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Mini Review

The Unsolved Mystery of PARK3 Locus of Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disease, characterized by debilitating symptoms of tremor, rigidity and bradykinesia. Usually the onset of PD is late in life, ~60 years old, and the rate of PD is increased with age. In case it is seen before the age of 50, it is called young-onset PD. The cause of Parkinson's disease is generally unknown, but believed to involve both genetic and environmental factors. In 1996, the mapping and subsequent identification of the first mutations responsible for PD were reported. Since then, causative locus/genes were identified from familial PD patients as PARK1 to PARK23 in order. PARK3 was identified as a 3.2 cM region on 2p13 in 2 families by Gasser., *et al.* in 1998 and including 14 genes. Among them, SPR might be a critical gene to cause PD, however, it is still controversial. In this review, we would like to summarize and discuss the current knowledge of PARK3 locus and function of SPR.

Keywords: *Parkinson's Disease; PARK3; SPR; BH4; SNP*

Abbreviations

BH4: Tetrahydrobiopterin; LOD: Logarithm of the Odds; PD: Parkinson's Disease; SNP: Single-Nucleotide Polymorphism; SPR: Sepiapterin Reductase; TH: Tyrosine Hydroxylatse

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease, characterized by debilitating symptoms of tremor, rigidity and bradykinesia. Usually the onset of PD is late in life, ~60 years old, and the rate of PD is increased with age. In case it is seen before the age of 50, it is called young-onset PD. The cause of Parkinson's disease is generally unknown, but believed to involve both genetic and environmental factors. In 1996, the mapping and subsequent identification of the first mutations responsible for PD [1,2]. Since then, causative locus/genes were identified from familial PD patients as PARK1 to PARK23 in order. PARK3 was identified as a 3.2 cM region on 2p13 in 2 families by Gasser., *et al.* in 1998 [3].

Discussion

Gasser., *et al*. described a genetically linked haplotype on 2p13, which is composed of markers D2S2115, D2S291, D2S2111, D2S2109, D2S2110, D2S145 and D2S1394 in familial PD patients from southern Denmark and northern Germany [3]. In 2001, West., *et al*. the same group, further analyzed coding sequence of candidate 14 genes of these families to identify the causative gene. However, within the region, they could not identify any potential pathogenic mutations, despite of single nucleotide polymorphisms in NP220, NN84AG, Ccth, PIR1, GCS1 and SEMAW [4].

DeStefano., *et al*. found that PARK3 influences age of onset in PD by genome--wide linkage analysis using variance-component methodology in the GenePD study (D2S1777, MaxLOD = 2.08 at 99 cM) [5]. In this region, they proposed the TGF-a, cytochrome P450, SPR and CML2 as candidates. Similarly, Karamohamed., *et al*. analyzed SNP in 2.2 Mb region from 527 patients of 264 families and found that a hap-

lotype at PARK3 locus influences onset age for PD. A mean age of TT homozygotes for rs1876487 (G/T) is 7.4-year younger than that of GT and GG genotypes. Interestingly, two SNPs, rs1876487 and rs1150500, flanking SPR genes were associated with younger onset of PD [6].

In 2004, a genome-wide linkage study was performed in 227 affected sibling pairs from 199 pedigrees with PD in Europe and US. 4 regions including 2p11-q12 were newly identified. This region was located next to PARK3 locus ~ 17 cM away [7].

To extend the study from Karamohamed's group, Sharma *et al.*, performed SNP analysis around SPR region in 122 European sibship families and found higher LOD scores from two SPR-flanking markers D2S2110 and D2S1394 and seven SNP markers around SPR gene. They identified strong linkage disequilibrium block of 45 kb including entire SPR gene [8].

SPR plays an important role in the biosynthesis of tetrahydrobiopterin (BH4) as it catalyzes the NADPH-dependent reduction of various carbonyl substances, including derivatives of pteridines, such as sepiapterin and 6-Pyruvoyl-tetrahydrobiopterin. The product of latter, BH4, is a cofactor for phenylalanine hydroxylase, tyrosine hydroxylase and tryptophan hydroxylase. Therefore, it is BH4 is important to convert tyrosine to L-dopa, which is a precursor of dopamine. SPR knockout mice were generated by Yang et al and Takazawa., *et al.* in 2006 and 2008, respectively and appeared lethality by 8 weeks after birth [9,10]. The KO mice showed a tremor-like phenotype and the content of monoamine, namely dopamine, noradrenaline and serotonin in the brain are strongly reduced. Interestingly, the level of tyrosine hydroxylase was reduced to 10% only in the brain, not in adrenal gland, suggesting that TH protein amounts in the brain are dependent on the amount of BH4 [9].

Human patients with SPR mutation has been reported by Blau., *et al*, Bonafe., *et al*, and other groups. Mutations with R150G, 5bp del, -13G-A, P163L, K251X and G102C, in SPR gene cause dopa responsive dystonia, indicating the importance of SPR for extrapyramidal motor system [11-16]. Postmortem brain in PD patients appeared 4 times increase of SPR level by real time RT-PCR, but the other BH4 synthesis enzymes were not affected, suggesting that SPR might play in a toxic way in PD or be up-regulated to compensate insufficient amount of BH4 and/or dopamine [17].

According to the biochemical function, it is likely that mutation in SPR gene cause dystonia/PD. However, it is still controversial whether SPR is the causative gene for PD or not. In 1999, Klein., *et al.* analyzed 85 German PD patients and 85 controls for shared markers on chromosome 2p. They could not find the linkage on the 2p, suggesting that mutation on 2p is not a common cause of PD [18].

In the Genetic Epidemiology of Parkinson Disease (GEO-PD), SNP analysis for 6547 cases and 9321 controls was performed by Sharma., *et al.* in 2011 [19]. In total, there is no association with the SPR gene. However, they reported patients from North European/Scandinavian descent for rs1876487 has strong association (odds ratio = 0.82; p = 0.003). This result suggests that the association is founder effect.

Next to PARK3, the association between SNP in rs7577851, located in the 16th intron of AAK1 gene in the 2p14, and onset of PD was found by Latourelle and colleagues ($p = 8.7x10^{-6}$) [20]. The SNP was located in 16th intron of AAK1 gene, which regulates endocytosis by phosphorylating the mu^{-2} subunit of adaptor protein-2.

Besides of SPR gene, SFXN5 and TGFa in 2p13 were already confirmed not to correlate with PD [21-22]. Recently, Deng's group analyzed two F--box only proteins, FBXO41 and FBXO48, located in 2p13.2 and 2p13.3, respectively from Chinese Han patients with PD [23-24]. Statistically, they could not find any significance in both genes, however, the frequency of rs526106 A allele in FBXO41 was higher in female patients with PD.

Conclusion

In summary, after ~20 years from the finding of PARK3 locus, the causative gene is still controversial. Although the importance of SPR gene for producing dopamine was confirmed in vitro and in vivo using knockout mice, only founder's effect was reported in northern Europe so far. In near future, the global analysis using NGS might be helpful to uncover the mystery of PARK3.

Conflict of Interest

The authors declare no conflict of interest.

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