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Adenosine A_{2A} receptor availability in cerebral gray and white matter of patients with Parkinson's disease

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ABSTRACT

Objective: Atrophic changes in cerebral gray matter of patients with PD have been reported extensively. There is evidence suggesting an association between cortical gyrification changes and white matter abnormalities. Adenosine A_{2A} receptors have been shown to be upregulated in cerebral white matter and on reactive astrocytes in preclinical models of neurodegenerative diseases. We, therefore, sought to investigate *in vivo* changes in A_{2A} receptor availability in cerebral gray and white matter of PD patients and its association with gray matter atrophy.

Methods: Eighteen patients with PD without dyskinesia and seven healthy controls were enrolled for this study. Brain MRI and dynamic PET scan was acquired with [^{11}C]TMSX radioligand which binds selectively to A_{2A} receptors. FreeSurfer software was used to segment cerebral gray and white matter structures. The resulting masks were used to calculate region specific volumes and to derive distribution volume ratios (*DVRs*), after co-registration with PET images, for the quantification of specific [^{11}C]TMSX binding.

Results: We showed an increase in A_{2A} receptor availability in frontal ($P < 0.001$) and parietal ($P < 0.001$) white matter and a decrease in occipital ($P = 0.02$) gray matter of PD patients as compared to healthy controls. A decrease in gray matter volume ratios was observed in frontal ($P < 0.01$), parietal ($P < 0.001$), temporal ($P < 0.01$) and occipital ($P < 0.01$) ROIs in patients with PD versus healthy controls.

Conclusions: Our results suggest a role of A_{2A} receptor-based signaling in the neurodegenerative changes seen in the cerebral gray and white matter of patients with PD.

1. Introduction

Parkinson's disease (PD) is primarily characterized by progressive loss of nigral dopaminergic neurons mainly projecting to the striatum. In addition, widespread deposition of *α*-synuclein within the neurons is one of the pathological hallmarks of PD. The dopamine deficiency in the motor region of the striatum results in the cardinal features of PD such as bradykinesia and rigidity [1]. However, PD pathology is not confined to substantia nigra or the striatum. *α*-Synuclein aggregation starts in the lower brainstem nuclei during pre-symptomatic stages and spreads to the neocortex in symptomatic stages of the disease [2]. Cerebral gray and white matter changes in PD have been studied extensively *in vivo* using T1 weighted MRI and diffusion tensor imaging. Although the results are quite heterogenous, atrophic changes in the frontal and parietal gray matter areas of early/moderate PD are consistent findings in most longitudinal studies [3]. The molecular mechanisms underlying these changes are yet to be fully understood.

Adenosine A_{2A} receptors are highly enriched in the striatopallidal medium spiny neurons of the indirect pathway. We have previously reported a targeted decrease in A_{2A} receptor availability in the caudate of patients with early stage PD and an increase in the pallidum of patients with moderate stage PD [4]. However, A_{2A} receptors are also known to be expressed in cerebral gray and white matter areas [5,6]. Under physiological conditions, A_{2A} receptors selectively control synaptic plasticity after being activated by ATP derived adenosine [7]. Recent evidence shows that A_{2A} receptors present on axon initial segment also play a role in modulating axonal excitability and conduction speed [6]. The surge of adenosine in pathological conditions

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triggers the transition of A_{2A} receptors from a neuromodulatory to a predominantly neurodegenerative role [8,9]. In preclinical studies, neuronal A_{2A} receptors have been shown to modulate neurotoxic effects of *a*-synuclein [10]. Upregulation of A_{2A} receptors in various neuroinflammatory and neurodegenerative diseases has been observed [11, 12]. However, their role in PD related cerebral neurodegenerative changes has not been studied. Hence, we sought to conduct an exploratory investigation to assess changes in A_{2A} receptor availability using [^{11}C]TMSX PET imaging in cerebral gray and white matter of patients with PD (Fig. 1).

2. Methods

2.1. Study participants

Eighteen patients with idiopathic PD and seven healthy controls were enrolled for this study. Patients were enrolled from the neurology outpatient clinics of Turku University Hospital and through the forums of Finnish Parkinson's Foundation. The study protocol was accepted by the Ethics Committee of the Hospital District of Southwest Finland. Written informed consent was obtained from all study participants as per the principles of the Declaration of Helsinki. All patients fulfilled the clinical diagnostic criteria of idiopathic PD without dyskinesia [13]. Unified Parkinson's disease rating scale (UPDRS), Levodopa equivalent dose (LED), Mini mental status examination (MMSE) and disease duration (starting from the onset of motor symptoms) were recorded as a part of the clinical evaluation. Evaluation for UPDRS and MMSE was performed while the patients were 'off' their dopaminergic medication during the same visit as for the PET imaging.

Table 1
Demographics and clinical parameters of healthy controls and PD patients.

	Healthy Controls (n = 7)	PD Patients (n = 18)	*P*-value
Sex (F/M)	5/2	9/9	0.41
Age (years)	58.6 (±9.9)	66.1 (±7.6)	0.06
Disease duration (years)	NA	8.4 (5.6–10.8)	
UPDRS I	NA	1.4 (±1.5)	
UPDRS II	NA	7.3 (±3.6)	
UPDRS III	NA	24.8 (±8.5)	
UPDRS IV	NA	1.5 (±1.6)	
UPDRS V	NA	2.3 (±0.5)	
LED (mg)	NA	462.1 (±390.9)	
MMSE	Not available	28.7 (±0.8)	
Injected dose (MBq)	494.9 (±25.4)	492.4 (±21.0)	0.52
Radiochemical purity (%)	97.7 (±0.5)	97.5 (±0.5)	0.50
Injected mass (ug)	0.62 (±0.3)	0.49 (±0.3)	0.34

Sex was compared using Fisher's Exact Test. Students t-test was used for the rest of the parameters.
UPDRS: Unified Parkinson's disease rating Scale, LED: Levodopa equivalent dose, MMSE: Mini mental status examination, PD: Parkinson's disease, NA: Not applicable.

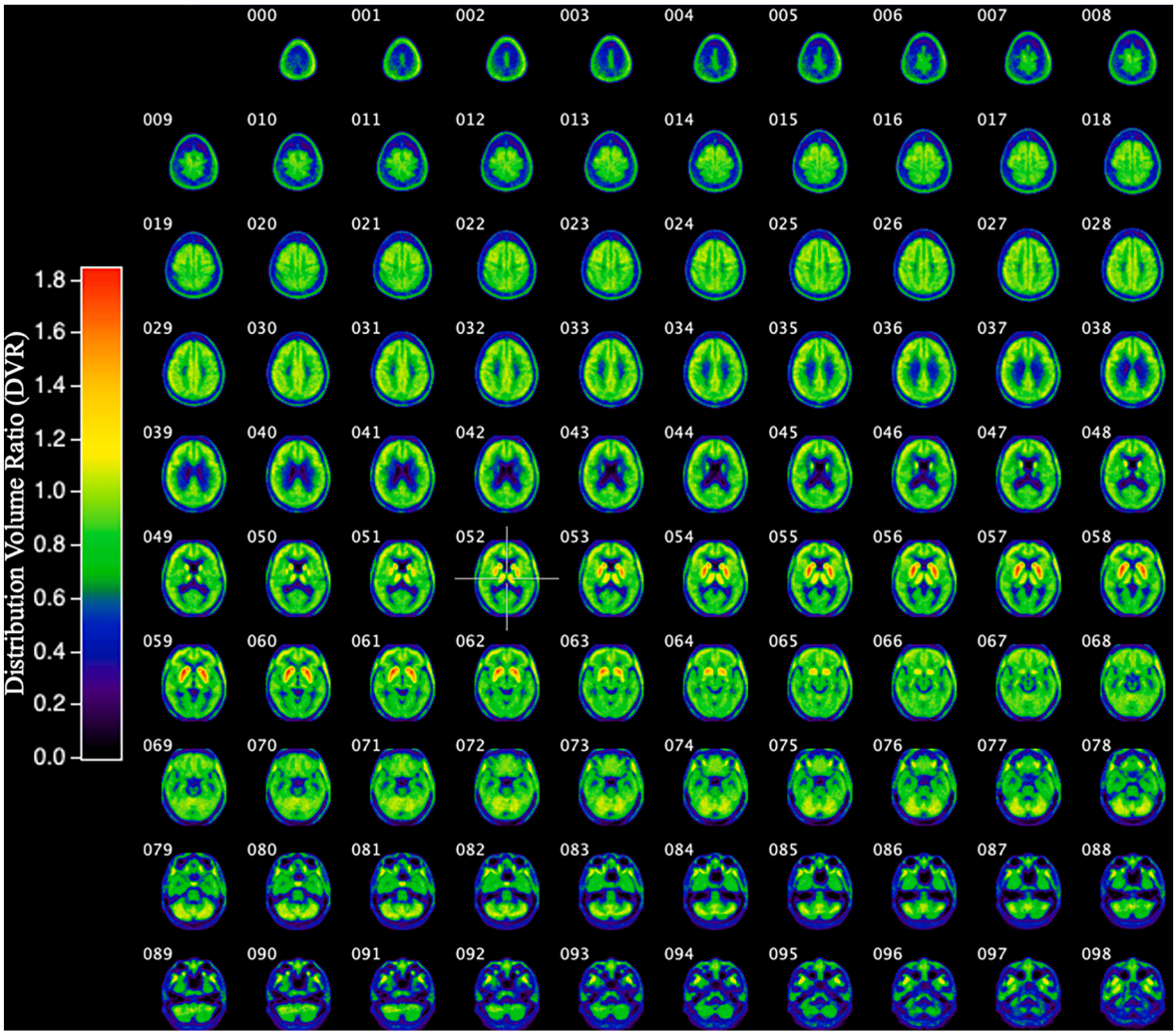

Fig. 1. Mean distribution (DVR) of [^{11}C]TMSX radiotracer in 18 patients with Parkinson's disease (PD).

Demographics and clinical features of patients with PD and healthy controls are summarized in Table 1. Exclusion criteria included significant comorbidities or any active neurologic condition apart from PD. Considering the antagonistic effects of caffeine on adenosine receptors, all patients were instructed to avoid caffeinated beverages 24 h before the [^{11}C]TMSX PET scan. Patients also temporarily stopped their dopaminergic medications 12–24 h before the scan, as described in our earlier work [4].

2.2. [^{11}C]TMSX PET and MRI imaging

The methodology of [^{11}C]TMSX radioligand production and PET/MR acquisition protocol has been described in detail in our earlier studies [4,12,14]. Briefly, scanning was performed using ECAT high resolution research tomograph PET scanner (HRRT, CTI PET Systems, Knoxville, TN, USA) with a spatial resolution of 2.5 mm in radial and axial directions. A 6-min transmission scan followed by 60-min dynamic emission scan with 27 timed frames (6 × 10, 1 × 30, 5 × 60, 5 × 150, and 8 × 300 s; total 3600 s) was acquired. Brain MRI was performed using Philips Gyroscan Intera 1.5 T Nova Dual scanner (Philips, Best, Netherlands) acquiring 3D axial T1 weighted sequence for anatomical reference and volumetric analysis. MR images were processed and co-registered with PET images using statistical parametric mapping 12 (SPM12, Wellcome Centre for Human Neuroimaging, London, UK) software. MR T1-weighted images were parcellated into distinct anatomical regions with Freesurfer software to generate frontal, parietal, occipital and temporal white and gray matter regions of interests (ROI) [15]. The acquired gray and white matter volumes were corrected for total intracranial volume of individual patients and these parenchymal fractions (volume ratios) were used for volumetric analysis. The region specific binding of [^{11}C]TMSX was quantified as distribution volume ratios (*DVR*) using Logan reference tissue-input method within 20–60 min time interval. This was applied to ROI specific time activity curves (TAC) using the clustered gray matter reference region derived from supervised clustering algorithm (SVCA) using modified Super-PK software, as validated previously [4]. To account for the possible spill in from high binding regions, erosion of the voxels was applied on cerebral gray and white matter masks by eroding a single rim of voxels (1.22 mm) from the outer edge.

2.3. Statistical analyses

Statistical analyses were performed using GraphPad Prism software (v9.4.1, San-Diego, California, USA) and RStudio (RStudio 2021.09.0 + 351). The normality distribution of the data was evaluated graphically and with Shapiro-Wilk test. Sex differences were evaluated using non-parametric Fischer's exact test. Independent *t*-test was utilized to check for differences between age, injected dose, radiochemical purity and injected mass of healthy controls and patients with PD. To investigate ROI-level changes, unpaired *t*-test was used with Bonferroni

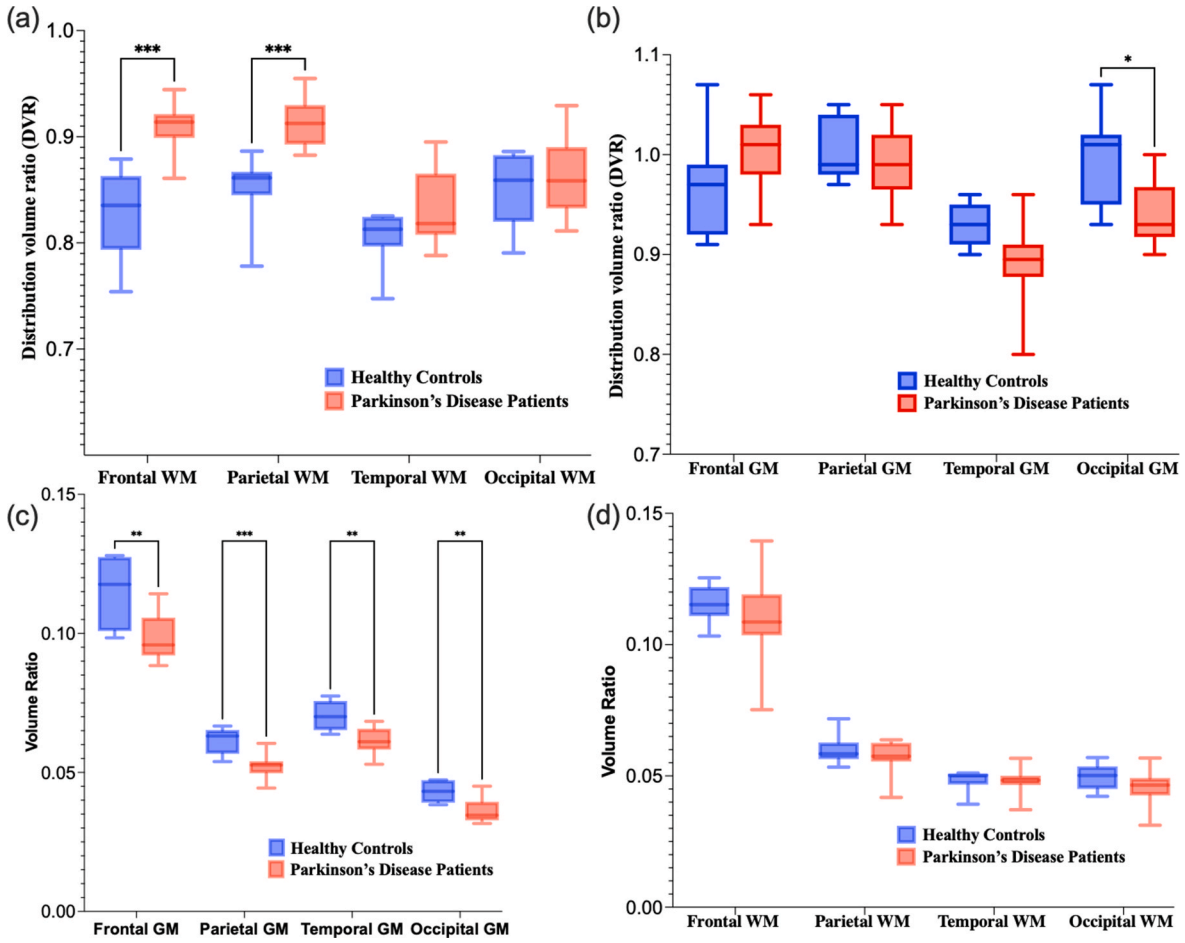

Fig. 2. Box plots comparing [^{11}C]TMSX PET parameters and MR derived volume ratios of healthy controls and patients with Parkinson's disease (PD) (a) Box-plot representing [^{11}C]TMSX PET distribution volume ratios (*DVR*) of cerebral white matter (WM) regions of interest **(b)** Box-plot representing [^{11}C]TMSX PET distribution volume ratios (DVR) of cerebral gray matter (GM) regions of interest **(c)** Box-plot comparing volume ratios of cerebral gray matter (GM) regions of interest of healthy controls and patients with PD **(d)** Box-plot comparing volume ratios of cerebral white matter (WM) regions of interest of healthy controls and patients with PD. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

correction for multiple comparisons applied afterwards. Pearson correlation was utilized to assess the association between volume ratios and *DVR*s. To account for potential confounding effects, the statistical analyses were adjusted for age and sex as covariates using ANCOVA. *P*-values <0.05 from two-tailed tests were regarded statistically significant for all analyses.

3. Results

No difference was observed for sex ($P = 0.41$), age ($P = 0.06$), injected dose ($P = 0.52$), radiochemical purity ($P = 0.50$) or injected mass ($P = 0.34$) between healthy controls and patients with PD.

ROI-level analysis showed an increase of A_{2A} receptor availability in the bilateral frontal ($P < 0.001$) and parietal ($P < 0.001$) white matter ROIs of patients with PD as compared to healthy controls (Fig. 2a). No statistically significant differences were observed in temporal ($P = 0.80$) and occipital white matter areas ($P > 0.99$) between patients with PD and controls. Furthermore, a decrease in A_{2A} receptor availability was observed in occipital gray matter ($P = 0.02$) of patients with PD compared to healthy controls (Fig. 2b). No differences were observed in frontal ($P = 0.35$), parietal ($P > 0.99$) and temporal gray matter areas ($P = 0.06$) between patients with PD and controls. Decrease in gray matter volume ratios was observed in frontal ($P < 0.01$), parietal ($P < 0.001$), temporal ($P < 0.01$) and occipital ($P < 0.01$) ROIs in patients with PD in comparison with healthy controls (Fig. 2c). No difference was observed in white matter volume ratios of frontal, parietal, temporal and occipital areas as compared to healthy controls ($P > 0.05$, Fig. 2d).

We also observed an association between higher A_{2A} receptor availability in frontal white matter and decreased frontal gray matter volume ($R = -0.52$, $P = 0.03$) but the correlation was not significant after correction for multiple comparison ($P = 0.12$). No significant correlations were observed between white matter *DVR*s and gray matter volumes of parietal ($R = -0.03$, $P > 0.99$), temporal ($R = -0.14$, $P > 0.99$) and occipital ($R = -0.08$, $P > 0.99$) regions. We observed an association between higher temporal gray matter *DVR* and temporal gray matter volume ($R = 0.63$, $P = 0.005$, adjusted $P = 0.02$). However, we found no correlation between frontal, parietal and occipital *DVRs,* and their corresponding volumes ($P > 0.05$). No association was seen between white matter *DVRs* of frontal, parietal, temporal and occipital regions, and the corresponding white matter volumes ($P > 0.05$). Similarly, we did not find any association between white and gray matter *DVRs* of frontal, parietal, temporal and occipital areas with any of the clinical parameters ($P > 0.05$).

4. Discussion

The present work investigated A_{2A} receptor availability in cerebral gray and white matter regions and its association with gray matter atrophy. Our study demonstrated that A_{2A} receptor availability is significantly increased in frontal and parietal white matter and decreased in occipital gray matter of patients with PD compared to healthy controls. Moreover, we showed that increased A_{2A} receptor availability in frontal white matter correlates with decreased frontal gray matter volume. We also observed an association between A_{2A} receptor availability in temporal gray matter and its volume.

An increasing number of studies have suggested loss of gyrification in the frontal and parietal lobes of patients with PD [16]. Alterations in the cerebral white matter integrity, such as decreased fractional anisotropy (FA) precede the gray matter changes as well as cognitive deficits [17]. Increased *α*-synuclein aggregation and axonal collateralization are believed to trigger the pathological changes in cerebral white matter regions [18]. Furthermore, there is evidence of a temporal association between cortical gyrification changes and white matter abnormalities [19]. It has also been postulated that neurodegeneration primarily spreads from subcortical regions upwards to the cerebral cortex [20]. Up-regulation of A_{2A} receptors on reactive astrocytes has been demonstrated in animal models of neurodegenerative diseases [21] and increased A_{2A} receptor activation results in astrocyte proliferation as well as a decrease in Na^+/K^+–ATPase activity [22]. This leads to a decrease in glutamate uptake, an increase in glutamate mediated excitotoxicity and subsequent neuronal death. Based on our data and the above-described evidence from animal experiments, we hypothesize that the neurodegenerative changes observed in the gray matter may associate with A_{2A} receptors expressed primarily on reactive astrocytes in the white matter.

It has been suggested that an increase in neuronal A_{2A} receptor activation results in an increase of NMDA receptor function and, consequently, Ca^{2+} entry dysfunction [23]. This dysfunction increases the propensity of *α*-synuclein to form intraneuronal aggregates, which leads to neuronal death in PD [24]. Indeed, a blockade of A_{2A} receptors has been shown to prevent neurotoxicity and cell death induced by *α*-synuclein oligomers [10]. Interestingly, consumption of caffeine, an adenosine receptor antagonist, is also known to reduce the risk of PD [25].

More recent evidence has indicated that A_{2A} receptor activation in the initial axonal segment and nodes of Ranvier alters excitation and decreases signaling speed, respectively [6]. Disruption in the functional connectivity of sensorimotor, dorsal attention and default mode networks has been reported in patients with PD without significant white matter changes [26]. Decreased white matter connectivity in the frontoparietal nodes has also been shown in PD patients [26]. It is plausible that increased A_{2A} receptor availability in the frontal and parietal white matter seen in our results could contribute to the decreased signaling and functional connectivity changes seen in patients with PD. This could also explain the improvement of motor symptoms observed in PD patients after caffeine consumption [27].

We observed higher A_{2A} receptor availability in parietal white matter but, unlike frontal lobe, without an association with decreased parietal gray matter volume. Similarly, A_{2A} receptor binding in occipital and temporal white matter was at par with healthy controls despite significant decrease in gray matter volumes. In PD, cortical pathology spreads from caudal to rostral brain regions with increased disease severity. Therefore, atrophic changes in occipital, parietal and temporal cortices precede frontal atrophy [28,29]. The longer disease duration and higher severity of our patients could explain why the association between increased A_{2A} receptor availability and decreased gray matter volume is only limited to frontal lobe.

We also found a decrease in occipital gray matter A_{2A} receptor availability in patients with PD as compared to healthy controls. Interestingly, we also found an association between higher temporal gray matter A_{2A} receptor binding and temporal gray matter volume. The observed decrease of A_{2A} receptor availability in occipital gray matter as well as the association we observe in the temporal gray matter suggests a possible indication of the degeneration of viable A_{2A} receptor expressing neurons in these regions.

In summary, we have demonstrated using PET imaging, higher A_{2A} receptor availability in frontal and parietal white matter in patients with PD compared to controls. We hypothesize that A_{2A} receptor prevalence in the white matter may promote neuroaxonal damage contributing to the pathogenesis in PD, similarly to what has been described in various other neurodegenerative conditions. Future studies are required in PD patients to explore further the prevalence and significance of A_{2A} receptor expression in the cerebral white matter at various stages of the disease.

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[IW, ER, JOR].

Ethics approval

The study protocol was accepted by the Ethics Committee of the Hospital District of Southwest Finland and abided to the principles of the Declaration of Helsinki.

Data statement

The raw data used in the preparation of this article can be shared in anonymized format by a reasonable request of a qualified investigator who has a research plan with ethical and institutional approval.

Authors' contributions

Conceptualization: [Laura Airas], [Eero Rissanen]; Methodology: [Jouni Tuisku], [Riitta Parkkola], [Markus Matilainen]; Formal analysis and investigation: [Imran Waggan], [Eero Rissanen], [Jouni Tuisku], [Markus Matilainen]; Writing - original draft preparation: [Imran Waggan]; Writing - review and editing: [Imran Waggan], [Eero Rissanen], [Laura Airas], [Juha Rinne], [Jouni Tuisku]; Funding acquisition: [Laura Airas]; Resources: [Laura Airas]; Supervision: [Eero Rissanen], [Juha Rinne], [Laura Airas].

All authors have approved this version of the manuscript.

Declaration of competing interest

Authors declare no conflict of interest.

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