

Dual-Risk axis: *GBA1* mutations and occupational pesticide exposure in Parkinson's disease

Journal of Parkinson's Disease

1–8

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DOI: 10.1177/1877718X251412233

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Abstract

Background: Occupational pesticide (OcP) exposure and pathogenic *GBA1* variants are established risk factors for Parkinson's disease (PD). However, whether they interact to influence disease onset or severity remains uncertain.

Objective: To determine the prevalence of OcP exposure and other lifestyle risks in relation to *GBA1* status and their interactions on age of onset (AOO) and clinical scores in a well-characterized PD cohort.

Methods: We analyzed 505 people with PD (PwP) enrolled in the Ankara Parkinson's Disease Registry (ANPAR). *GBA1* variants were identified using next-generation sequencing; benign or uncertain variants were excluded. Structured, face-to-face interviews collected data on history of OcP exposure, history of head trauma, smoking, coffee and tea consumption habits. PwP with and without *GBA1* variants were compared using unadjusted and adjusted tests. General linear models assessed gene—environment interactions on AOO, non-motor, and motor scores.

Results: Fifty-two PwP (10.3%) carried pathogenic *GBA1* variants. OcP exposure was more common in carriers than non-carriers (36% vs. 22%; adjusted OR 1.98, 95%CI: 1.07–3.67, $p = 0.031$). No other risk factor differed between groups. Smoking independently delayed AOO, but there were no significant *GBA1* × risk/lifestyle factor interactions for AOO or for motor/non-motor scores. Head trauma, coffee, tea, and OcP exposure showed neither main nor interaction effects on severity indices.

Conclusion: OcP exposure is reported more often by individuals carrying pathogenic *GBA1* variants, supporting a gene—environment “dual-hit” model. However, OcPs did not modify AOO or disease severity once PD was manifest.

Plain language summary title

Pesticide Exposure is Associated with *GBA1* Mutations in Parkinson's Disease

Plain Language Summary

Parkinson's disease is a neurological disorder that mainly affects movement but also other functions. Genetic, environmental and lifestyle factors may contribute to this disease. One of the strongest genetic risk factors is carrying a harmful change (mutation) in the *GBA1* gene. For environmental risks, exposure to pesticides also increases the likelihood of Parkinson's disease. However, not everybody having a *GBA1* mutation develop disease. This suggests that additional risks may be necessary for the development of disease. In this study, we investigated the effects of several risk factors including pesticide exposure for their association with *GBA1* mutations. We also investigated the impact of these factors on age of disease onset and disease severity. To do this, we examined 505 people with Parkinson's disease from the

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Ankara Parkinson's Disease Registry (ANPAR). All participants completed interviews about their lifestyle and exposures such as pesticide contact, head trauma, smoking, and coffee or tea consumption habits. We then compared people with and without *GBA1* variants to see if there were any differences in these factors. We found that one every 10 patients carried a *GBA1* mutation. Pesticide exposure was reported more often in patients carrying a *GBA1* mutation. However, pesticide exposure did not have a significant effect on the age at which the disease started. Among the other lifestyle factors, only smoking delayed the onset of the disease. Other factors showed no effect on age of disease onset and severity. Our findings support the idea of a dual-hit model, meaning that having both a harmful *GBA1* variant and pesticide exposure may increase the risk of Parkinson's disease. This highlights the complex interaction between genetic and environmental mechanisms for the development of Parkinson's disease.

Keywords

exposome, pesticide, *GBA1*, gene-environment, Parkinson's disease

Introduction

The global rise of prevalence in Parkinson's disease (PD)¹ has been linked to environmental influences collectively termed as exposome.² Based on this recognition, PD has been defined as an environmental disease.³ This may be plausible because the pathology starts in the olfactory bulb and dorsal motor nucleus of vagus—structures that connect the brain to the external environment. Within this environment, occupational pesticide (OcP) exposure is a well-documented risk factor for PD, supported by evidence from cell cultures to animal studies, to prospective risk or geographical studies.^{4–9} Depending on the type or intensity of exposure, OcPs increase the risk as much as two-fold.^{10–12} However, despite the strong link, OcP exposure is a risk factor rather than an absolute determinant of a future synucleinopathy. Probably, OcPs cause an overt PD pathology only when they disrupt cells that are already predisposed or vulnerable.

Another notable risk factor for PD is pathogenic variations in the glucosylceramidase beta-1 (*GBA1*, formerly *GBA*) gene, which can be found around 5–15% of people with PD (PwP).^{13,14} The *GBA1* encodes the lysosomal enzyme glucocerebrosidase. It has been proposed that, pathogenic variants impair enzyme activity, rendering the autophagic-lysosomal pathway vulnerable and lead to defective clearance and accumulation of alpha-synuclein aggregates.^{15,16} The risk of developing PD in *GBA1* mutation carriers is increased by up to 20-fold,¹⁴ depending on the variant severity. In addition, PwP carrying a *GBA1* mutation (PwP + *GBA1*) have an earlier onset, faster disease progression, and enriched non-motor manifestations.¹⁷

While the *GBA1* is a recognized genetic risk, many individuals with a *GBA1* mutation will never experience PD—even the ones carrying severe variants. This suggests the role of additional genetic, lifestyle or environmental factors that modulate the penetrance of *GBA1*-associated susceptibility into manifest PD, via a dual-hit mechanism. One potential candidate is the OcP exposure. OcPs may aggravate vulnerable lysosomal systems and disrupt misfolded alpha-synuclein clearance.⁸ Having said that, to this day, the existing

data on associations between the *GBA1* variant status and OcP exposure as well as other risk/lifestyle factors are limited to few studies.^{18–20} Moreover, whether *GBA1*-related impact on age of onset (AOO) and disease severity is confounded by other factors is yet to be defined. Therefore, in this study, we investigated the *i*) the prevalence of OcP exposure and other risk factors with respect to *GBA1* carrier status and *ii*) their combined effect on AOO and clinical features.

Materials and methods

The ANPAR cohort and the assessments

Since 2020, Turkish PwP have been enrolled and followed by the Department of Neurology, Ankara University School, as part of the ANkara PARKinson's Disease Registry (ANPAR). Assessments cover detailed sociodemographic information, lifestyle and environmental information, disease-related information, motor and non-motor scales and quality of life. Detailed information on the assessment protocol of the ANPAR can be found in previous reports.²¹ Written informed consent was obtained from all patients for inclusion in the study. The study was approved by the Ethics Committee of Ankara University School of Medicine, and all procedures followed the Declaration of Helsinki.

Genetic investigations

GBA1 variants were identified in blood samples using next-generation sequencing. The “American College of Medical Genetics and Genomics Criteria” were used to assess the pathogenicity of the identified variations. In PwP with a detected *GBA1* variant, a whole-exome sequencing was performed to rule out monogenic causes of PD. Details of the genetic assessments and the *GBA1* prevalence in the ANPAR cohort were reported elsewhere.²¹

Assessment of OcP exposure and other risk/lifestyle factors

As part of the ANPAR assessments, structured face-to-face questionnaires were given to capture risk factors. Among

Table 1. Comparison of the groups with and without *GBA1* variant carriers.

	PwP-WT _{GBA1} (n = 437)	PwP + <i>GBA1</i> (n = 52)	p value
Age, years, mean (SD)	64.4 (10.8)	61.7 (11.6)	0.118
Male sex, n (%)	223 (51)	31 (60)	0.241
Disease duration, years, median (IQR)	4.0 (6.2)	6.0 (8.4)	0.007
Age of onset, years, mean (SD)	59.0 (11.9)	54.9 (11.5)	0.019
First degree family history, n (%)	74 (16.9)	9 (17.6)	0.946
History of head trauma, n (%)	88 (21.7)	11 (21.2)	0.932
History of OcP exposure, n (%)	101 (22.3)	19 (36.5)	0.027
≤10 years, n (%)	55 (12.1)	10 (19.2)	
>10 years, n (%)	46 (10.2)	9 (17.3)	
Coffee consumption, cups/d, median (IQR)	1 (2)	1.5 (3.5)	0.726
Tea consumption, cups/d, median (IQR)	3 (2)	3 (2)	0.956
Smoking, pack-years, median (IQR)	0 (15)	0 (14)	0.677
MDS-UPDRS-I, mean (SD)	12.5 (7.1)	13.4 (8.7)	0.425
MDS-UPDRS-II, median (IQR)	12 (13)	17 (12.5)	0.270
MDS-UPDRS-III, mean (SD)	38.6 (17.5)	40.1 (18.2)	0.571
MDS-UPDRS-IV, median (IQR)	0 (5)	1 (10)	0.025
MDS-UPDRS-total, mean (SD)	69.1 (32.6)	74.2 (32.3)	0.286
PDQ-39, mean (SD)	50.8 (29.5)	55.0 (29.4)	0.336

PwP, patients with Parkinson's disease; WT_{GBA1}, wildtype for *GBA1*; SD, standard deviation; IQR, interquartile range; OcP, occupational pesticide; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; PDQ, Parkinson's disease questionnaire.

those, the “history of head trauma” was defined as head traumas causing loss of consciousness, involvement in traffic accidents or long-term contact sports. OcP exposure was defined as any contact with agricultural pesticides in farms, vineyards or gardening activities. “Smoking intensity” was calculated as lifetime pack-years. “Coffee and tea consumption” were recorded as lifetime habits of cups per day. Metabolic risk factors (diabetes mellitus type-II, body mass index and waist circumference) were excluded because they were collected after diagnosis and no temporal relationship could be constructed. Since the latency period between the last date of OcP exposure and diagnosis was available for only 65 PwP, this variable was also excluded from the analysis.

Statistical analysis

Participants were divided into two groups as PwP carrying a *GBA1* variant (PwP + *GBA1*) and PwP who are wildtype for *GBA1* (PwP-WT_{GBA1}). Benign or unknown variants were excluded from the PwP + *GBA1* group. First, groups were compared regarding risk/lifestyle factors using unadjusted tests. Factors reaching $p < 0.05$ were re-examined in regression models controlling for confounding and interactions. To test *GBA1*-environment interactions on AOO, we built five univariate general linear models (GLM) with sex and *GBA1* status included as fixed variables plus *GBA1* × factor interactions (*GBA1* × history of head trauma, OcP exposure, coffee consumption, tea consumption, smoking). The impact of these factors on motor (MDS-UPDRS-III) and non-motor (MDS-UPDRS-I) scores were evaluated using same models with disease duration added as an additional covariate.

Because this part was an exploratory analysis, p-values were adjusted according to Bonferroni ($p = 0.05/5$ factors = 0.01). Main effects of the risk factors were given unadjusted. All analyses were performed using the IBM SPSS Statistics version 30.0.

Results

Frequency of factors in PwP + *GBA1*

Data of 505 PwP were evaluated of whom 68 (13.5%) carried a *GBA1* variant. Sixteen PwP carrying benign or unknown variants were excluded, leaving 52 PwP + *GBA1* (10.3%). More detail on the genetic profile of this cohort has been given in the Supplement and in previous reports.²¹ PwP + *GBA1* had earlier AOO and longer disease duration despite younger mean age (Table-1). Regarding the factors investigated, 21% of all PwP reported previous head trauma and 22% reported contact with OcPs. The history of OcP exposure was associated with PwP + *GBA1* group with an odds ratio of 1.96 ($p = 0.027$). No other risk/lifestyle factor differed significantly between groups (Table-1).

To confirm the unadjusted association of OcP exposure with *GBA1* status, a multivariable logistic regression was performed. The model included age, sex, and OcP exposure as predictors and *GBA1* status as the dependent variable. The overall model provided modest explanatory power (likelihood-ratio $\chi^2 = 8.223$ on 3 df, $p = 0.042$; Nagelkerke $R^2 = 3.4\%$). After adjustment, individuals who reported OcP exposure had nearly twice the odds of carrying a *GBA1* mutation compared with unexposed individuals (adjusted OR = 1.98, 95% CI: 1.07–3.67, $p = 0.031$) similar to the

contingency table. Neither age, nor male sex showed a significant association. Adding coffee or tea consumption, smoking, or head trauma one at a time did not reach statistical significance to be included in the model (all $p > 0.20$) or change the pesticide OR estimate (all $\Delta\beta < 7\%$), indicating that OcP exposure is independently associated with *GBA1* carrier status.

To examine the robustness of the association between *GBA1* status and OcP exposure, we performed sensitivity analyses using alternative variant classifications: (i) including VUSs to the PwP + *GBA1* group and (ii) restricting the PwP + *GBA1* group to only severe variants. In both analyses, the proportion of pesticide exposure remained higher among PwP + *GBA1* (VUS-included: 30.9% vs. 22.7%, $p = 0.14$; only-severe PwP-*GBA1*: 37.5% vs. 22.7%, $p = 0.17$), indicating a consistent trend across definitions. However, statistical significance was attenuated, likely reflecting smaller group sizes (only-severe PwP + *GBA1* $n = 16$) or variant heterogeneity. These results suggest that while the association direction is robust, its magnitude is sensitive to variant classification in our cohort.

Effect of risk/lifestyle factors on age of onset and clinical scores

The main effects and the interactions of each risk factor with *GBA1* carrier status were investigated with GLMs separately with sex and *GBA1* as fixed covariates. First, the main effect of the *GBA1* status (with covariate sex) was determined. *GBA1* carriers had a younger mean age at onset (54.9 ± 11.5 years) compared to non-carriers (58.9 ± 11.9 years), corresponding to an estimated $B = 3.90 \pm 1.73$ years (95%CI: 0.49–7.31; $p = 0.025$). Age at onset did not differ between men (57.8 ± 12.3 years) and women (59.2 ± 11.5 years; $p = 0.19$). The sex \times *GBA1* interaction was non-significant indicating that the impact of *GBA1* variants on AOO was comparable for both sexes. Inclusion of other factors to the model showed that only smoking showed a main effect. Each pack-year of cigarette exposure is associated with a 0.082 ± 0.024 -year delay in onset (95%CI: 0.02–0.14), yielding a cumulative delay of 4 years in a 50 pack-year smoker. Apart from that, history of head trauma, OcP exposure, habitual coffee or tea consumption had no significant main effect. Furthermore, no interaction effect was detected between the *GBA1* status with other factors. For the assessment of motor and non-motor scores, disease duration was added to sex and *GBA1* status. The results showed that the included factors showed neither a main effect nor an interaction with the *GBA1* carrier status ($p > 0.01$). Details of the constructed models are given in the Supplement.

Discussion

The mechanisms leading to manifest disease in individuals carrying PD-associated risks are unclear. In this study, we

investigated the interactions between the *GBA1* carrier status and environmental or lifestyle factors for their effect on overall frequency, age of onset and clinical severity of PD. We have found that PwP carrying a *GBA1* variant were almost twice as likely to report OcP exposure suggesting a potential gene-environment interaction in PD pathology via a dual-hit mechanism.

In our cohort, OcP exposure was reported in 22% of all PwP. To put this value in perspective, 14.8% of Turkey's employed population in 2024 worked in the agricultural sector—a group with higher exposure potential.²² Population-based studies from other countries reported lower exposure rates among non-PD individuals, such as 4.1% in the Dutch Lifelines cohort²³ and 5.3–11.6% among controls in U.S. case—control studies.^{24,25} These values suggest that OcP exposure in our PD cohort may be higher than non-PD population, linking occupational exposure to increased PD risk. Among the PwP + *GBA1*, 36% reported such a history. This value exceeds that of the PPMI cohort (17%),¹⁸ but approximates to Greek (29%)²⁶ and Chinese data (37.4%)¹⁹ implying that Turkish, Greek and Chinese PwP may have more rural lifestyle than participants in PPMI. Regarding the association between the risk or lifestyle factors and *GBA1* status, few reports are available in the literature. One Ashkenazi-Jewish study reported more frequent head injury in *GBA1* p.N370S carriers²⁷ a finding could not be replicated by our data and the 23andme population.²⁰ Different definitions of trauma and narrow variant selection may explain the inconsistency. For coffee/tea consumption or smoking, our results are in line with previous work showing no difference in PwP with or without *GBA1* mutations.^{19,20,26,27} A summary of these findings were given in the Table-2.

In terms of pesticides, most prior investigations found higher OcP exposure in PwP + *GBA1*, similar to ours.^{18,19,26} A 2018 Greek study noted a similar pattern in PwP + *GBA1* compared to genetically undefined PwP, with a higher OR (6.3) than ours.²⁶ In 2024, the analysis of the PPMI data also showed a 5.4-fold enrichment in reports of OcP exposure in PwP + *GBA1* than non-manifesting carriers (NMCs) (Table-3).¹⁸ Of note, *LRRK2* variant carriers showed no such association. Another recent Chinese study compared PwP with NMCs and reported that history of OcP (and also solvent) exposure was related to PwP in *GBA1* carriers with an odds of 8.4.¹⁹ Notably, in this study, variants of uncertain significance were also included in the *GBA1* group. Reporting such findings from non-European ancestry populations is important suggesting that such an impact may be independent of ethnic or geographical influences. By contrast, the large 23andMe dataset detected no association between *GBA1* carrier status and pesticide exposure, as well as between other factors.²⁰ However, the analysis included only three common risk alleles (p.E326 K, p.T369 M and p.N370S), leaving out other risk or severe variants and relied on a single yes/no exposure question. The Parkinson's Environment and Genes (PEG) study, on the other hand,

Table 2. Studies investigated the frequency/association of risk/lifestyle factors in PwP + GBAI.

	Coffee consumption	Tea consumption	History of head trauma	History of pesticide exposure	Smoking/tobacco consumption
Simitsi et al. ²⁶ (2018)	No association OR = 0.35 (0.11–1.12) [†]	NE	NE	Positive association OR = 6.34 (1.24–32.25) [†]	No association OR = 0.67 (0.21–2.15) [†]
Yahalom et al. ²⁷ (2020)	No association OR = 0.98 (0.34–2.85) [†]	No association OR = 1.06 (0.56–2.02) [†]	Positive association OR = 3.34 (1.51–7.39) [†]	NE [‡]	No association OR = 1.0 (0.53–1.90) [†]
Reynoso et al. ²⁰ (2024)	NE [‡]	NE [‡]	No association OR = 1.08 (0.89–1.30)	No association OR = 0.97 (0.81–1.17)	Negative association OR = 0.82 (0.72–0.93)
Brown et al. ¹⁸ (2024)	NE	NE	NE	Positive association OR = 5.4 (1.7–18.5)	NE
Zhang et al. ¹⁹ (2025)	NE	No association OR = 0.35 (0.10–1.27)	NE	Positive association OR = 8.40 (2.50–28.20)	Negative association OR = 0.18, (0.05–0.62)
Our data	No association	No association	No association OR = 1.06 (0.52–2.15)	Positive association OR = 1.98 (1.07–3.67)	No association

NE, not evaluated; OR, odds ratio.

[†]OR calculated post hoc based on raw counts reported in the paper ± Rural living was assessed; pesticide exposure and farming were not evaluated separately. [‡] caffeine consumption was evaluated collectively; coffee and tea consumption were not assessed separately

Table 3. Studies investigated pesticide exposure in PwP + *GBA1*.

	Study population	N of Groups and Comparison	OR for <i>GBA1</i> -PD (95%CI)	Impact on AOO/severity/progression
Simitsi et al. ²⁶ (2018)	Greek	PwP + <i>GBA1</i> (n = 35) vs. PwP-undefined (n = 35)	6.3 (1.24–32.25)	NE/NE/NE
Reynoso et al. ²⁰ (2024)	23andme	PwP + <i>GBA1</i> (n = 1,438) vs. PwP-non- <i>GBA1</i> (n = 17,381)	0.97 (0.81–1.17)	NE/NE/NE
Brown et al. ¹⁸ (2024)	PPMI	PwP + <i>GBA1</i> (n = 47) vs. <i>GBA1</i> -NMC (n = 155)	5.4 (1.7–18.5)	NE/NE/NA
Zhang et al. ¹⁹ (2025)	Chinese	PwP + <i>GBA1</i> (n = 107) vs. <i>GBA1</i> -NMC (n = 59)	8.40 (2.50–28.20)	NE/NE/NE
Our study	Turkish	PwP + <i>GBA1</i> (n = 52) vs. PwP-non- <i>GBA1</i> (n = 437)	1.98 (1.07–3.67)	NA/NA/NE

N, number; OR, odds ratio; 95% CI, 95% confidence interval; AOO, age of onset; NE, not evaluated; NA, no association; *GBA1*, glucosylceramidase beta-1; PwP + *GBA1*, patients with Parkinson's disease-glucosylceramidase beta-1; PD, Parkinson's disease; *GBA1*-NMC, glucosylceramidase beta-1-non-manifesting carriers; PwP-*GBA1*_{WT}, patients with Parkinson's disease-wildtype for glucosylceramidase beta.

supported an association between exposure to cotton-cluster pesticides and lysosomal mechanisms. Using a geographic information system based model and an extensive data on OcP use, the authors tested a genetic panel of 85 genes related with mitophagy, autophagy and lysosomal function, and found that 36 variants of 26 genes (including *GBA1*) were enriched in PwP with a history of exposure.²⁸ This study provided important insights into gene—environment interactions in lysosomal stress using a homogeneous group of occupational pesticides (cotton cluster), and expanded the dual-hit model to individuals with genetic susceptibilities in lysosome-related pathways beyond *GBA1*. Independent studies should follow to test the generalizability of the findings with populations with different agricultural practices.

Previous studies have explored a range of gene-environment interactions on risk or AOO in PD.^{29–33} However, studies focused on *GBA1*-environment interactions are scarce. In our cohort, we tested whether the collected five risk and lifestyle factors modify the impact of *GBA1* carrier status on AOO and disease severity in PwP. As expected, *GBA1* variant carriers in our cohort had younger AOO, which we reported earlier.²¹ In addition, smoking demonstrated a delaying effect. Other risk factors showed neither an effect on AOO nor an interaction with the *GBA1* carrier status. The lack of *GBA1* x smoking interaction also suggests that these two factors influence through distinct biological mechanisms. These results also differ from a single Ashkenazi-Jewish study which found a *GBA1*-head trauma interaction indicating a younger onset in PwP with both risks,²⁷ but align with a recent study (which did not investigate OcP exposure) which also found no interaction between the *GBA1* status and coffee consumption or tobacco use on AOO.²⁰ With regard to disease severity, we found neither a main effect nor an interaction between the *GBA1* carrier status and other investigated factors, similar to the analysis of the PPMI data which found no significant


additional impact with OcP exposure on disease severity or progression.¹⁸ However, while the above mentioned PEG study did not investigate the effect of lysosomal variants on AOO, it found that OcP exposure is linked to a faster progression in people carrying particular lysosomal variants,²⁸ underscoring the heterogeneity within the lysosomal genetic landscape. Taken together, current evidence is inconclusive on whether OcP exposure accelerates disease progression. Available studies are few, genetically diverse and used variable exposure metrics producing wide confidence intervals. To determine if OcP exposure meaningfully aggravates the disease course in lysosomal variant carriers, large-scale multicentre studies with detailed genetic stratification and uniform methods of risk quantification are required.


Limitations of the current study also need to be mentioned. First, our data on OcP captured only duration of exposure, not frequency or intensity, which prevented fully quantification of cumulative dose. Future studies should include more standardized and validated tools such as the “Agricultural Health Study”.³⁴ Likewise, specific classes of OcPs could not be determined, a common challenge in environmental epidemiology. The lack of a control group is another limitation, as it prevents direct comparison of OcP exposure between PwP and non-PD individuals. A potential recall bias is also unavoidable in self-reported surveys. Furthermore, although *GBA1* variants were comprehensively screened, the effects of individual variant subtypes could not be analyzed separately, due to the limited statistical power. Also, other genes reported to be associated with OcP exposure^{33,35–38} were not evaluated. Moreover, the absence of NMCs carrying *GBA1* variants precludes direct interpretation of penetrance estimation for PD. In addition, as mentioned, metabolic factors and dietary habits which could interact with OcP exposure were missing.³⁹ Additional confounding factors such as


rural residence and socioeconomic status which influence exposure were also not assessed in this study. Despite these constraints, the comprehensive assessment of risk and lifestyle factors, a structured face to face questionnaire reducing the risk of misclassification in data are the major strengths of the study.


In conclusion, our findings suggest that OcP exposure may serve as a secondary environmental insult, exacerbating lysosomal dysfunction in genetically susceptible individuals, but does not modify AOO or disease severity. Future work should incorporate larger, variant-stratified cohorts, standardized assessment tools and biomarker-based exposure verification to create more genetically and environmentally focused samples.

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Ethical considerations

The study was approved by the Ethics Committee of Ankara University School of Medicine (approval number: I4–209–20), and all procedures followed the Declaration of Helsinki.

Consent to participate

A written informed consent was obtained from all patients for inclusion in the study

Funding

Funding for genetic tests achieved with the unconditional scientific support of Pfizer Inc. (Grant number: 62051201).

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

Data are available upon reasonable request.

Supplemental material

Supplemental material for this article is available online.

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