Functional monoamine oxidase B gene intron 13 polymorphism predicts putaminal dopamine turnover in de novo Parkinson's disease

Matthias Löhle, Graziella Mangone, Martin Wolz, Bettina Beuthien-baumann, Liane Oehme, Jörg van den Hoff, Jörg Kotzerke, Heinz Reichmann, Jean-christophe Corvol, Alexander Storch

7. Mulak A, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterol 2015;21(37):10609-10620.
8. Bedarf JR, Hildebrand F, Coelho LP, et al. Functional implications of microbial and viral gut metagenome changes in early stage L-DOPA-naive Parkinson's disease patients. Genome Med 2017; 9(1):39.
9. Heintz-Buschart A, Pandey U, Wicke T, et al. The nasal and gut microbiome in Parkinson's disease and idiopathic rapid eye movement sleep behavior disorder. Mov Disord 2018;33(1): 88-98.
10. Hill-Burns EM, Debelius JW, Morton JT, et al. Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome. Mov Disord 2017;32(5):739-749.
11. Keshavarzian A, Green SJ, Engen PA, et al. Colonic bacterial composition in Parkinson's disease. Mov Disord 2015;30(10): 1351-1360.
12. Minato T, Maeda T, Fujisawa Y, et al. Progression of Parkinson's disease is associated with gut dysbiosis: two-year follow-up study. PLoS One 2017;12(11):e0187307.
13. Petrov VA, Saltykova IV, Zhukova IA, et al. Analysis of gut microbiota in patients with Parkinson's disease. Bull Exp Biol Med 2017; 162(6):734-737.
14. Sampson TR, Debelius JW, Thron T, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell 2016;167(6):1469-1480. e12.
15. Scheperjans F. Gut microbiota, 1013 new pieces in the Parkinson's disease puzzle. Curr Opin Neurol 2016;29(6):773-780.
16. Scheperjans F, Aho V, Pereira PA, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord 2015; 30(3):350-358.
17. Gray MT, Munoz DG, Gray DA, et al. Alpha-synuclein in the appendiceal mucosa of neurologically intact subjects. Mov Disord 2014;29(8):991-998.
18. Svensson E, Horvath-Puho E, Stokholm MG, et al. Appendectomy and risk of Parkinson's disease: A nationwide cohort study with more than 10 years of follow-up. Mov Disord 2016;31(12): 1918-1922.
19. Marras C, Lang AE, Austin PC, et al. Appendectomy in mid and later life and risk of Parkinson's disease: A population-based study. Mov Disord 2016;31(8):1243-1247.
20. Palacios N, Fitzgerald K, Roberts AL, et al. A prospective analysis of airborne metal exposures and risk of Parkinson disease in the nurses' health study cohort. Environ Health Perspect 2014;122(9):933-938.
21. Palacios N, Fitzgerald KC, Hart JE, et al. Air pollution and risk of Parkinson's disease in a large prospective study of men. Environ Health Perspect 2017;125(8):0807011.
22. Mendes A, Goncalves A, Vila-Cha N, et al. Appendectomy may delay Parkinson's disease Onset. Mov Disord 2015;30(10): 1404-1407.
23. Houser MC, Chang J, Factor SA, et al. Stool immune profiles evince gastrointestinal inflammation in Parkinson's disease. Mov Disord 2018 [Epub ahead of print].
24. de Oliveira Machado SL, Bagatini MD, da Costa P, et al. Evaluation of mediators of oxidative stress and inflammation in patients with acute appendicitis. Biomarkers 2016;21(6):530-537.
25. Ferris M, Quan S, Kaplan BS, et al. The global incidence of appendicitis: a systematic review of population-based studies. Ann Surg 2017;266(2):237-241.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Functional Monoamine Oxidase B Gene Intron 13 Polymorphism Predicts Putaminal Dopamine Turnover in De Novo Parkinson's Disease

Matthias Löhle, MD,[1,2*] Graziella Mangone, MD, PhD,[3] Martin Wolz, MD,[4] Bettina Beuthien-Baumann, MD,[5,6,7] Liane Oehme, PhD,[5] Jörg van den Hoff, PhD,[6] Jörg Kotzerke, MD,[5] Heinz Reichmann, MD,[8] Jean-Christophe Corvol, PhD[3] and Alexander Storch, MD[1,2*]

[1]Department of Neurology, University of Rostock, Rostock, Germany [2]German Centre for Neurodegenerative Diseases (DZNE) Standort Rostock, Rostock, Germany [3]Sorbonne Université, INSERM UMRS1127 and CIC-1422, CNRS UMR7225, Assistance Publique Hôpitaux de Paris, ICM, Department of Neurology, Hôpital Pitié-Salpêtrière, Paris, France [4]Department of Neurology, Elblandklinikum Meißen, Meissen, Germany [5]Department of Nuclear Medicine, Technische Universität Dresden, Dresden, Germany [6]Positron Emission Tomography Division, Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany [7]German Cancer Research Centre (DKFZ), Radiology, Heidelberg, Germany [8]Department of Neurology, Technische Universität Dresden, Dresden, Germany

ABSTRACT: Objective: The objective of this study was to evaluate the effects of common functional polymorphisms in genes involved in dopamine metabolism on striatal dopamine turnover in de novo Parkinson's disease (PD).

***Corresponding authors**: Drs. Matthias Löhle and Alexander Storch, Department of Neurology, University of Rostock, Gehlsheimer Straße 20, 18147 Rostock, Germany; matthias.loehle@med.uni-rostock.de, alexander.storch@med.uni-rostock.de

Funding agencies: The initial randomized trial was supported by an unrestricted grant from Pfizer Pharma, Berlin, Germany. The research leading to these results has received addition funding from the program "Investissements d'Avenir" ANR-10-IAIHU-06. The financial sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Relevant conflicts of interests/financial disclosures: A.S. and H.R. have received unrestricted research grants, speaker honoraria, and consultancy fees from Pfizer Pharma GmbH, Berlin, Germany. The other authors have no other conflict of interest to report related to this article.

Received: 27 March 2018; **Revised:** 23 May 2018; **Accepted:** 25 May 2018

Published online 14 September 2018 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27466

Methods: This was an observer-blinded cohort study investigating effects of common functional polymorphisms in dopa decarboxylase (*DDC*, rs921451), monoamine oxidase B (*MAOB*; rs1799836), catechol-O-methyltransferase (*COMT*, rs4680), and dopamine transporter/solute carrier family 6 member 3 (*DAT/SLC6A3*, variable number tandem repeats) genes on ^{18}F-fluorodopa uptake and an effective distribution volume ratio (inverse of dopamine turnover) measured by ^{18}F-fluorodopa PET in 28 untreated PD patients.
Results: Patients carrying the $MAOB^{CC/(C)/CT}$ genotype (low/intermediate enzyme activity) had a lower dopamine turnover in the putamen (higher mean effective distribution volume ratio) when compared with patients with $MAOB^{TT/(T)}$ genotype (high enzyme activity). Striatal PET measures were not different between variants in the remaining genes.
Conclusions: The *MAOB* (rs1799836) polymorphism predicts putaminal dopamine turnover in early PD with the $MAOB^{TT}$ allele linked to high enzyme activity leading to higher intrinsic dopamine turnover, which has been demonstrated to constitute a risk factor for motor complications.

Key Words: dopamine metabolism; positron emission tomography (PET); dopamine turnover; monoamine oxidase B (MAOB); functional gene polymorphisms; Parkinson's disease

Parkinson's disease (PD) is characterized by a progressive loss of dopaminergic neurons of the substantia nigra pars compacta projecting to the striatum. Motor symptoms only emerge after a substantial loss of striatal dopaminergic nerve terminals has already occurred,[1] which implies that a variety of compensatory mechanisms take place in the preclinical phase of PD.[2] One of these compensatory mechanisms is an increase of putaminal dopamine turnover, which can be measured with ^{18}F-fluorodopa PET even earlier than changes in dopamine synthesis and storage.[3–6] Moreover, an extensively elevated dopamine turnover in early PD has been discussed as intrinsic risk factor for the development of motor complications.[7,8] Conversely, mild elevation of putaminal dopamine turnover in de novo PD has been shown to be associated with a lower risk for motor complications.[9]

Although previous studies have demonstrated that age and levodopa treatment as known clinical risk factors for motor complications correlate with dopamine turnover in early PD,[8,10] it remains unclear whether functional polymorphisms in genes involved in dopamine metabolism intrinsically contribute to individual changes of dopamine turnover. Thus, we aimed to investigate whether common functional polymorphisms in the dopa decarboxylase (*DDC*, rs921451),[11] monoamine oxidase B (*MAOB*, rs1799836),[12] catechol-O-methyltransferase (*COMT*, rs4680)[13] and dopamine transporter/solute carrier family 6 member 3 (*DAT/SLC6A3*, variable number tandem repeats)[14–16] genes were predictive for striatal ^{18}F-fluorodopa uptake and dopamine turnover measured by extended ^{18}F-fluorodopa PET imaging[3,10,17,18] in de novo PD.

Participants and Methods

This observer-blinded cohort study analyzed participants with diagnostic criteria defined PD from a previous randomized clinical trial[10,19] who had received extended ^{18}F-fluorodopa PET imaging prior to any antiparkinsonian treatment. Participants underwent genetic testing of selected functional polymorphisms during subsequent follow-up. We included all remaining participants from the PET study for whom blood collection was possible. From the original cohort of 40 patients, 6 had died (2 from pulmonary embolism, 4 from unknown causes), 4 were lost to follow-up, and 2 had been diagnosed with essential tremor (both had normal putaminal K_{occ} values).

Motor symptoms and activities of daily living were estimated using the Unified PD Rating Scale (UPDRS),[20] disease stage was assessed with the Hoehn and Yahr scale.[21] Clinical evaluations were carried out in drug-naïve patients by movement disorder trained physicians blinded to PET data (M.L., M.W.). Clinical and genetic testing had approval from the ethics committee at Technische Universität Dresden, Dresden, Germany Dresden (EK91052003), the clinical trial was registered with ClinicalTrials.gov (NCT00153972). Written informed consent was obtained from all participants.

PET measurements were carried out in drug-naïve participants using a 3D ECAT EXACT HR + system (Siemens/CTI, Knoxville, Tennessee) as described previously[3,10] (refer to Supplementary Methods for details). In short, we applied a tissue reference model in which the activity curve of the occipital cortex served as input function for calculation of the tissue input uptake rate constant K_{occ} and effective distribution volume ratio (EDVR).[17,18] K_{occ} and (EDVR) from the left and right sides were averaged for each scan.[10]

Genotyping of the common functional polymorphisms *DDC* (rs921451),[11] *MAOB* (rs1799836),[12] *COMT* (rs4680),[13] and *DAT/SLC6A3* (variable number tandem repeats, VNTR)[14–16] was performed as described previously (refer to Supplementary Methods for details). In brief, genomic DNA was extracted by standard methods from venous blood samples and polymorphisms were analyzed by an allelic discrimination Taqman assay (Applied Biosystems, Foster City, California). Positive control DNA template and negative control (DNA/RNA-free water) were included in each genotyping panel. *DAT*-VNTR polymorphism was determined by standard polymerase chain reaction

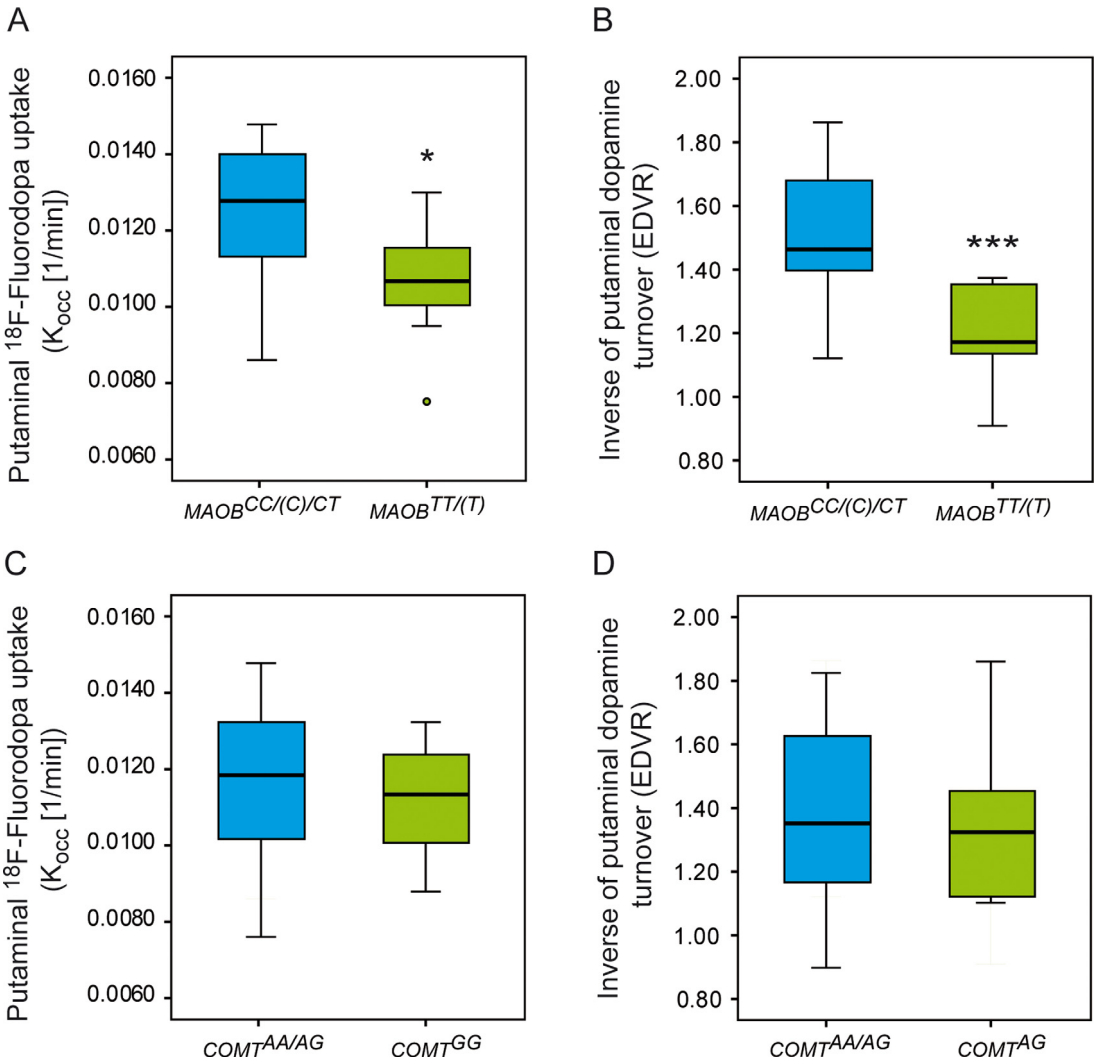

FIG. 1. Effects of monoamine oxidase B (*MAOB*) rs1799836 and catechol-O-methyl transferase (COMT) rs4680 genotypes on putaminal ^{18}F-fluorodopa-PET measures in de novo Parkinson's disease patients. The boxplots show putaminal ^{18}F-fluorodopa-PET uptake (A,C) and putaminal effective distribution volume ratio (EDVR) as the inverse of the dopamine turnover dopamine (B,D) with respect to the *MAOB* rs1799836 genotype (A,B) and the *COMT* rs4680 genotype (C,D). In the plots, boxes represent the interquartile range, horizontal lines the medians, and the antennas the range excluding outside values (defined as values beyond lower/upper quartile ± 1.5 times interquartile range). $^{*}P < .05$ and $^{***}P < .001$ when compared with $MAOB^{C(C)/CT}$ (unpaired 2-sided *t*-test). [Color figure can be viewed at wileyonlinelibrary.com]

(PCR) followed by agarose gel electrophoresis using the KAPA 2G Fast ReadyMix PCR Kit (KK5101, Roche, Basel, Switzerland). To investigate effects of gene polymorphisms on PET measures, patients were dichotomized into low/intermediate enzyme/transporter activity ($DDC^{CC/CT}$, $MAOB^{CC/(C)/CT}$, $COMT^{AA/AG}$, $DAT^{\leq 9/\leq 10}$) and high enzyme/transporter activity (DDC^{TT}, $MAOB^{TT/(T)}$, $COMT^{GG}$, $DAT^{10/10}$; Supplementary Table S1).[11–16]

Statistical analyses were performed with IBM SPSS statistics, version 23.0 (IBM Corporation, Armonk, New York). Comparisons of demographic, clinical, genetic, and PET data between the groups were made with unpaired *t*-test or Mann–Whitney *U* test, or χ^2 test, as appropriate. To account for potentially confounding factors on the comparison of PET measures, we additionally performed an analysis of covariance (ANCOVA), in which age, UPDRS part III score, and symptom duration were entered as continuous covariates and gender as fixed factor. If not mentioned otherwise, data are displayed as means ± standard deviation or numbers and percentages. The significance level (2-tailed) was set at $P < .0125$ to correct for multiple comparisons using the Bonferroni method.

Results

Our cohort included 28 patients (19 [68%] men, 9 [32%] women; mean age 60.3 ± 9.4 years), who had been diagnosed 1.8 ± 2.0 years after the onset of motor symptoms. Mean age at disease onset was 57.3 ± 9.2 years, and mean UPDRS motor score was 19.4 ± 7.6. Genotyping revealed allele frequencies

TABLE 1. ^{18}F-fluorodopa-PET measures in de novo Parkinson's disease patients with respect to *MAOB* rs1799836 genotypes

	Overall cohort	$MAOB^{CC/(C)/CT}$	$MAOB^{TT/(T)}$	P^a	*F* and *P* values from ANCOVA analysis[b]
Participants, n	28	15	13		
K_{occ} (1/min), ^{18}F-fluorodopa uptake					
Caudate nucleus	0.0162 ± 0.0024	0.0170 ± 0.0028	0.0154 ± 0.0018	.091	$F = 0.781$, $P = .387$
Putamen	0.0117 ± 0.0019	0.0124 ± 0.0020	0.0108 ± 0.0015	.023	$F = 4.450$, $P = .047$
Anterior putamen	0.0154 ± 0.0025	0.0163 ± 0.0027	0.0145 ± 0.0020	.056	$F = 2.969$, $P = .100$
Posterior putamen	0.0081 ± 0.0017	0.0084 ± 0.0017	0.0078 ± 0.0016	.341	$F = 0.447$, $P = .511$
EDVR, inverse of DA turnover					
Caudate nucleus	2.00 ± 0.38	2.09 ± 0.34	1.87 ± 0.39	.113	$F = 0.781$, $P = .387$
Putamen	1.38 ± 0.25	1.52 ± 0.23	1.20 ± 0.14	**<.001**	**$F = 13.863$, $P = .001$**
Anterior putamen	1.86 ± 0.38	2.04 ± 0.37	1.66 ± 0.30	**.006**	$F = 5.963$, $P = .024$
Posterior putamen	0.98 ± 0.20	1.08 ± 0.22	0.86 ± 0.10	**.003**	**$F = 8.762$, $P = .007$**

Data are means ± standard deviations. ANCOVA, analysis of covariance; EDVR, Effective distribution volume ratio from ^{18}F-fluorodopa positron emission tomography; *MAOB*, monoamine oxidase B. K_{occ}, ^{18}F-fluorodopa uptake from positron emission tomography.

[a] *P* values are from unpaired 2-sided *t*-tests comparing $MAOB^{C(C)/CT}$ and $MAOB^{TT}$ alleles. *P* values of < .0125 (2-sided) were considered significant to correct for multiple comparisons using the Bonferroni method and have been marked in bold.

[b] *F* and *P* values are from ANCOVA comparing $MAOB^{CC/(C)/CT}$ and $MAOB^{TT/(T)}$ alleles and controlling for the candidate covariates age, UPDRS part III motor score as a measure of disease severity and symptom duration as well as gender as fixed factor. *P* values of < .0125 (2-sided) were considered significant to correct for multiple comparisons using the Bonferroni method and have been marked in bold.

similar to those reported in databases for all polymorphisms tested (Supplementary Table S1). All genotypes were in the Hardy-Weinberg equilibrium. We did not detect significant differences of demographic and clinical variables after stratification for genotypes in the selected gene variants (Supplementary Table S2).

Patients carrying the $MAOB^{CC/(C)/CT}$ (rs1799836) genotype, which is associated with low/intermediate enzyme activity in the brain,[12] had a higher EDVR (lower dopamine turnover) in the whole putamen compared to patients carrying the $MAOB^{TT/(T)}$ genotype that has been linked to high enzyme activity (Fig. 1, Table 1). We also observed slightly higher ^{18}F-fluorodopa uptake (K_{occ}) in the $MAOB^{CC/(C)/CT}$ (rs1799836) genotype, which was not significant after correction for multiple comparisons. No differences were detected between genotypes of the remaining genes (Fig. 1, Supplementary Tables S3-S5). The difference in EDVR between *MAOB* (rs1799836) genotype groups was confirmed in separated analysis of anterior and posterior portions of the putamen with similar distribution between the 2 putaminal regions. In contrast, we found no differences for K_{occ} and EDVR between groups in the caudate nucleus for all genotypes (Table 1).

Because PET measures had been reported to potentially correlate with age, gender, and disease severity,[8,9] we additionally calculated ANCOVAs to control for the candidate covariates age, UPDRS motor score, symptom duration, and gender. Adjustment for these potential confounders largely confirmed the differences of putaminal EDVR between the *MAOB* (rs1799836) genotype groups (Table 1). No significant differences of PET measures were observed for the remaining genotype comparisons (Supplementary Tables S3-S5). Moreover, we did not identify significant interactions between genotype groups when calculating ancillary ANCOVAs for K_{occ} and EDVR with Bonferroni correction.

Discussion

We provide first evidence that a common functional variation in the *MAOB* gene leads to differences in putaminal dopamine metabolism as measured by extended ^{18}F-fluorodopa PET imaging in patients with early untreated PD. We found that the $MAOB^{CC/(C)/CT}$ rs1799836 genotype (associated with low/intermediate enzyme activity in the brain) resulted in lower putaminal dopamine turnover when compared with the $MAOB^{TT/(T)}$ genotype (high enzyme activity).

^{18}F-fluorodopa uptake (K_{occ} from standard PET scanning 10-60 minutes after tracer administration) is assumed to mainly reflect tracer influx and central DDC activity.[22] Previous studies have indicated that common *DDC* polymorphisms (including rs921451) modulate the therapeutic response to levodopa without changing levodopa metabolism in the periphery, suggesting that *DDC* polymorphisms and resulting variations in DDC activity influence bioavailability of dopamine in the CNS.[11] Indeed, subsequent PET studies in healthy volunteers provided evidence that 1 of 4 common *DDC* haplotypes is predictive of ^{18}F-fluorodopa uptake in healthy humans.[23] Although this haplotype contains a major allele that is in linkage disequilibrium with rs921451,[23] we did not find any difference of ^{18}F-fluorodopa uptake with respect to *DDC* (rs921451) genotypes in our PD cohort. However, this haplotype is not uniquely defined by this single polymorphism.[23] Further studies are needed to assess the relationship between *DDC* genetics, central DDC activity, and levodopa response in PD.

In contrast to DDC, COMT and MAO-B as catabolizing enzymes in the dopamine metabolism are proposed to particularly influence dopamine turnover as measured by extended ^{18}F-fluorodopa PET protocols.[3,24–26] Accordingly, PD patients carrying the functional

$COMT^{GG/GG}$ (rs4680) genotype associated with low enzyme activity[13] showed lower late ^{18}F-fluorodopa uptake (measure of dopamine turnover) when compared with $COMT^{AA/AA}$ carriers in the frontal cortex but not the striatum.[24] In agreement, *COMT* (rs4680) genotypes in our cohort did not predict striatal dopamine turnover in early PD patients. This observation is in contrast to our findings on MAO-B as the other main dopamine catabolizing enzyme: in close agreement with biochemical analyses showing a correlation of $MAOB^{CC/(C)/CT}$ rs1799836 genotype with low/intermediate enzyme activity in postmortem human brain tissue,[12] our study demonstrated that the $MAOB^{CC/(C)/CT}$ genotype is associated with lower putaminal dopamine turnover. We also observed a nonsignificant increase of ^{18}F-fluorodopa uptake with this genotype, which is in agreement with studies showing that K_{occ} is to some extent sensitive to dopamine turnover even if calculated in the first 90 minutes after tracer injection.[18]

Although previous ^{18}F-fluorodopa PET studies reported that decreased DAT levels are directly associated with higher dopamine turnover,[27] we did not observe any effects of the *DAT/SLC6A3* (VNTR) genotype known to influence DAT expression[14–16] on dopamine turnover in our cohort. The reasons for this discrepancy remain unclear but might be related to differences in DAT level estimation between studies (direct quantification by PET imaging by Sossi and colleagues,[27] only indirect assumption in our approach).

Although we present data on one of the largest PD cohorts with systematic EDVR measurement by PET imaging, our study has several limitations. First, the cohort size and consequently the genotype group sizes are relatively small, which generated the need for statistical adjustment to confounding variables and may limit generalizability to a less homogenous population. Second, our data were generated from white patients selected at one university-based movement disorder outpatient center and is thus primarily reflective for patients of similar background and setting. Third, although patient groups were clinically indistinguishable at the time of PET imaging, we cannot completely exclude that the compositions of the various genotype groups may relevantly differ, particularly because genotype group sizes in some cases were relatively small after dichotomization. On the contrary, statistical adjustment for major demographic and clinical covariates largely confirmed our unadjusted analyses.

Together, our study suggests that the functional *MAOB* gene intron 13 (rs1799836) polymorphism predicts putaminal dopamine metabolism in early untreated PD with the $MAOB^{TT}$ allele linked to high enzyme activity leading to higher intrinsic dopamine turnover, which has been shown to be associated with a higher subsequent risk for motor complications.[9] Future studies are warranted to investigate whether this polymorphism modulates the risk or the time of onset of motor complications in PD and whether individual assessment of this gene polymorphism might be helpful for early risk stratification in PD patients. ●

Acknowledgments: The authors would like to thank all patients and their relatives for their willingness to participate in our study. Furthermore, we are grateful for help of the members of our movement disorders outpatient clinic at Technische Universität Dresden, the PET division of the Helmholtz-Zentrum Dresden-Rossendorf, and the Coordination Center for Clinical trials at Technische Universität Dresden (particularly Uta Schwanebeck and Xina Grählert).

References

1. Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. J Neuro Sci 1973;20:415-455.
2. Calne DB, Zigmond MJ. Compensatory mechanisms in degenerative neurologic diseases. Insights from parkinsonism. Arch Neurol 1991; 48:361-363.
3. Oehme L, Perick M, Beuthien-Baumann B, et al. Comparison of dopamine turnover, dopamine influx constant and activity ratio of striatum and occipital brain with (1)(8)F-dopa brain PET in normal controls and patients with Parkinson's disease. Eur J Nucl Med Mol Imaging 2011;38:1550-1559.
4. Sossi V, de La Fuente-Fernandez R, Holden JE, et al. Increase in dopamine turnover occurs early in Parkinson's disease: evidence from a new modeling approach to PET 18 F-fluorodopa data. J Cereb Blood Flow Metab 2002;22:232-239.
5. Sossi V, de la Fuente-Fernandez R, Holden JE, Schulzer M, Ruth TJ, Stoessl J. Changes of dopamine turnover in the progression of Parkinson's disease as measured by positron emission tomography: their relation to disease-compensatory mechanisms. J Cereb Blood Flow Metab 2004;24:869-876.
6. Sossi V, de la Fuente-Fernandez R, Nandhagopal R, et al. Dopamine turnover increases in asymptomatic LRRK2 mutations carriers. Mov Disord 2010;25:2717-2723.
7. de la Fuente-Fernandez R, Schulzer M, Mak E, Calne DB, Stoessl AJ. Presynaptic mechanisms of motor fluctuations in Parkinson's disease: a probabilistic model. Brain 2004;127:888-899.
8. Sossi V, de la Fuente-Fernandez R, Schulzer M, Adams J, Stoessl J. Age-related differences in levodopa dynamics in Parkinson's: implications for motor complications. Brain 2006;129:1050-1058.
9. Löhle M, Mende J, Wolz M, et al. Putaminal dopamine turnover in de novo Parkinson disease predicts later motor complications. Neurology 2016;86:231-240.
10. Storch A, Wolz M, Beuthien-Baumann B, et al. Effects of dopaminergic treatment on striatal dopamine turnover in de novo Parkinson disease. Neurology 2013;80:1754-1761.
11. Devos D, Lejeune S, Cormier-Dequaire F, et al. Dopa-decarboxylase gene polymorphisms affect the motor response to L-dopa in Parkinson's disease. Parkinsonism Relat Disord 2014;20:170-175.
12. Balciuniene J, Emilsson L, Oreland L, Pettersson U, Jazin E. Investigation of the functional effect of monoamine oxidase polymorphisms in human brain. Hum Genet 2002;110:1-7.
13. Syvanen AC, Tilgmann C, Rinne J, Ulmanen I. Genetic polymorphism of catechol-O-methyltransferase (COMT): correlation of genotype with individual variation of S-COMT activity and comparison of the allele frequencies in the normal population and parkinsonian patients in Finland. Pharmacogenetics 1997;7:65-71.
14. Heinz A, Goldman D, Jones DW, et al. Genotype influences in vivo dopamine transporter availability in human striatum. Neuropsychopharmacology 2000;22:133-139.
15. Mill J, Asherson P, Browes C, D'Souza U, Craig I. Expression of the dopamine transporter gene is regulated by the 3' UTR VNTR: evidence from brain and lymphocytes using quantitative RT-PCR. Am J Med Genet 2002;114:975-979.

16. VanNess SH, Owens MJ, Kilts CD. The variable number of tandem repeats element in DAT1 regulates in vitro dopamine transporter density. BMC Genet 2005;6:55.

17. Sossi V, Doudet DJ, Holden JE. A reversible tracer analysis approach to the study of effective dopamine turnover. J Cereb Blood Flow Metab 2001;21:469-476.

18. Sossi V, Holden JE, de la Fuente-Fernandez R, Ruth TJ, Stoessl AJ. Effect of dopamine loss and the metabolite 3-O-methyl-[18F] fluoro-dopa on the relation between the 18F-fluorodopa tissue input uptake rate constant Kocc and the [18F]fluorodopa plasma input uptake rate constant Ki. J Cereb Blood Flow Metab 2003;23: 301-309.

19. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55: 181-184.

20. Fahn S, Elton R, UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden C, Calne D, eds. Recent Developments in Parkinson's Disease. 2nd ed. Florham Park, NJ: Macmillan Healthcare Information 1987;153-163, 293-304.

21. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427-442.

22. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab 1983;3:1-7.

23. Eisenberg DP, Kohn PD, Hegarty CE, et al. Common variation in the DOPA decarboxylase (DDC) gene and human striatal DDC activity in vivo. Neuropsychopharmacology 2016;41:2303-2308.

24. Wu K, O'Keeffe D, Politis M, et al. The catechol-O-methyltransferase Val(158)Met polymorphism modulates fronto-cortical dopamine turnover in early Parkinson's disease: a PET study. Brain 2012;135:2449-2457.

25. Ceravolo R, Piccini P, Bailey DL, Jorga KM, Bryson H, Brooks DJ. 18F-dopa PET evidence that tolcapone acts as a central COMT inhibitor in Parkinson's disease. Synapse 2002;43:201-207.

26. Ruottinen HM, Niinivirta M, Bergman J, et al. Detection of response to COMT inhibition in FDOPA PET in advanced Parkinson's disease requires prolonged imaging. Synapse 2001;40:19-26.

27. Sossi V, de la Fuente-Fernandez R, Schulzer M, Troiano AR, Ruth TJ, Stoessl AJ. Dopamine transporter relation to dopamine turnover in Parkinson's disease: a positron emission tomography study. Ann Neurol 2007;62:468-474.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.