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ORIGINAL ARTICLE

# Hereditary Patterns and Secondary Malignancies in Familial Nasopharyngeal Carcinoma

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**OBJECTIVE**

This study aimed to evaluate the clinicopathological characteristics and familial aggregation patterns of nasopharyngeal carcinoma (NPC) in a large cohort from a non-endemic region.

**METHODS**

Medical records of 1,132 NPC patients treated at the Istanbul University Oncology Institute between 1985 and 2020 were retrospectively reviewed. Familial NPC was categorized based on the total number of affected members per cluster: low-frequency (two affected individuals, including the proband) and high-frequency (three or more affected individuals, including the proband). Analysis focused on pathologically confirmed cases, documenting relationships among first-degree relatives (FDRs) and second-degree relatives (SDRs), demographic data, histopathology, and treatment outcomes.

**RESULTS**

Twenty-four families with ≥2 affected members were identified, representing a familial NPC frequency of 2.1% within the study population. Of these, 18 families (75%) involved FDRs, with 14 probands (58.3%) having affected siblings. Two families met criteria for high-frequency familial NPC (≥3 affected individuals per family). The median age of probands was 42.5 years (range: 12–70), with undifferentiated non-keratinizing carcinoma (World Health Organization type 3) histology being the most prevalent (66.7%). In addition, a family history of non-NPC malignancies among relatives was documented in 20.8% of families (n=5).

**CONCLUSION**

Familial aggregation occurs in approximately 2.1% of NPC cases in our cohort, predominantly clustering among siblings. These findings highlight that detailed family history evaluation and heightened clinical awareness for siblings are essential in clinical practice.

**Keywords:** Familial aggregation; frequency; nasopharyngeal carcinoma; non-endemic; secondary malignancy.
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## INTRODUCTION

The etiology of nasopharyngeal carcinoma (NPC) involves a complex interplay between environmental triggers and genetic susceptibility.[1,2] Along with Epstein-Barr virus (EBV) infection, environmental risk factors such as dietary nitrosamines, tobacco use, and occupational exposure to wood dust play significant

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roles in the development of the disease. In recent years, a growing body of research has underscored the importance of genetic predisposition, identifying key associations with human leukocyte antigen Class I genes and various molecular markers.[1,2]

While Southeast Asia remains the primary endemic region for NPC, familial aggregation is a well-documented etiological hallmark in these high-incidence areas.[3] Reports from China have described extreme clusters, such as 15 affected individuals across four generations within a single family.[4] In endemic regions, studies indicate that more than 5% of patients have an affected first-degree relative (FDR), who faces a significantly elevated risk.[5–8] Familial NPC is not limited to only endemic populations; but it is also observed in intermediate- or low-incidence regions.[9] Although the overall prevalence is lower in non-endemic cohorts, the risk for immediate family members remains disproportionately high.

Comparative studies between familial and sporadic NPC have evaluated clinicopathological characteristics such as age, sex, histological subtype, and EBV serology. Familial cases typically present at a younger age while preserving the male predominance observed in sporadic cases.[10] Furthermore, an increased incidence of non-NPC malignancies has been observed among these families, particularly in non-endemic areas. For instance, familial clusters in Greenland natives have shown a co-occurrence of NPC and salivary gland tumors, while other reports suggest an increased risk of EBV-related Burkitt lymphoma within NPC-prone lineages.[11,12]

Despite these global insights, data from Türkiye—an intermediate-risk region — remain sparse. In the English literature, there is currently only one reported case of familial NPC from Türkiye.[13] To address this significant data gap, we retrospectively evaluated patients who were treated for NPC at our institution over the past 35 years (1985–2020). This study aims to describe the clinical characteristics and familial aggregation patterns of NPC within a large Turkish cohort, providing essential epidemiological insights from a non-endemic region.

## MATERIALS AND METHODS

### Definition and Identification of Familial NPC

The familial history of NPC was retrospectively reviewed using patient medical records. Based on the number of affected relatives, patients were categorized into two groups: low-frequency familial NPC, with one additional NPC case within the family; and high-frequency familial NPC, with two or more additional NPC cases within the family consistent with classification approaches used in Cao et al.'s study.[14]

Each patient's NPC diagnosis was pathologically confirmed, and all had a documented family history. All families were identified through a single proband. In cases where more than one family member was treated for NPC at our clinic, the first enrolled patient was designated as the proband.

The family history of the patients was reported by the probands. However, in cases where an affected relative with NPC was not treated at our institution, pathological confirmation of diagnosis was required for inclusion. Family relationships were classified as follows: FDRs included parents, siblings, and children; SDRs comprised aunts, uncles, nieces, nephews, grandparents, and grandchildren.

A total of 26 families with at least two members diagnosed with NPC were identified. Two families were excluded due to only distant blood relations (e.g., cousins), and the remaining 24 families were included in the analysis.

### Statistical Analysis

Descriptive statistics were used to summarize the clinicopathological features of the cohort. Categorical variables were presented as frequencies and percentages, while quantitative variables were expressed as medians and ranges.

Baseline demographic and clinicopathological characteristics (age at diagnosis, sex distribution, and WHO histological subtypes) were compared between the familial NPC cohort (n=24 probands) and the sporadic registry (n=1,098). Continuous variables were compared using the Mann–Whitney U test, whereas categorical variables were evaluated using the Chi-square test or Fisher's exact test, as appropriate. Two-sided $p<0.05$ was considered statistically significant.

The median follow-up period was calculated from the date of initial pathological diagnosis to the date of the last clinical visit or death. Statistical analyses were conducted using IBM Statistical Package for the Social Sciences Statistics for Windows, version 26.0 (IBM Corp., Armonk, N.Y., USA). Due to the limited sample size and low event rate within the familial cohort, as well as varying follow-up completeness across the 35-year historical sporadic registry, formal Kaplan–Meier modeling and comparative survival analyses were not conducted; survival outcomes were reported descriptively as exploratory data.

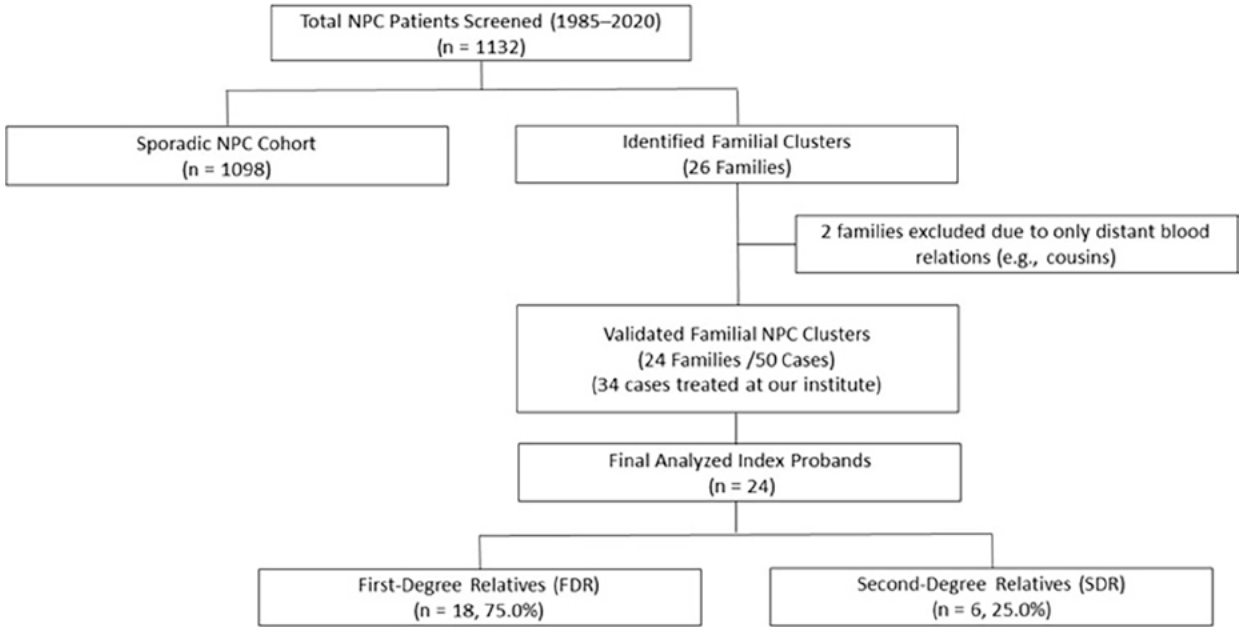



**Fig. 1.** Flow diagram of patient screening, cohort stratification, and patient selection for familial NPC.
NPC: Nasopharyngeal carcinoma; FDR: First-degree relative, SDR: Second-degree relative.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Istanbul University, Oncology Institute (Date: April 17, 2026, No:4029480). Informed consent was obtained from all individual participants who were alive at the time of the study.

## RESULTS

Among the 1,132 NPC patients screened, 24 familial clusters were identified, representing a familial NPC frequency of 2.1%. Among the 50 familial NPC cases, 34 had received treatment at our institute. After excluding 10 relatives who were part of the same clusters, the final analysis focused on 24 probands (Fig. 1).

Of these 24 families, 18 (75%) involved FDRs, and 6 (25%) involved second-degree relatives (SDRs). Two families met the criteria for high-frequency familial NPC (≥3 affected individuals).

### Clinical Characteristics of Probands

The demographic, histopathological, and treatment characteristics of the 24 probands are summarized in Table 1. The majority of familial clusters (18/24) involved FDRs, with a striking predominance of sibling-to-sibling occurrences (14/24, 58.3%). The median age at diagnosis was 42.5 years (range: 12–70). Undifferentiated non-keratinizing carcinoma (World Health Organization type 3) was the most frequent histological subtype (66.7%).

Induction chemotherapy was administered to 79.2% of the probands, while 41.7% received concurrent chemoradiotherapy. After a median follow-up of 57.3 months (range: 4.8–236), 19 patients (79.2%) remained alive. Of the five deaths, four were due to disease progression, and one was related to a second primary malignancy (SPM). Specifically, one patient developed metastatic colon cancer 2 years after the initial diagnosis of NPC and succumbed to the disease a year later. Another patient had a history of seminoma, treated 8 years before the NPC diagnosis.

### Comparison between Familial and Sporadic NPC Cohorts

Baseline demographic and clinicopathological features of familial probands (n=24) and the sporadic registry (n=1,098) are summarized in Table 2. Notably, a statistically significant difference was observed in sex distribution: while the sporadic cohort demonstrated a typical male predominance, the familial cohort was characterized by a higher proportion of female patients (p=0.011).

### High-Frequency Familial NPC Clusters

In the first high-frequency family, three of six siblings were diagnosed with NPC, two of whom ultimately

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**Table 1** Patient characteristics of the probands

| | Frequency | % |
|---|---|---|
| Sex | | |
| Female | 13 | 54.2 |
| Male | 11 | 45.8 |
| Histopathology | | |
| WHO 1 | 2 | 8.3 |
| WHO 2 | 6 | 25.0 |
| WHO 3 | 16 | 66.7 |
| Relationship | | |
| Proband-Sibling | 12 | 50.0 |
| Proband-Niece/Nephew | 5 | 20.8 |
| Proband (Mother)-daughter | 3 | 12.5 |
| Proband (Father)-son | 1 | 4.2 |
| Proband-Aunt | 1 | 4.2 |
| Proband-Sibling-Sibling | 1 | 4.2 |
| Proband-Son-Sibling | 1 | 4.2 |
| Overall stage | | |
| 2 | 4 | 16.7 |
| 3 | 12 | 50.0 |
| 4a | 8 | 33.3 |
| IC | | |
| Yes | 19 | 79.2 |
| No | 5 | 20.8 |
| Concurrent ChT | | |
| Yes | 10 | 41.7 |
| No | 14 | 58.3 |
| Treatment response | | |
| CR | 20 | 83.3 |
| PD | 1 | 4.2 |
| PR | 3 | 12.5 |
| Recurrence site | | |
| Distant metastasis | 2 | 8.3 |
| Local recurrence | 2 | 8.3 |
| Locoregional recurrence | 2 | 8.3 |
| Regional recurrence | 2 | 8.3 |
| No recurrence | 16 | 66.7 |
| Last status | | |
| Alive | 19 | 79.2 |
| Ex (Progression) | 4 | 16.7 |
| Ex (SPM) | 1 | 4.2 |

NPC: Nasopharyngeal carcinoma; WHO: World Health Organization; IC: Induction chemotherapy; ChT: Chemotherapy; CR: Complete response; PD: Progressive disease; PR: Partial response; Ex: Exitus; SPM: Second primary malignancy.

**Table 2** Comparison of baseline clinicopathological characteristics between familial probands and the sporadic nasopharyngeal carcinoma cohort

| Parameter | Familial cohort (Probands, n=24) | Sporadic cohort (n=1,098) | p |
|---|---|---|---|
| Age at diagnosis (years) | | | |
| Median (range) | 42.5 (12–70) | 48.0 (6–85) | 0.415 |
| Sex, n (%) | | | 0.011 |
| Female | 13 (54.2) | 315 (28.7) | |
| Male | 11 (45.8) | 783 (71.3) | |
| Histological subtype, n (%) | | | 0.902 |
| WHO type 1 | 2 (8.3) | 98 (8.9) | |
| WHO type 2 | 6 (25.0) | 304 (27.7) | |
| WHO type 3 | 16 (66.7) | 660 (60.1) | |
| Unspecified | 0 (0.0) | 36 (3.3) | — |

Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Histopathological comparison was performed among cases with documented subtypes (n=1,062 sporadic vs. n=24 familial). WHO: World Health Organization.

died from the disease. Additional malignancies in this family included breast cancer (mother), mesothelioma (father), and gastric cancer (paternal grandfather). In the second high-frequency family, NPC was diagnosed in the proband, the proband's son, and a sibling. No other malignancies were reported in this family (Table 3 and Fig. 2).

### Family History of Non-NPC Malignancies in Relatives

In five of the 24 families (20.8%), at least one first- or second-degree relative was diagnosed with a non-NPC malignancy, including breast, prostate, and laryngeal cancers, mesothelioma, gastric cancer, and chronic myeloid leukemia (CML) (Table 4).

## DISCUSSION

In this study, we investigated the clinical and demographic characteristics of familial NPC within a large cohort in Türkiye. Our analysis identified a familial frequency of 2.1%. Notably, the majority of familial clusters (75%) involved FDRs, with a striking predominance of sibling-to-sibling occurrences.

The reported rate of familial NPC in endemic regions typically ranges from 5.8% to 19%.[5–8] For instance, in a prospective study involving 200 patients from an en-

**Table 3** Patients with high-frequency familial nasopharyngeal carcinoma

| Family | Patient | Year of diagnosis | Sex | Age | Stage | Relationship | Last status |
|---|---|---|---|---|---|---|---|
| Family 1 | 1.1 | 1991 | F | 24 | T3N3M0 | Proband | NED |
| | 1.2 | 1992 | F | 25 | T1N2M0 | Sibling | Ex |
| | 1.3 | 2021 | M | 50 | T1N3M1 | Sibling | Ex |
| Family 2 | 2.1 | 2007 | F | 64 | T2N1M0 | Proband | Ex |
| | 2.2 | 2007 | M | 38 | Unknown | Son | Ex |
| | 2.3 | 2012 | F | 53 | T2N2M0 | Sibling | NED |

F: Female; M: Male; Ex: Exitus; NED: No evidence of disease.

**Table 4** History of non-NPC malignancies among family members of probands

| Family no | Affected relative | Relation to proband | Malignancy type (non-NPC) |
|---|---|---|---|
| Family 1 | Relative 1 | Paternal grandfather | Gastric |
| | Relative 2 | Mother | Breast |
| | Relative 3 | Father | Mesothelioma |
| Family 2 | Relative 1 | Mother | CML |
| Family 3 | Relative 1 | Sibling | Breast |
| Family 4 | Relative 1 | Father | Larynx |
| Family 5 | Relative 1 | Uncle | Larynx |
| | Relative 2 | Uncle | Prostate |

CML: Chronic myeloid leukemia; NPC: Nasopharyngeal carcinoma.

demic region, familial NPC – defined strictly as having an affected FDR – was identified in 15.5% of cases.[15] When applying this same strict definition to our cohort, the rate of familial NPC was 1.6%. Furthermore, while Loh et al.[15] reported 31 FDRs and 4 SDRs among their familial cases, our study identified 18 FDRs and 6 SDRs.

Extensive studies in endemic regions have explored the risk of familial aggregation using large cohorts, often comparing the risk among relatives of NPC patients with that of the general population. Across these large-scale cohort and registry investigations, an elevated familial risk has been consistently demonstrated among FDRs, with estimated risk elevations ranging from 1.2- to 4.6-fold.[16–18]

Family clustering of NPC is uncommon but has been well-documented even among non-endemic populations. One of the few register-based cohort studies to assess familial cancer risk in a low-incidence region was conducted by Liu et al.[19] in Sweden. Their findings revealed that the risk for NPC among FDRs remained significantly elevated (relative risk [RR]: 4.29), a result strikingly consistent with data from endemic cohorts.

The risk of other malignancies in the families of NPC probands varies. In endemic areas, studies generally indicated that the excessive risk is largely restricted to NPC.[16,17] However, a broader perspective is provided by the registry-based study in Sweden, a low-incidence region, where FDRs of NPC probands

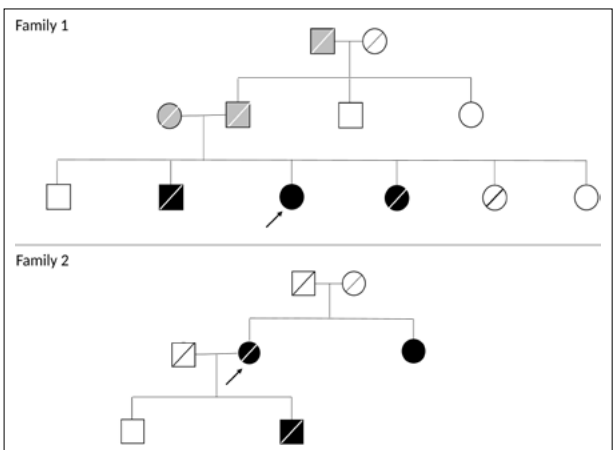



**Fig. 2.** Pedigrees of high-frequency nasopharyngeal carcinoma (NPC) families. Symbols: Squares indicate males; circles indicate females; black symbols represent NPC; gray symbols represent other malignancies; diagonal lines indicate deceased individuals.

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exhibited increased risks for salivary gland, laryngeal, prostate, and thyroid cancers.[19] The elevated incidence of salivary gland cancer in this cohort mirrors findings from studies in Greenland.[20] Along with salivary gland carcinoma, the RRs of uterine and cervix carcinoma were also significantly increased in the study by Friborg et al.[20] Our cohort displayed a notable diversity of non-NPC malignancies. In five of the 24 families (20.8%), at least one member was diagnosed with a non-NPC cancer. The most prominent example was a high-frequency familial NPC cluster where two siblings of the proband were affected; this family also had a significant history of other cancers, including breast cancer (mother), mesothelioma (father), and gastric cancer (paternal grandfather). Other observed malignancies included CML, prostate cancer, and laryngeal cancer.

Beyond familial clustering, the occurrence of SPMs in NPC patients themselves represents a distinct clinical entity. In the Taiwanese cohort, increased risks of secondary cancers (head and neck, bone, and hematopoietic systems) were primarily attributed to the late effects of radiotherapy (RT) rather than genetic predisposition.[17] These findings underscore the critical need for refining RT techniques, such as the use of intensity-modulated radiation therapy or proton therapy, and maintaining rigorous long-term surveillance. In our study, two patients developed non-NPC malignancies: one was diagnosed with metastatic colon and the other with seminoma.

The distribution of affected relatives within familial clusters is variable, though siblings consistently demonstrate the highest risk.[15,16] In our cohort of 24 families, 14 probands (58.3%) had affected relatives who were their siblings. Similarly, Liu et al.,[18] in their large-scale case-control study in Southern China, noted a significantly stronger association with maternal and sibling histories than with paternal history. The most striking evidence of this risk comes from Huang et al.,[21] who utilized the Taiwan National Health Insurance Research Database to reveal a 9.23-fold increased risk for siblings. Our findings reinforce this global pattern, suggesting that sibling-targeted screening may be the most high-yield strategy in familial NPC management.

An important point of debate in familial NPC is whether the clinical behavior of familial cases differs from that of their sporadic counterparts. While Loh et al.[15] reported no significant differences in clinical characteristics, other large-scale studies suggest a distinct biological profile for familial disease. For instance, Huang et al.[21] demonstrated a younger age of onset in familial cases (35.5 vs. 39.0 years; $p<0.0001$) within a Taiwanese cohort. This was further corroborated by Cao et al.[14] in high-risk Southern Chinese populations, where "high-frequency" familial NPC cases presented significantly earlier than sporadic cases (39 vs. 46 years). In our cohort, although familial probands presented at a younger median age than sporadic patients (42.5 vs. 48.0 years), the difference did not reach statistical significance ($p=0.415$). Interestingly, a distinct and statistically significant female predominance was observed among familial probands compared to the marked male predominance in sporadic cases (54.2% vs. 28.7%, $p=0.011$). Survival comparisons between cohorts were not performed due to historical registry limitations.

Beyond the age of onset, the prognostic significance of familial aggregation is particularly noteworthy.[14] Ouyang et al.[22] identified a first-degree family history as an independent favorable prognostic factor for both overall survival and distant metastasis-free survival. These findings suggest that familial NPC may represent a biologically distinct subset of the disease. While an underlying familial susceptibility may contribute to an earlier onset of malignancy, the resulting tumors may paradoxically exhibit a more indolent clinical course or a more robust response to contemporary therapeutic regimens. Consistent with this, our cohort demonstrated a high complete response rate (83.3%) and favorable survival outcomes (79.2% alive at a median follow-up of 57.3 months).

While high-frequency familial clusters (defined as families with ≥3 affected members) are more common in endemic regions, they remain rare in non-endemic areas.[16] Nevertheless, sporadic reports have documented such occurrences in low-incidence populations.[10] Our series contributes to this rare body of evidence with two distinct high-frequency families. In the first family, three siblings were diagnosed with NPC. In the second family, the disease affected the proband, one of the proband's siblings, and the proband's son. The importance of familial clustering in non-endemic regions, such as Türkiye, is further highlighted by the case report from Kara et al.[13] Although genetic analysis was performed on the proband and two living relatives, no specific germline susceptibility mutation was identified, suggesting that familial aggregation may involve multifactorial genetic or environmental factors rather than a single causative gene. We were unable to perform genetic analysis due to the retrospective nature of the cohort and the long study period beginning in the 1980s, when routine genetic testing was not available.

In addition to genetic susceptibility, environmental and infectious factors are also believed to contribute to familial clustering of NPC.[10,15–17,20,21] Previous studies have suggested that shared EBV exposure within families, combined with host genetic susceptibility, may contribute to the development of NPC. Shared environmental exposures such as dietary factors, tobacco exposure, and occupational carcinogens may also be relevant in families with similar lifestyles and living conditions. Therefore, familial NPC is generally considered a multifactorial disease resulting from the interaction between genetic predisposition, EBV infection, and environmental exposures rather than a purely hereditary cancer syndrome. In our cohort, EBV status and molecular viral analyses were not systematically available due to the retrospective design, the long study period, and the limited availability of historical virological data.

### Limitations of the Study

This study represents one of the largest familial NPC cohorts from a non-endemic Mediterranean region, spanning over three decades of follow-up. However, it is not without limitations. As a retrospective, single-center study, the familial NPC rate may be underestimated since family members were not systematically contacted after the probands' death. The EBV status of the patients was not systematically available, which limited our ability to evaluate viral contribution to familial clustering. Furthermore, as our institution is a tertiary referral oncology center, potential referral bias may have enriched the proportion of complex or familial clusters identified in this cohort. In addition, given the limited sample size, long-term survival endpoints were considered exploratory, precluding comprehensive multivariate or Kaplan–Meier survival comparisons. Finally, genetic analysis could not be performed due to the retrospective design and limited availability of biological samples. Future prospective studies incorporating molecular and genomic profiling are needed to understand better the genetic and environmental susceptibility factors of NPC in Türkiye.

## CONCLUSION

Our study confirms a familial NPC frequency of 2.1%. While this is lower than that in endemic regions, the high concentration of cases among FDRs – particularly siblings – and the presence of other primary malignancies suggest an underlying genetic susceptibility. Given these findings, siblings of NPC patients in non-endemic regions could be considered a subgroup that may benefit from increased clinical awareness.

**Ethics Committee Approval:** The study was approved by the Istanbul University, Oncology Institute Ethics Committee (no: 4029480, date: 17/04/2026).

**Informed Consent:** Informed consent was obtained from all individual participants who were alive at the time of the study.

**Conflict of Interest Statement:** None declared.

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**Peer-review:** Externally peer-reviewed.

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