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KEY GENETIC SIMILARITIES AND DIFFERENCES BETWEEN ALZHEIMER'S DISEASE AND PARKINSON DISEASE

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Abstract
Recent research point to several similarities between Alzheimer's disease and Parkinson disease. Given that the major difference between the two diseases is the fact that Parkinson disease mainly exhibit motor impairments and only secondarly cognitive decline and Alzheimer's disease hallmark is cognitive loss, we tried to evidentiate several key molecular differences and similarities. In this way, we found that Alzheimer's disease is also characterized by mild motor decline which is exhibited before any cognitive symptoms and that several genetic hallmarks may be actually common in these two diseases. Also, it was suggested that the molecular hallmarks of Alzheimer's disease may equally contribute to cognitive and motor decline. Furthermore, evidence regarding the overlapping genetic traits were presented and discussed alongside the description of Parkinson's disease genetic loci.

Abbreviations: AD – Alzheimer's disease, APP – amyloid protein precursor, βAP - beta-amyloid peptide; MAPT – microtubule associated protein tau; NFT – neurofibrillary tangles; PD – Parkinson disease, Swe/Ind – Sweedish/Indian mutations; Swe/Lon – Sweedish/London mutations.

Key words*:* Polymorphism, motor deficiencies, cognitive deficiencies, punctiform mutation, neurodegeneration.

Introduction

In nearly two decades of research, it had been shown that many neurological syndromes involve mostly movement discrepancies, but also cognitive disordering and tissue atrophy. PD can be considered a mixted-symptomes disorder. Thus, it can be considered paucy movement disorder characterized by rest tremor, bradykinesia, rigidity, postural instability, freezing phenomena, and flexed posture (Litvan et al., 2003), but also, according to Goldman and Fahn (2015), a cognitive decline tendency disorder due to recent research which showed that PD patients can also experience dementia-like symptoms (Buter et al., 2008). Many systems of classification refer to PD as to a group of

syndromes and distribute the many features of PD as different type-PD syndromes: primary Parkinsonism (the main idiopathic or genetic disorder, commonly known as entirely motor neurodegenerative), secondary Parkinsonism (insults to the brain), Parkinson-plus syndromes (including progressive supranuclear palsy, multiple system atrophy and corticobasal degeneration), and heredo-degenerative disorders (in which Parkinsonism is not the primary clinical feature) (Goldman and Fahn, 2015).

In this way, it seems that the need of differential diagnosis techniques led to the identification of those which include magnetic resonance imaging such as T1-weighted volumetric technique (also used in Alzheimer's disease study) in order to quantify atrophy areas via image analysis of caudate nucleus and putamen, iron quantification (Martin et al., 2008) or multimodal testing (Peran et al., 2010).

Physiopathologically speaking, PD can be characterized by the loss of dopaminergic neurons located in the substantia nigra pars compacta (Bergman and Deuschl, 2002). This can affect the stratium in the caudal and front portions of the caudate nucleus resulting in dopaminergic depletion (Rodriguez-Oroz et al., 2009). Studies show that the typical classic motor symptoms appear when at least 60% of dopaminergic nigral cells die. This usually happens by the age of 50 or 60 (Hassan et al., 2015). Another classical feature of PD is the accumulation of eosinophilic intracytoplasmic inclusions (Lewy bodies) that contain ubiquitin in the central core and α-synuclein in the halo (Goldman and Fahn, 2015).

On the other hand, Alzheimer's disease (AD) involves a pathological progressive neurodegenerative state occurring mainly in elders and being characterized by various symptoms depending on individuality, and physiological, neurological, and molecular states. Behind the visible altered cognitive performances stand several molecular processes which are the actual source of the impairments on cognitive functions and intellectual abilities loss (Balmus et al., 2015).

Being the most severe neurodegenerative diseases, AD is yet insufficiently characterized meaning that cause and progression are not clearly correlated. Furthermore, it seems that AD-like symptomatology may be a common feature of 85+ years elders, and no treatment is known yet to cure, stop or slow this disease (Brookmeyer et al., 2007; Mölsä et al., 1986). Presently, the diagnostic charts include more than the original three stages of AD (mild, moderate, and severe) which were determined based on the cognitive deficit exhibited by the patient (ART, 2008; NIA, 2011). Sperling et al. (2011) enhanced the stage chart by adding new stages: presymptomatic AD, mild cognitive impairment due to AD, and AD dementia (with the already known three stages). Today it is thought that preceding the neuropsychiatric symptoms are the molecular accumulations of βAP and NFT which happens in time with no visible symptoms defining presymptomatic AD (Sperling et al., 2011). Thus, researchers find this stage

the most important due to the fact that no irreversible effect on the cognition is seen, and hypothesize that if discovered at this stage, it may be curable (Sperling et al., 2011).

Also, Bruchman and Bennett (2011) suggest that the preclinical phase of AD is marked by some motor decline traits which actually foretell the cognitive decline. Over the last decade increasing evidences point to a link between motor function and the risk of developing AD (Bruchman and Bennett, 2011). Several motor function studies were previously conducted in AD patients after clinical diagnosis and the structural and functional brain alterations were demonstrated in older individuals with and without AD incapable simple and complex motor tasks (Hebert et al., 2010; Jahng et al., 2011). In this way, muscle bulk and muscle strength are associated with lower motor performances whereas physical frailty seems to be almost a ubiquitous symptom in AD. Also, several Parkinsonian signs including bradykinesia, rigidity and resting tremor, and posture disturbances are currently associated with AD as risk factors or predicting a more rapid cognitive decline previous or following AD diagnosis (Wilson et al., 2003; Portet et al., 2009).

Role of genetics and environment in PD development

Studying PD tendency to spread through the families of those affected and the MPTP parkinsonism developing neurotoxin (Porras et al., 2012), it have been shown that both genetic and environmental factors equally contribute to PD occurrence. It seems that the discovery of many genes that can contribute in a monogenic way to PD occurrence, made the term 'idiopathic PD' to be no longer used in favor of 'primary parkinsonism'. Large community studies and twin studies confirmed a multifactorial inheritance as a main mechanism for PD and a clearly genetic origin of earlier than 50 years of life onset PD (Marder et al., 1996; Tanner et al., 1999).

Genetically speaking, until today, eight genes have been discovered as associated with PD in a Mendelian form of inheritance (four autosomal dominant, four autosomal recessive). There are a number of rare genetic variations not yet confirmed as PD susceptibility genes. The PD associated genes are conveniently named as Parkinson associated genes and numbered in chronological order. Most of the classification systems refer to inheritance tendency, locus susceptibility or monogenic feature of locus mutations. Another relevant classification would be based on the type of locus modification. In this way, susceptibility loci can be altered by mutations, polymorphisms, large rearrangements, or polyallelle occurrence.

Mutations can be very common causes of susceptibility, these beeing point mutations, deletions, substitutions, insertions, duplications, triplications, or

even copy number variants. Thus, the mutations of synuclein α gene can cause an excess of synuclein that influence both age of onset and severity (copy number variants more common and severe than point mutations) (Polymeropoulos et al., 1996; Singleton et al., 2003; Puschmann et al., 2013; Lesage and Brice, 2009; Houlden and Singleton, 2012). Similarly, PARK4 was originally mislinked to another locus, but in fact it has been shown that it is a triplication of a large chromosomal region containing PARK1 (Singleton et al., 2003), was linked to AD susceptibility.

A very large susceptibility locus, PARK2 (parkin gene), can possess many exon rearrangements, point mutations, duplications, triplications, insertions, and deletions, that can alter pigmented nuclei neuronal structure resulting in neuronal loss and locomotor dysfunction caused by mitochondrial impairment and cellular apoptosis (Houlden and Singleton, 2012; Poulopoulos et al., 2012). Also, PARK6 (PTEN-induced putative kinase 1, PINK1) mutations are responsible for 1–9% of early-onset PD which makes them the most common autosomal recessive cause of PD and are believed to trigger an aberrant depolarization mechanism of mitochondrial membrane which cause apoptosis (Lesage and Brice, 2009).

PARK7 locus can be involved in oxidative stress defense and cell survival. Its mutations can cause an increase in reactive oxygen species production creating elevated mitochondrial permeability-transition pore openings that can lead to apoptosis (Lev et al., 2013). The mutations of PARK8 (dardarin, leucine-rich repeat kinase-2) appear to trigger autophagy, but because they are predisposing to non-skin cancers, Crohn's disease and leprosy too, their exact mechanism is yet to be determined though G2019S mutation is extremely common in populations (Ashkenazy, North African Berbers, Basques) with PD (Healy et al., 2008; Alcalay et al., 2009). PARK14 (phospholipase A2, group VI) is associated to neurodegeneration with brain iron accumulation. It can mutate and lead to fatty acid metabolism disturbances which lead to parkinsonism at young ages (Lu et al., 2012).

Similarly, PARK17 (vacuolar protein sorting 35) in mutated variant, can cause a very rare PD type associated with dementia (Zimprich et al., 2011), PARK18 (eukaryotic translation initiation factor 4-gamma 1) mutations can cause discrepancies in mRNA translation, is barely associated with a mild form of PD of unknown mechanism (Chartier-Harlin et al., 2011), PARK19 (dinactyn 1) can get mutated and inherited in an autosomal dominant way and cause a PD-like motor neurons disease, also associated with depression due to tau protein and organelle poor trafficking mostly (Farrer et al., 2009); and PARK20 (synaptojanin 1) mutations can cause synaptic vesicles poor recycling leading to synaptic transmission unbalance, also found in Down's syndrome, Alzheimer's disease, and learning deficits disorders.

Very rare mutations have been confirmed in PARK9 (lysosomal type 5 P-type ATPase trans membrane active transporter) susceptibility locus and associated with neurodegeneration with brain iron accumulation. This is considered as a risk factor to PD (Di Fonzo et al., 2007).

Interestingly, PARK15 (F-box protein 7) may be involved in ubiquitin-mediated pathways, but its mutations are not well studied (Bonifati, 2012).

Polymorphisms and polyallelic state are quite rare in PD susceptibility loci. Many polimorphisms of unknown clinical relevance were found in PARK2 locus. Some polymorphisms of PARK1 can be considered a risk factor. PARK5 (ubiquitin carboxy terminal hydrolase), yet unconfirmed loci, exhibit a polymorphism in a Northern German family with autosomal dominant PD. This was considered a risk factor for sporadic PD (Maraganore et al., 1999).

Also, there are some unconfirmed loci that cannot be assigned to any of the categories above due to the lack of informations. In this way, PARK3 (sepiapterin reductase) was found in a small group of European families with autosomal dominant PD (Sharma et al., 2011), but not relevantly tied to PD susceptibility. Similar cases are PARK10 to PARK13 that are unconfirmed susceptibility loci. One interesting case is the PARK12 susceptibility locus, the only one X-linked (Hicks et al., 2002; Pankratz et al., 2002; Hardy et al., 2006; Krüger et al., 2011). There is PARK16 (Na^+/Mg^{2+} exchanger, Mg^{2+} efflux system, SCL41A1) too that is not fully confirmed as a PD susceptibility locus, but recent research (Kolisek et al., 2013) showed that a substitution can be associated with PD through a gain-of-function mutational mechanism.

Genetic links between PD and AD

Similar motor dysfunctions were also observed in AD animal models expressing either human four-repeat tau or diverse mutant human tau isoforms (Whirts and Bayer, 2008). Motor deficits and reduced performance in sensorimotor tasks were also described leading to the idea that a partial link between AD and PD exists, in regarding the genetic features of both of the diseases.

While JNPL3 transgenic mice show progressive motor disturbance (Lewis et al., 2000), a first link between AD and PD rises. The fact that mice which overexpress in the brain tau isoforms or variants are found to develop tau-positive lesions which lead to motor weakness (Ishihara et al. 1999) is clear evidence that molecular defects that occur in the presymptomatic stage of AD does not necessarily lead to cognitive impairments, but also to sensorimotor effects. Motor function damage goes even further in another transgenic mice model expressing human mutant tau P301L (Higuchi et al. 2005) and human mutant tau P301S

being characterized by severe paraparesis at young age due to abundant hyperphosphorylated tau filaments (Allen et al., 2002).

Since tau gene mutations seems not to be a hallmark trait of AD, the association between AD and motor disturbances characteristic to PD may be questionable. Therefore, supplementary arguments can be brought to discussion due to the fact that motor disturbances were found also in APP mutant transgenic mice. Although many studies show no differences in motor performances in APP mutants, there are also several positive reports. In this way, APP23 transgenic mice (Van Dam et al. 2003), and aged APP Swe/Ind transgenic mice showed a decline in motor performance in simple motor tasks (Lee et al. 2004) within a year before the typical disease-related pathology (Wirths and Bayer, 2011). Also presenilin 1 knockdown associated with APP Swe/Lon mutations seems to degenerate even more the motor activity (Wirths et al., 2006, Wirths et al., 2007). This suggests that several motor impairments may be actually a common trait of AD exhibited in early stages, even before the cognitive decline occurs.

In similar transgenic animal models studies was showed that even the common AD risk factors may compromise motor activity when present. In this way, APOE4 mice models exhibited age-dependent axonopathy, reduced locomotor activity and swimming inability linked to hyperphosphorylation of tau (Tesseur et al. 2000). Also, increased tau phosphorylation and tau-positive inclusions were reported in a different ApoE 4 transgenic mouse model (Brecht et al. 2004), but shown that only under the control of enolase or Thy1 promoters (Tesseur et al. 2000) suggesting that the motor activity impairment may be a neuron-specific defect and not conditioned by the surrounding glial matrix integrity and function.

These findings were partially demonstrated by a large genetic research study based on genome-wide association studies for both AD and PD in which is showed that although dominantly inherited mutations of MAPT lead to frontotemporal dementia with parkinsonism, rare MAPT variants may increase the risk for AD due to the fact that tau modulates Aβ-associated Alzheimer's neurodegeneration (Desikan et al., 2015). Also, it seems that tau-associated polymorphisms are important in MAPT transcript levels modulation which further affects medial temporal lobe volume loss.

Also they suggest that a concomitant AD and PD pathogenesis may occur but consisting evidence (small cohort of autopsy confirmed AD cases and controls rs393152 allele study) indicated no overlapping of the two studied pathologies. It was showed that MAPT mutations may influence Alzheimer's neurodegeneration in the absence of APOE4 form.

Conclusions

1. Parkinsons disease is mainly a motor impairment disease, but cognitive decline was also observed.
2. Alzheimer's disease is a complex disease marked by severe cognitive loss and secondarly motor impairments.
3. Several similarities between the sensorimotor and cognitive neuronal matrix were observed in both diseases.
4. Key genetic loci point to an overlap on Alzheimer's and Parkinson's diasease genetic and molecular traits.
5. Although many Alzheimer's disease animal models show motor impairments, further research is needed in establishing the real overlap between the two diseases.

References

1. Alcalay R.N., Mejia-Santana H., Tang M.X., et al., (2009) - Motor phenotype of LRRK2 G2019S carriers in early-onset Parkinson disease, Arch Neurol., 66(12), 1517–1522.
2. Allen B., Ingram E., Takao M., Smith M.J., Jakes R., et al., (2002) - Abundant tau filaments and nonapoptotic neurodegeneration in transgenic mice expressing human P301S tau protein, J Neurosci., 22, 9340–9351.
3. Alzheimer's Research Trust, (2008) - Alzheimer's diagnosis of AD.
4. Balmus I.M., Ciobica A., Negura A., Negura L., Anton E., (2015) - Basic aspects in selecting a suitable transgenic rodent model for Alzheimer's Disease, Psych Danub., 27, 338-345.
5. Bergman H., Deuschl G., (2002) - Pathophysiology of Parkinson's disease: from clinical neurology to basic neuroscience and back, Mov. Disord., 17 (Suppl 3), S28–S40.
6. Bonifati V, (2012) - Autosomal recessive parkinsonism. Parkinsonism Relat Disord., 18(suppl 1), S4–S6.
7. Brecht W.J., Harris F.M., Chang S., Tesseur I., Yu G.Q., et al., (2004) - Neuron-specific apolipoprotein e4 proteolysis is associated with increased tau phosphorylation in brains of transgenic mice. J Neurosci., 24, 2527–2534.
8. Brookmeyer R., Johnson E., Ziegler-Graham K., Arrighi H.M., (2007) - Forecasting the global burden of Alzheimer's disease, Alzheimers Dement., 3(3), 186–91.
9. Buchman A.S., Bennett D.A., (2011) - Loss of motor function in preclinical Alzheimer's disease, Expert Rev Neurother., 11(5), 665–676.

10. Buter T.C., Van den Hout A., Matthews F.E., Larsen J.P., Brayne C., Aarsland D., (2008) - Dementia and survival in Parkinson disease: a 12-year population study, Neurol., 70, 1017–1022
11. Chartier-Harlin M.C., Dachsel J.C., Vilariño-Güell C., et al., (2011) - Translation initiator EIF4G1 mutations in familial Parkinson disease. Am J Hum Genet., 89(3), 398–406.
12. Desikan R.S., Schork A.J., Wang Y., Witoelar A., Sharma M., et al., Genetic overlap between Alzheimer's disease and Parkinson's disease at the MAPT locus, Mol Psychiatry, 20(12), 1588–1595.
13. Di Fonzo A., Chien H.F., Socal M., et al., (2007) - ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease, Neurol., 68(19), 1557–1562.
14. Farrer M.J., Hulihan M.M., Kachergus J.M., et al., (2009), DCTN1 mutations in Perry syndrome. Nat Genet., 41(2), 163–165.
15. Goldman J.S., Fahn S., (2015) - Chapter 68 - Genetics of Parkinson Disease and Related Diseases, In Rosenberg R.N., Pascual J.M. (eds.), Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, 5th Edition, Academic Press, Elsevier, 769-778.
16. Hardy J., Cai H., Cookson M.R., et al., (2006) - Genetics of Parkinson's disease and parkinsonism, Ann Neurol., 60(4), 389–398.
17. Hassan O.M., Veiga J.J., Martin-Fernandez J.J., (2015) - Chapter 11 – Cognitive Decline and Dementia in Parkinson's Disease, In Martin C.R., Preedy V., Diet and Nutrition in Dementia and Cognitive Decline, Academic Press, Elsevier, 113–125.
18. Healy D.G., Falchi M., O'Sullivan S.S., et al. (2008) - Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study, Lancet Neurol., 7(7), 583–590.
19. Hebert L.E., Bienias J.L., Mccann J.J., Scherr P.A., Wilson R.S., Evans D.A., (2010) - Upper and lower extremity motor performance and functional impairment in Alzheimer's disease, Am. J. Alzheimers Dis. Other Demen., 25(5), 425–431.
20. Hicks A.A., Petursson H., Jonsson T., et al., (2002) - A susceptibility gene for late-onset idiopathic Parkinson's disease, Ann Neurol., 52(5), 549–555.
21. Higuchi M., Zhang B., Forman M.S., Yoshiyama Y., Trojanowski J.Q., Lee V.M. (2005) - Axonal degeneration induced by targeted expression of mutant human tau in oligodendrocytes of transgenic mice that model glial tauopathies, J Neurosci., 25, 9434–9443.
22. Houlden H., Singleton A.B., (2012) - The genetics and neuropathology of Parkinson's disease. Acta Neuropathol., 124(3), 325–338.

23. Ishihara T., Hong M., Zhang B., Nakagawa Y., Lee M.K., Trojanowski J.Q., Lee V.M. (1999) - Age-dependent emergence and progression of a tauopathy in transgenic mice overexpressing the shortest human tau isoform, Neuron, 24, 751–762.
24. Jahng G-H., Xu S., Weiner M., Meyerhoff D., Park S., Schuff N., (2011) - DTI studies in patients with Alzheimer's disease, mild cognitive impairment, or normal cognition with evaluation of the intrinsic background gradients, Neuroradiol., 1-14-14.
25. Kolisek M., Sponder G., Mastrototaro L., Smorodchenko A., Launay P., et al., (2013) - Substitution p.A350V in Na+/Mg2+ Exchanger SLC41A1, Potentially Associated with Parkinson's Disease, Is a Gain-of-Function Mutation, PLoS One., 8(8), e71096.
26. Krüger R., Sharma M., Riess O., et al., (2011) - A large-scale genetic association study to evaluate the contribution of Omi/HtrA2 (PARK13) to Parkinson's disease, Neurobiol Aging., 32(3), 548.e9–548.e18.
27. Lee K.W., Lee S.H., Kim H., Song J.S., Yang S.D., Paik S.G., Han P.L., (2004) - Progressive cognitive impairment and anxiety induction in the absence of plaque deposition in C57BL/6 inbred mice expressing transgenic amyloid precursor protein, J Neurosci Res., 76, 572–580.
28. Lesage S., Brice A., (2009) - Parkinson's disease: from monogenic forms to genetic susceptibility factors. Hum Mol Genet., 18(R1), R48–R59.
29. Lev N., Barhum Y., Pilosof N.S., et al. (2013) - DJ-1 protects against dopamine toxicity: implications for Parkinson's disease and aging, J Gerontol A Biol Sci Med Sci., 68(3), 215–225.
30. Lewis J., McGowan E., Rockwood J., Melrose H., Nacharaju P., et al., (2000) - Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein, Nat Genet, 25, 402–405.
31. Litvan I., Bhatia K.P., Burn D.J., Goetz C.G., Lang A.E., et al., (2003) - Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders, Mov. Disord., 18, 467–486.
32. Lu C.S., Lai S.C., Wu R.M., et al., (2012) - PLA2G6 mutations in PARK14-linked young-onset parkinsonism and sporadic Parkinson's disease, Am J Med Genet B Neuropsychiatr Genet., 159B(2), 183–191.
33. Maraganore D.M., Farrer M.J., Hardy J.A., et al., (1999) - Case-control study of the ubiquitin carboxy-terminal hydrolase L1 gene in Parkinson's disease, Neurol., 53(8), 1858–1860.

34. Marder K., Tang M.X., Mejia H., et al., (1996) - Risk of Parkinson's disease among first-degree relatives: a community-based study, Neurol., 47(1), 155–160.
35. Martin W.R., Wieler M., Gee M., (2008) - Midbrain iron content in early Parkinson disease: a potential biomarker of disease status, Neurol., 70, 1411–1417.
36. Mölsä P.K., Marttila R.J., Rinne U.K., (1986) - Survival and Cause of Death in Alzheimer's Disease and Multi-Infarct Dementia, Acta Neurol Scand., 74(2), 103–7.
37. National Institute on Aging, (2011) - About Alzheimer's Disease: Symptoms.
38. Pankratz N., Nichols W.C., Uniacke S.K., et al., (2002) - Genome screen to identify susceptibility genes for Parkinson disease in a sample without parkin mutations, Am J Hum Genet. 71(1), 124–135.
39. Péran P., Cherubini A., Assogna F., Piras F., Quattrocchi C., Peppe A., et al., (2010) - Magnetic resonance imaging markers of Parkinson's disease nigrostriatal signature, Brain, 133, 3423–3433.
40. Polymeropoulos M.H., Higgins J.J., Golbe L.I., et al., (1996) - Mapping of a gene for Parkinson's disease to chromosome 4q21-q23. Science, 274(5290), 1197–1199.
41. Porras G. , Li Q., Bezard E., (2012) - Modeling Parkinson's Disease in Primates: The MPTP Model, Cold Spring Harb Perspect Med., 2(3), a009308.
42. Portet F., Scarmeas N., Cosentino S., Helzner E.P., Stern Y., (2009) - Extrapyramidal signs before and after diagnosis of incident Alzheimer disease in a prospective population study, Arch Neurol., 66(9), 1120-6.
43. Poulopoulos M., Levy O.A., Alcalay R.N., (2012) - The neuropathology of genetic Parkinson's disease. Mov Disord., 27(7), 831–842
44. Puschmann A., (2013) - Monogenic Parkinson's disease and parkinsonism: clinical phenotypes and frequencies of known mutations. Parkinsonism Relat Disord., 19(4), 407–415.
45. Rodriguez-Oroz M.C., Jahanshahi M., Krack P., Litvan I., Macias R., et al., (2009) - Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms, Lancet Neurol., 8, 1128–1139.
46. Sharma M., Maraganore D.M., Ioannidis J.P., et al. (2011) - Role of sepiapterin reductase gene at the PARK3 locus in Parkinson's disease, Neurobiol Aging, 32(11), 2108.e1–2108.e5.
47. Singleton A.B., Farrer M., Johnson J., et al., (2003) - Alpha-Synuclein locus triplication causes Parkinson's disease, Science, 302(5646), 841.

48. Sperling R.A, Aisen P.S., Beckett L.A., Bennett D., Craft S., et al., (2011) - Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement., 7(3), 280–292.
49. Tanner C.M., Ottman R., Goldman S.M., et al., (1999) - Parkinson disease in twins: an etiologic study, JAMA., 281(4), 341–346.
50. Tesseur I., Van Dorpe J., Spittaels K., Van den Haute C., Moechars D., Van Leuven F., (2000) -Expression of human apolipoprotein E4 in neurons causes hyperphosphorylation of protein tau in the brains of transgenic mice. Am J Pathol 156, 951–964.
51. Van Dam D., D'Hooge R., Staufenbiel M., Van Ginneken C., Van Meir F., De Deyn P.P., (2003) -Age-dependent cognitive decline in the APP23 model precedes amyloid deposition. Eur J Neurosci., 17, 388–396.
52. Wilson R.S., Schneider J.A., Bienias J.L., Evans D.A., Bennett D.A., (2003) - Parkinsonian like signs and risk of incident Alzheimer disease in older persons, Arch Neurol., 60(4), 539-44.
53. Wirths O., Bayer, T.A., (2008) - Motor impairment in Alzheimer's disease and transgenic Alzheimer's disease mouse models, Genes, Brain and Behavior, 7, 1–5.4.
54. Wirths O., Weis J., Kayed R., Saido T.C., Bayer T.A., (2007) – Age-dependent axonal degeneration in an Alzheimer mouse model. Neurobiol Aging., 28, 1689–1699.
55. Wirths O., Weis J., Szczygielski J., Multhaup G., Bayer, T.A., (2006) - Axonopathy in an APP/PS1 transgenic mouse model of Alzheimer's disease. Acta Neuropathol., 111, 312–319.
56. Zimprich A., Benet-Pagès A., Struhal W., et al. (2011) - A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease, Am J Hum Genet., 89(1), 168–175.