宣武医院刘疏影医师在Lancet Neurology上发文揭示帕金森病基因型-表型机制

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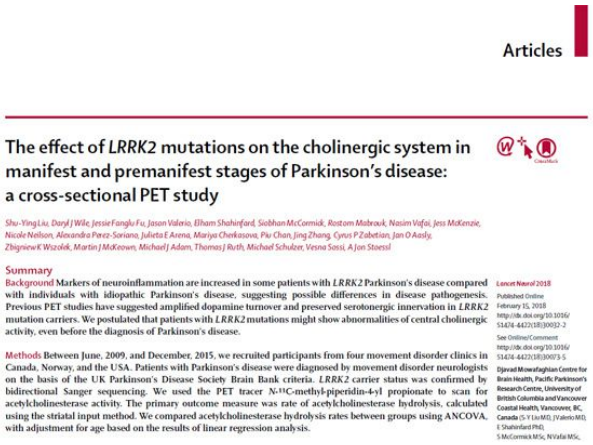
首都医科大学宣武医院神经内科刘疏影医师于2月15日在《Lancet Neurology》（IF 26.28）上发表论文，题目为“The effect of LRRK2 mutations on the cholinergic system in manifest and premanifest stages of Parkinson's disease: a cross-sectional PET study”。刘疏影医师为第一作者，加拿大哥伦比亚大学A Jon Stoessl为责任作者。该研究揭示了帕金森病致病基因LRRK2携带者及患者遗传表型的神经递质机制。

TOP



Articles

The effect of *LRRK2* mutations on the cholinergic system in manifest and premanifest stages of Parkinson's disease: a cross-sectional PET study

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Summary

Background Markers of neuroinflammation are increased in some patients with *LRRK2* Parkinson's disease compared with individuals with idiopathic Parkinson's disease, suggesting possible differences in disease pathogenesis. Previous PET studies have suggested amplified dopamine turnover and preserved serotonergic innervation in *LRRK2* mutation carriers. We postulated that patients with *LRRK2* mutations might show abnormalities of central cholinergic activity, even before the diagnosis of Parkinson's disease.

Methods Between June, 2009, and December, 2015, we recruited participants from four movement disorder clinics in Canada, Norway, and the USA. Patients with Parkinson's disease were diagnosed by movement disorder neurologists on the basis of the UK Parkinson's Disease Society Brain Bank criteria. *LRRK2* carrier status was confirmed by bidirectional Sanger sequencing. We used the PET tracer N-^{11}C-methyl-piperidin-4-yl propionate to scan for acetylcholinesterase activity. The primary outcome measure was rate of acetylcholinesterase hydrolysis, calculated using the striatal input method. We compared acetylcholinesterase hydrolysis rates between groups using ANCOVA, with adjustment for age based on the results of linear regression analysis.

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帕金森病是老年人群中最常见的运动障碍性疾病，黑质多巴胺神经元缺失、alpha-突触核蛋白沉积为其特征性病理标志。但是，帕金森病作为一个疾病主体在临床症状体征等疾病表型上存在高度异质性，而相关致病基因繁多，为研究、诊断及治疗带来了诸多挑战。LRRK2基因是晚发型帕金森病最常见致病基因，证据表明其携带者常较非携带者具有更好的认知功能、嗅觉功能、睡眠节律同时疾病进展相对较慢，血、脑脊液炎症因子指标较高，而目前上述临床特点即基因表型产生的机制尚不能由已知证据解释。

刘疏影医师在首都医科大学脑科学研究院与加拿大英属哥伦比亚大学联合培养期间发现，LRRK2携带者脑内乙酰胆碱能系统功能上调能够解释该亚型的临床特征，同时此乙酰胆碱能递质增加可能与该基因相关的炎症系统激活互为因果。研究者使用胆碱能特异性分子标志物11C-PMP及正电子断层计算机扫描成像发现，临床前期及临床期的LRRK2携带者大脑皮质、默认网络相关脑区、边缘网络相关脑区及丘脑的乙酰胆碱酯酶水解速率均明显上升，

提示LRRK2基因对脑内乙酰胆碱能递质具有上调作用；正常老年人脑内乙酰胆碱酯酶靶点数量水平随年龄上升逐渐下降，呈负相关关系；特发性帕金森病患者脑内乙酰胆碱酯酶靶点数量下降。经年龄校正，LRRK2携带者脑内乙酰胆碱能活性上调依然存在。

该研究确定了LRRK2携带者脑内乙酰胆碱能系统较特发性帕金森病患者反常上调，该上调可能解释了该亚型的临床特点，并可能与乙酰胆碱在炎症调节中的重要作用相关。以上研究结果为进一步探索LRRK2亚型的特殊性及炎症机制致帕金森病的研究前景提供了证据支持。

相关附件

论文原文.pdf

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