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Clinical variability in Chinese families with Parkinson disease and SNCA duplication, including the shortest 139kb duplication

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SNCA gene copy number gain has been reported as a genetic cause for autosomal dominant Parkinson's disease (PD) [1], but it has not been described in Chinese patients. We identified two PD families (Fig. 1A and B) with *SNCA* duplications (1.04%) among 193 Chinese patients with familial PD: a 139kb duplication in family A and a 5.4Mb duplication in family B (Fig. 1C). The 139kb duplication is the smallest one so far reported [2]. The two index patients shared many clinical phenotypes including a positive family history, bradykinesia and rigidity, and non-motor symptoms such as REM sleep behavior disturbance (RBD), anosmia, constipation and autonomic dysfunction, and depression.

Proband 1 (AIII: 1) in family A came to the movement disorder Clinic at age 63 with visual hallucinations which had started one month earlier, and was diagnosed with PD. He had no tremor or postural instability but presented with bradykinesia and rigidity of the right arm that gradually spread to the left side. Dystonia was also observed in the left leg, and improved after sleep. RBD and hyposmia developed at the ages of 51 and 55 respectively. He had dementia based on a decreased Mini–Mental Status Examination (MMSE) score with dysfunction in all five cognitive subdomains, especially in memory (supplementary Table). Severe reduction of DAT binding was present bilaterally in the anterior and posterior putamen, and caudate nuclei (Fig. 1 E) (Fig. 1 G) as well as increased FDG uptake putamina bilaterally (referred to as the PD-related metabolic pattern (PDRP)) (Fig. 1F). Following administration of 300mg levodopa and 2mg trihexyphenidyl daily, his condition was greatly improved. His younger brother (AIII:8), who was evaluated at the age of 45 years, developed slowness and clumsiness of the left arm at age 24 without progression, and with absence of non-motor symptoms and normal DAT and PET imaging (Fig. 1E and F). Since he was on sodium valproate treatment (1.5g/day) due to epilepsy which had developed at the age of 21 years, he was thought to have drug induced parkinsonism. The younger aunt of the proband (AII:5, 75yo), presented with tremor, bradykinesia and postural instability, and also suffered from depression. An older aunt (AII:4, 80yo) was a *SNCA* duplication carrier with no clinical symptoms.

The onset of PD in the proband 2 (BIII:1) of family B was 38 years. Additional distinct motor symptomatology included dragging his feet, and constant falling. He had depression, constipation, hyposmia and RBD but no hallucinations. Although the blood pressure on standing was normal, he suffered from orthostatic dizziness from time to time. His neuropsychological tests indicated normal MMSE score but some deficits in the visuospatial domain and abnormal in Similarity test and Delayed recall for executive and memory domains respectively within two consecutive years. He was diagnosed with mild cognitive impairment (MCI). There was a marked reduction of DAT uptake in the posterior putamen (Fig. 1E). He had a good response to levodopa started at the age of 38 years, but additional combinations of drugs (with a levodopa equivalent daily dose of 1500mg) failed to control progress for 8 years. He subsequently underwent deep brain stimulation (DBS). The proband's mother (BII:1) presented with tremor, bradykinesia, rigidity and postural instability, and she had a good response to levodopa. She had similar non-motor symptoms as her son, except for an absence of autonomic dysfunction. The proband's aunt (BII:3) was diagnosed with PD at 34 years of age and committed suicide 5 years after onset. The age of onset of affected individuals in family B was usually young but that was not a triplication or homozygous duplication. His younger brother (BIII:2) was a carrier but remained clinically unaffected.*SNCA*-related Parkinson's disease displays a heterogenous range of clinical phenotypes [1,3]. *SNCA* copy number variants are associated with specific clinical features such as impaired cognitive functions and psychiatric disorders [4]. In our study, only 50.0% (2/4) and 66.6% (2/3) of individuals with *SNCA* duplication in family A and family B, respectively, developed PD by age 50, suggesting its incomplete penetrance as previously reported. We noted an age of onset (AAO) of 61 years for proband 1 (AIII:1) with a shorter duplication size of SNCA, whose 80-year-old aunt (AII:4) was asymptomatic. This contrasted to AAO of 38 years for proband 2 (BIII:1) and his mother, with an AAO of 69 years. Target-based next-gene sequencing encompassing 40 PD risk genes (including *SNCA*) did not find additional known risk factors for both probands. Increased disease severity and penetrance associated with duplication size [5] might be validated in future studies.

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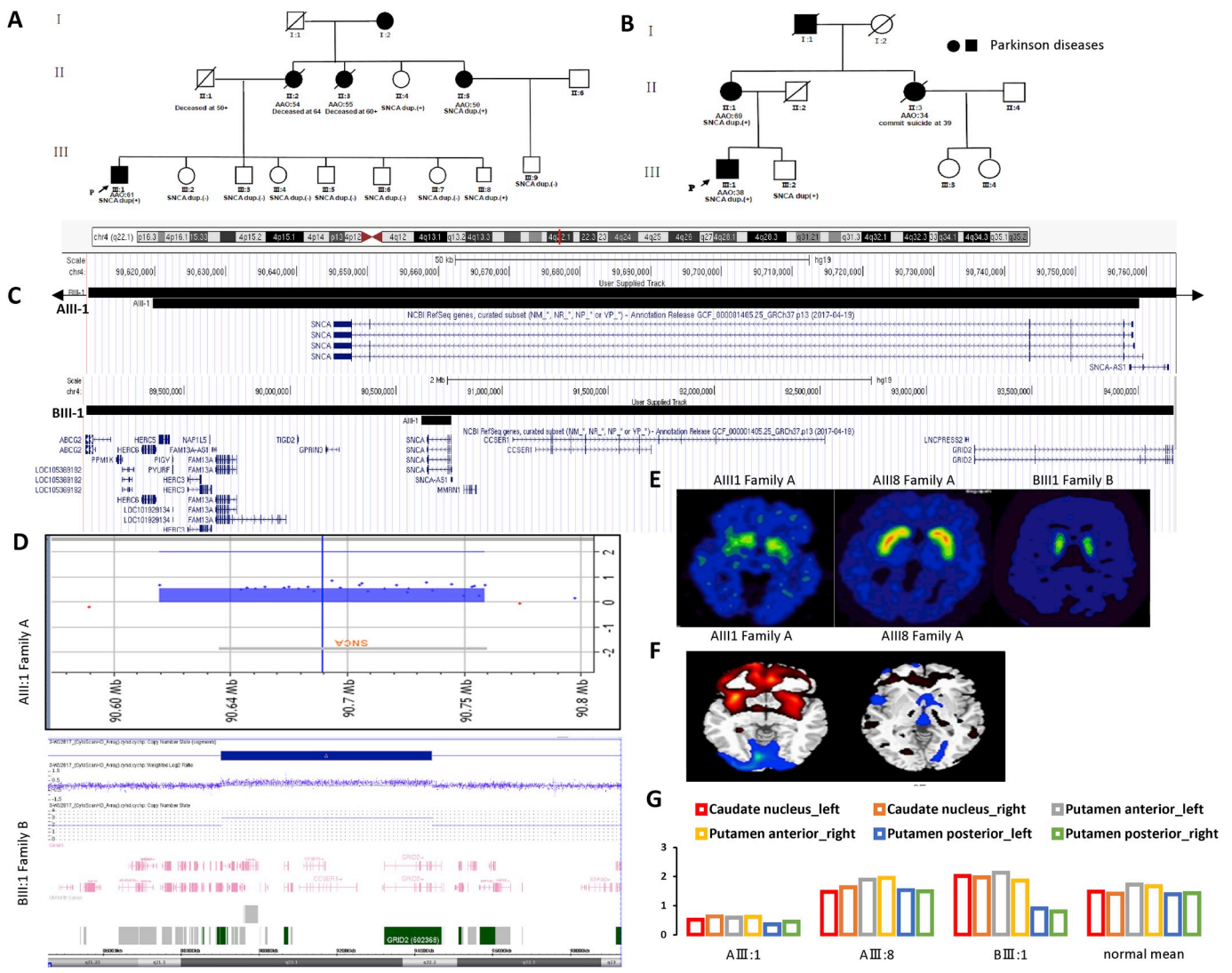

Fig. 1. Pedigree of the two families, *SNCA* duplications and neuroimage analysis. A) pedigree of family A; B) pedigree of family B; C) A genome review of *SNCA* duplication in the two probands of family A (AIII-1) and family B (BIII-1) (black colored custom track) (hg19). D) aCGH scatter plot of the proband of family A: a 139kb duplication (chr4: 90,619,755-90,758,893) containing *SNCA* gene without 5UTR. CytoScan HD plot of the proband of family B: a 5,421kb duplication (chr4: 89,030,559–94,451,215) encompassing tens of genes. E) DAT-PET and FDG-PET study. A severe reduction of DAT in proband of family A (AIII:1), no significant alterations in DAT-PET in the younger brother in family A (AIII:8) and a mild reduction of DAT was demonstrated in proband of family B (BIII:1). F) FDG–PET showed that hypermetabolism of FDG signal were localized in the bilateral putamen in proband of family A (AIII:1) but no significant alterations in the younger brother in family A (AIII:8). G) Uptake ratios of DAT in [11C]-CFT PET in the probands (AIII:1 and BIII:1) and other family member (AIII:8) carrying *SNCA* duplication. All images were processed using SPM5 software implemented in Matlab7.4.

Conclusion

Herein, we reported the first two Chinese families with *SNCA* duplications and identified the smallest duplication involving the *SNCA* locus to date.

Ethical compliance statement

All participants signed informed consent and the study was approved by the Ethics Committee of the Faculty of Medicine at Huashan hospital.

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Author's contribution

Yu-Jie Du and Yan Shen drafted the manuscript; Yi-Xuan Wang, Yi-Min Sun, Feng-Tao Liu, Chen Chen, Kui Chen contributed to clinical infomration collection including the cognitive assessments. Chuan-Tao Zuo was responsible for the PET/CT neuroimaging study and data evaluation; Jian Wang, Jian-Jun Wu, Huan Yu made PD diagnosis, interpreted clinical data and prescribed therapies. Yu An designed the study, genetic analysis and interpretation, supervised the study, revised the manuscript and made the final approval for submission and publication.

Declaration of competing interest

The authors do not have any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.09.030.

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