. Although there is no well-established trigger that induces the disease development, but latest research helped to understand some aspects of the disease. The present and future research can be an extremely useful tool to develop neuroprotective and remaining dopaminergic neurons preservation

therapies that will improve the quality of life of the PD patients. Moreover, it ould be of a great therapeutic value to optimize the therapy for the PD patients depending on their genetic background.

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