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Familial oral lichen planus: A new risk group for oral cancer?

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Abstract

Objective: The familial type of oral lichen planus (OLP) is rare, with a paucity of data regarding its clinical significance. Our objective was to characterize patients with familial OLP.

Methods: Families with at least two members diagnosed with OLP were included. Clinical and demographic data and medical history were recorded.

Results: Twenty families, 19 Jewish and 1 Arab, were identified. Of the Jewish families, 57.8% were non-Ashkenazi, originating mainly from central Asia. Of those with OLP there were 14 males and 23 females with an average age of 49.1. Dyslipidemia, cardiovascular, and thyroid disorders (27.7%, 22.2%, and 16.6%, respectively) were the most common comorbidities. Five patients from five distinct families had oral cancer, two with second primary.

Conclusions: To the best of our knowledge, this is the largest study describing familial OLP. The predominant and common ethnicity of the families with multiple members diagnosed with OLP may imply an ethnic tendency. The higher tendency of hypothyroidism and the high percentage of OSCC among familial OLP patients might be connected to familial OLP and the latter suggests that this population is predisposed to malignant transformation. Thus, this group should be considered as a high-risk group.

KEYWORDS
lichen planus, oral carcinoma, oral diseases, thyroid

1 | INTRODUCTION

Lichen planus (LP) is a relatively common chronic mucocutaneous disease predominantly affecting the skin and oral mucosa, although other mucous membranes and skin appendages can also be involved. Oral lichen planus (OLP) affects 0.5%–2% of the population with a predilection for women (60%–75% of patients) and middle age (Giuliani et al., 2019; Ioannides et al., 2020). Transformation of OLP lesions into oral squamous cell carcinoma (OSCC) is the most serious complication of the disease (Giuliani et al., 2019; González-Moles et al., 2020). Although the potential of OLP and lichenoid lesions for malignant transformation is subject to controversy [3] (González-Moles et al., 2020), according to the World Health Organization, OLP and oral lichenoid lesions are potentially malignant disorders [4] (Warnakulasuriya et al., 2021). Lifelong follow-up is the current recommendation to ensure early detection of cancerous lesions (Carrozzo et al., 2019) and recognition of patients at risk is therefore important.

The etiopathogenesis of OLP is not completely understood, but it is thought to be immune-mediated and multifactorial (Ioannides et al., 2020). Some reports suggest it is a response to

extrinsic antigens, altered self-antigens or super antigens (Khudhur et al., 2014). Others reported associations between LP and other medical conditions, such as autoimmune disorders, including thyroid diseases (Zhou et al., 2018), Type 1 diabetes mellitus (Bokor-Bratic et al., 2013), rheumatoid arthritis (De Porras-Carrique et al., 2023; Ioannides et al., 2020), or metabolic syndrome (Baykal et al., 2015).

The oral disease is characterized by relapses and remissions, and manifests as white reticular lesions, which can be accompanied by atrophic, erosive, ulcerative, or plaque-type areas. Lesions are frequently bilateral and symmetrical (Warnakulasuriya et al., 2021). OLP reduces patient quality of life due to burning sensations, discomfort, unpleasantness, or pain (Abdalla-Aslan et al., 2016) which can even prevent adequate nutrition (Czerninski et al., 2014).

Familial OLP is rare, and few cases have been reported worldwide [13–18] (Bermejo-Fenoll & Lopez-Jornet, 2006; Cassol-Spanemberg et al., 2019: Kofoed & Wantzin, 1985; Mahood, 1983; Sandhu et al., 2003; Singal, 2005). Therefore, specific characteristics or unique manifestations of the familial form of the disease are unclear. In order to elucidate details about this form of the disease and its malignant transformation, we identified families with OLP, and analyzed the demographic, medical background, clinical features, and incidence of malignant transformation of the patients.

2 | METHODS

2.1 | Participants

Patients routinely examined at the Department of Oral Medicine, Sedation and Imaging, Hebrew University-Hadassah School of Dental Medicine, Jerusalem, Israel, are regularly requested to provide information regarding their family's medical history, specifically regarding lichen planus. In this case, family members who were either active patients or opted for examination at the oral disease clinic were included.

The examinations were conducted by two skilled oral medicine specialists, who based their diagnoses on clinical observations and, in some cases, histological analysis. Additional data were gathered from medical documents and files stored at the medical center. Data collection included demographic data, medical history, and lifestyle, history of the disease and histological diagnosis, and clinical manifestations (oral and cutaneous).

Those families with at least two family members (including uncles and aunts) diagnosed with OLP were included in the study.

3 | RESULTS

Twenty families with familial OLP were identified (Figure 1). Out of them, three families (in which the patient reported an additional family member diagnosed with OLP) were only included regarding the ethnic origin data due to lack of cooperation from family members. The remaining 17 families included 37 OLP patients. (The data tables did not include a family member (Family 5) who had passed away many years before the study).

3.1 | Demographic data and lifestyle

Fourteen males and 23 females with an age range at the time of diagnosis of 14–70 years (mean = 49.1 years) were included. A summary of the ethnic origins of the families is presented in Table 1. Consanguinity was reported in 3 (17.6%) of the 17 families. Seven of the patients (19.4%) were smokers and 5 (13.8%) reported alcohol consumption (Table 1).

3.2 | Medical history and oral cancer

The most common comorbidities were dyslipidemia (10 patients, 27.7%), cardiovascular disease (8 patients, 22.2%), and thyroid diseases (6 patients, 16.6%). Other conditions are presented in Table 2.

Five OLP patients, from five different families, had OSCC (13.5% from a total 37 affected OLP patients): 3 had no known risk factors (smoking or alcohol consumption) and 2 reported a history of smoking (both stopped 30 years before their diagnosis) without alcohol consumption. An additional family member from a sixth family had OLP and tongue SCC but died preceding the study (not included in Table 2). Two of the 5 patients with OSCC had a second primary OSCC.

3.3 | Clinical characteristics

Thirteen (38.2%) of the 34 patients of which we have the data, had a history of pain with an intensity ranging from 2 to 10 on verbal analogue scale (VAS) and mean of 6.3. Seven patients reported discomfort (intensity ranging from 1–5 on verbal analogue scale -VAS of 1–10). The remaining patients were asymptomatic, and had missing data (data not shown). Buccal mucosa was the most prevalent site of involvement ($n = 28$) followed by the gingiva and dorsal tongue (Table 3). The reticular/plaque type was the most common ($n = 22$) followed by the red/erythematous type and the erosive type. Thirty patients (88.2%) had a bilateral distribution, and 4 had a unilateral distribution (3-data missing) (Table 3). Diagnostic oral biopsy information was available for 23 patients, 7 had signs of dysplasia (Table 3).

Four patients had dermatologic involvement (16%, 4 out of 24) with the scalp being the most involved site, and none reported receiving treatment for the skin involvement (Table 5).

4 | DISCUSSION

Oral lichen planus is a relatively common disease impairing quality of life and predisposing to malignancy. It is considered a sporadic

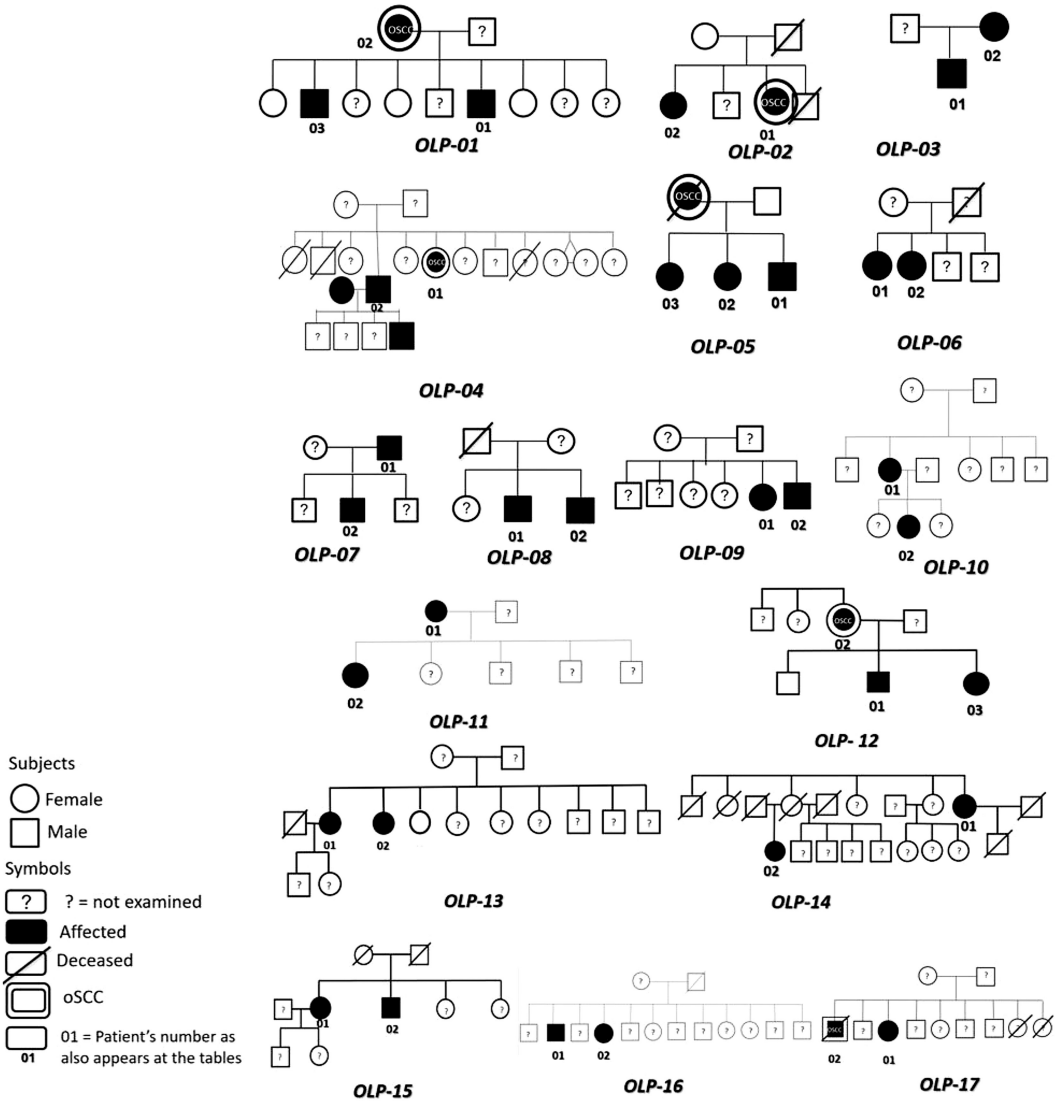

FIGURE 1 Pedigrees of families with members diagnosed with OLP. *For Family OLP-04, only individuals identified as full family members (designated by numbers) are included in the tables.

disease and cases of familial OLP are rare. While the incidence of familial LP reportedly varies from 1% to 11% of all LP patients (Bermejo-Fenoll & Lopez-Jornet, 2006), familial OLP is even less common (Lu et al., 2016). Between 1970 and 2020 there were publications on less than 50 families with familial LP, some with oral involvement [17–20], (Bermejo-Fenoll & Lopez-Jornet, 2006; Lu et al., 2016: Singal, 2005; Wang et al., 2020). In the current study we describe 20 families with familial OLP. To the best of our knowledge, this is the largest series of familial OLP reported in the English literature.

OLP usually affects individuals 30–80 years of age, mainly during middle age, with higher prevalence in women (Cheng et al., 2016). Familial OLP is reportedly more severe than the nonfamilial form with an earlier onset (Sandhu et al., 2003); however, in our study, the age and sex distribution were similar to those reported for sporadic OLP.

We found a higher percentage of cases in patients of non–Ashkenazi Jewish ethnicity, specifically those of Iran-Iraq-Kurdistan-Turkey Jews, comprising only 6% of the Israeli Jewish population (Israel Central Bureau of statistics-Jews by country of origin and age, n.d.). The largest ethnic Jewish groups in Israel are North African (Morocco and Tunisia) followed by Ashkenazi (European) Jews, but in the current study families from these ethnicities were the minority. This may be coincidental due to the small size of the cohort, or may imply a unique tendency of familial OLP among central Asia and Balkan area ethnicities.

In comparison, the prevalence of sporadic OLP worldwide was reported to be lower in Asian countries than in non-Asian countries (Li et al., 2020) and there have been reports of familial OLP of non-Jewish origin from various countries (Spain, England, Denmark, India, and China), (Bermejo-Fenoll & Lopez-Jornet, 2006; Cassol-Spanemberg et al., 2019; Kofoed & Wantzin, 1985; Lu et al., 2016; Mahood, 1983; Sandhu et al., 2003; Singal, 2005).

The most serious consequence of OLP is malignant transformation into SCC. Currently, OLP and oral lichenoid lesions are

TABLE 1 Demographic data and lifestyle/habits of affected participant.

	Member	Gender	Age at diagnosis	Ethnicity	Consanguinity*	Smoking	Alcohol consumption
Family OLP 01	1	m	41	Muslim Arab	Same region	-	-
	2	f	63			-	-
	3	m	41			yes	-
Family OLP 02	1	f	48	Iran	Parents first cousins	past	-
	2	f	63			yes	-
Family OLP 03	1	m	41	Russia	-	-	yes
	2	f	70		Grandparents first cousins	-	-
Family OLP 04	1	f	49	Kurdistan Iraq	-	-	-
	2	m	n/a		-	-	yes
Family OLP 05	1	m	14	Ashkenazi	-	-	-
	2	f	23		-	-	-
	3	f	22		-	-	-
Family OLP 06	1	f	n/a	Iraq	-	-	yes
	2	f	56		-	yes	-
Family OLP 07	1	m	69	Ashkenazi	-	past	yes
	2	m	38		-	yes	-
Family OLP 08	1	m	54	Turkey, Bulgaria	-	past	-
	2	m	46		-	yes	yes
Family OLP 09	1	f	67	Iraq	Parents 1st cousins	-	-
	2	m	66			-	-
Family OLP 10	1	f	22	Iraq	-	past	-
	2	f	NA		NA	NA	NA
Family OLP 11	1	f	66	Jew Kurdistan, Turkey	-	-	-
	2	f	32		-	-	-
Family OLP 12	1	m	42	Kurdistan, Greece -(Balkan)	-	yes	-
	2	f	50		-	-	-
	3	f	56		-	-	-
Family OLP 13	1	f	49	Iran, Iraq	-	-	-
	2	f	57		-	-	-
Family OLP 14	1	f	70	Greece Balkan Ashkenazi	-	yes	-
	2	f	65		-	past	-
Family OLP 15	1	f	54	Ashkenazi, Russia	-	past	-
	2	m	n/a		-	-	-
Family OLP 16	1	m	37	Yemen	-	-	-
	2	f	NA		-	-	-
Family OLP 17	1	f	50	Morocco	-	-	-
	2	m	51		-	Past	Past
Total participants	*37*	*m = 14 f = 23*	*Mean = 49.1*		*No cons.-28 Same reg-3 Parents 1st cousins-4 Grandpa 1st cousins-1 Unknown-1*	*No = 22 (61.1%) Yes = 7(19.4%) Past = 7 (19.4%) NA = 1*	*no = 31 (86.1%) yes = 5 (13.8%) NA = 1*
Non cooperative families (*n* = 3): Iran-Iraq-Kurdistan-Turkey/Yemen -Morocco/Europe Russia							
Ethnicity of all families (*N* = 20)				**Muslim Arab** 1 (5%)	**Jews-NA** 11 (55%)	**Jews-A** 5 (25%)	**Jews-M** 3 (15%)
of Jews (*N* = 19)					57.8%	26.3%	15.7%

Abbreviations: Jews A, Jews Ashkenazi; Jews M, Jews mixed; Jews NA, Jews non-Ashkenazi**; NA, not applicable; OLP, oral lichen planus.

*In two families, parents were first cousins, and in one family the grandparents of the mother were first cousins. One family had very low consanguinity with an unknown relation several generations back. **Jews -Non-Ashkenazi include: Iran-Iraq-Kurdistan-Turkey-Yemen, Morocco; Jews -Ashkenazi include-Europe Russia (no Balkan area); Jews mixed includes both groups.

TABLE 2 Medical history of affected participants.

	#	Gender	Age ex.	DL	HTN/MI	GID HD	HYPT	DM	OS/OA	Other	History of malignancy
Family OLP 01	1	m	42	+	−	−	−	−	−	−	−
	2	f	65	−	+ HTN	+ IBD	+	+	−	−	OSCC
	3	m	45	−	−	−	−	−	−	−	−
Family OLP 02	1	f	62	−	−	−	+	−	−	−	OSCC
	2	f	66	−	−	−	−	−	−	−	−
Family OLP 03	1	m	43	−	−	−	−	−	−	−	−
	2	f	75	−	+ HTN	+ PU	−	+	−	−	−
Family OLP 04	1	f	56	−	−	+ GERD	−	−	−	−	OSCC
	2	m	62	−	+ HTN	−	+	−	−	−	−
Family OLP 05	1	m	30	−	−	−	−	−	−	migraine	−
	2	f	36	−	−	−	+	−	−	−	−
	3	f	38	−	−	−	−	−	−	protein S deficiency	*-
Family OLP 06	1	f	66	+	+ HTN	−	−	+	−	−	−
	2	f	64	+	−	−	−	−	+ OS	glaucoma, psoriasis, hyperparathyroidism, psoriasis	−
Family OLP 07	1	m	72	−	−	−	−	−	−	hyperplastic prostate	−
	2	m	39	−	−	−	−	−	−	−	−
Family OLP 08	1	m	55	−	+ MI	+ Colon polyp	−	−	−	−	−
	2	m	46	−	−		−	−	−	−	−
Family OLP 09	1	f	71	−	−	−	+	+		asthma	−
	2	m	68	−	−	+ fatty liver	−	−	−	glaucoma	−
Family OLP 10	1	f	60	+	−	+	−	−	−	−	-
	1	f	NA			gastritis					-
Family OLP 11	1	f	71	+	−	−	−	−	+ OS	−	−
	2	f	36	−	−	−	−	−	−	−	−

TABLE 2 (Continued)

	#	Gender	Age ex.	DL	HTN/MI	GID HD	HYPT	DM	OS/OA	Other	History of malignancy
Family OLP 12	1	m	52	+	−	−	−	−	−	Gout	−
	2	f	81	+	+ HTN	−	−	+	−	−	OSCC (second primary)
	3	f	56	+	−	−	−	−	−	anemia	
Family OLP 13	1	f	70	+	+ HTN	−	+	−	−	−	−
	2	f	59	−	−	−	−	−	−	−	−
Family OLP 14	1	f	90	+	+ HTN	−	−	−	−	−	−
	2	f	71	−	−	−	−	−	−	−	−
Family OLP 15	1	f	74	−	−	−	−	−	+ OS	−	Past (breast cancer, follicular lymphoma)
	2	m	72	−	−	−	−	−	−	−	−
Family OLP 16	1	m	60	−	−	+ HBV	−	−	−	−	−
	2	f	65	−	−	−	−	−	−	−	−
Family OLP 17	1	f	50	−	−	−	−	−	−	_	−
	2	m	51	−	−	bile	−	−	−	Heart murmur	OSCC
Total participants	***37***	*m = 14 f = 23*		***10 27.7%***	***8 22.2%)***	***GI-6 16.6% hepatic-2 5.5%***	***6 16.6%***	***5 13.8%***	***3 8%***	***1 2.7***	*No: 31(83.7%) Yes: 6(16.6%) OSCC= 5(13.9%)**

Abbreviations: Age ex, age at examination; DL, dyslipidemia; DM, diabetes mellitus; GERD, gastro-esophageal reflux; GID, gastrointestinal disorders; H, Hashimoto thyroiditis; HD, hepatic diseases; HTN, hypertension; HYP.T, hypothyroidism; IBD, inflammatory bowel disease; MI, myocardial infraction; OA, osteoarthritis; OS, osteoporosis; OSCC, oral squamous cell carcinoma; PU, peptic ulcer.

*Family OLP5-mother with OLP had a tongue SCC and deceased prior to the study.

TABLE 3 Clinical and histological characteristics of affected participants.

	Member	Type of LP	Bilateral	Number of sites involved	Biopsy	Dysplasia at diagnostic biopsy	Dermatologic involvement
Family OLP 01	1	E	yes	5	+	Mild	Scalp
	2	E	yes	5	+	–	Scalp
	3	W	yes	2	+	–	–
Family OLP 02	1	R	yes	4	+	–	Shins
	2	W	yes	2	–	–	–
Family OLP 03	1	E	no	2	+	–	–
	2	E	yes	4	+	–	–
Family OLP 04	1	W	yes	2	+	Severe	–
	2	W	no	1	–	NA	–
Family OLP 05	1	W	yes	3	+	–	–
	2	W	yes	2	+	–	–
	3	W	yes	4	–	NA	–
Family OLP 06	1	R	yes	3	–	NA	Scalp
	2	E	yes	2	–	NA	–
Family OLP 07	1	E	yes	3	+	Mild	–
	2	R	yes	3	+	–	–
Family OLP 8	1	W	yes	2	+	–	–
	2	W	yes	1	–	NA	–
Family OLP 9	1	W	yes	1	+	Mild	–
	2	W	yes	3	+	–	NA
Family OLP 10	1	E	yes	6	+	-	-
	2	NA	NA	NA	NA	NA	NA
Family OLP 11	1	W, R	yes	3	–	Mild	NA
	2	W, R	yes	2	–	–	NA
Family OLP 12	1	W	yes	1	+	s	NA
	2	W, R	yes	4	+	Mild	–
	3	W	yes	1	–	–	–
Family OLP 13	1	W, R	yes	2	+	–	–
	2	W, B	yes	4	+	–	–
Family OLP 14	1	W	yes	4	–	–	NA
	2	R	no	1	+	–	NA
Family OLP 15	1	W	no	1	–	–	NA
	2	NA	NA	NA	NA	NA	NA

TABLE 3 (Continued)

	Member	Type of LP	Bilateral	Number of sites involved	Biopsy	Dysplasia at diagnostic biopsy	Dermatologic involvement
Family OLP 16	1	W	yes	2	+	–	NA
	2	NA	NA	NA	NA	NA	NA
Family OLP 17	1	R	Yes	3	+	NA	–
	2	W	Yes	3	+	Mild	–
Total participants	**37**	***W=22*** ***R=9*** ***E=7*** ***B=1*** ***NA=3***	***BL=30*** ***UL=4*** ***NA=3***	***Mean=2.6***		***Mild=6*** ***Severe=1*** ***No dysplasia=21*** ***NA=9***	***Scalp=3*** ***Shins=1*** ***No involvement=20*** ***NA=12***
Sites of intraoral involvement-*n* (%)* multiple oral sites per patient is possible							
Buccal mucosa 28(82.4%)	Gingiva 20 (58.8%)	Dorsal tongue 15 (44.1%)	Lateral tongue 13 (38.2%)	Hard palate 6 (17/6%)	Hard palate 6 (17/6%)	Floor of the mouth 3 (8.8%)	Lip or labial mucosa 2;2 (5.8%;5.8)

Abbreviations: B, bullous; E, erosive; NA, not applicable; R, red; W, white; (reticular and papular).

*Percentage of 34 patients, 3 had no data.

considered as potentially malignant disorders (Warnakulasuriya et al., 2021). The transformation rate of OLP to carcinoma is inconsistent in the literature but according to a recent publication by Warnakulasuriya et al., 2021 it is between 1% and 2%. There have only been a few cases of OSCC in familial OLP reported in the literature. Wang et al., 2011 described a Chinese family with OLP with severe oral reticular and erosive lesions, and 2 of the 5 affected individuals developed oral cancer at an early age. Bermejo-Fenoll & Lopez-Jornet, 2006, reported familial OLP in six families in Spain, none of whom developed oral cancer. According to Lu et al., 2016, among 18 OLP patients from eight families there were no malignant or premalignant lesions.

In the current study 5 out of 37 OLP patients developed SCC (13.5%), and there was a history of OLP and OSCC in the mother of an additional family. Out of the 20 families we analyzed, 6 (30%) had a member diagnosed with OLP and OSCC, of them 5 (25%) were female. Importantly, 2 had a second primary OSCC. This observation may suggest an increased risk of malignant transformation among patients with familial OLP.

Smoking and alcohol consumption are known risk factors for OSCC development and screened for in the families we examined. We found a lower alcohol consumption percentage than reported in Israel (43.1% for Jews and 15.3% for Arabs) (Israel Center for Disease Control 2007–2010). The percentage of smokers in our cohort is similar to the general Israeli population of 20.1% (Israel Center for Disease Control, 2013–2015). Two patients who developed SCC had a history of smoking (ceased 30 years before examination), and none of the OSCC patients was a current smoker. Taken together, our study participants were not at higher risk for oral cancer due to lifestyle decisions compared to the general population, reinforcing the assumption that familial OLP is an independent risk factor for oral cancer.

There was a higher percentage of hypothyroidism among the familial OLP patients (16.6%) than the general population in Israel (1.4%) (Rennert & Peterburg, 2001). The higher prevalence of thyroid diseases among OLP patients is well known Alrashdan et al., 2016; De Porras-Carrique et al., 2023; Robledo-Sierra et al., 2015). The prevalence in our study, 16.6%, was higher than reported in the literature for sporadic OLP patients. Although the reason for the higher association of thyroid diseases with OLP is still unknown, it may be due to a common autoimmune process Robledo-Sierra et al., 2015. While OLP is not associated with abnormal levels of antithyroid antibodies (Robledo-Sierra et al., 2018), the higher expression of thyroid-stimulating hormone receptor in OLP lesions suggests that some of the immunological mechanisms involved in autoimmune thyroid disease might play a role in the etiology of OLP. LP (oral and cutaneous) is reportedly associated with other autoimmune disorders (e.g., systemic lupus erythematosus, Sjögren syndrome) Kurago, 2016. We did not find that familial OLP patients were at a higher risk for other autoimmune diseases (one OLP patient had psoriasis). Other prevalent comorbidities in our study were dyslipidemia, cardiovascular diseases, and diabetes mellitus, with rates comparable to the general

Israeli population (30%, 20%, and 15%–19%, respectively) (Israel Center for Disease Control, 2013–2015; Israel diabetes registry report, 2019).

The clinical characteristics of the familial OLP patients were similar to those reported for OLP, with about two-thirds having either pain or discomfort at some point and 40% asymptomatic (Alrashdan et al., 2016). Sixty-two percent of the familial OLP patients had the white type and 48% had red and erosive or bullous types, at some point, which is analogous to the reported data for sporadic OLP (Carbone et al., 2009). In the present study, 82% of OLP lesions were bilateral, which is similar to sporadic OLP reported previously among patients in our clinic (Czerninski et al., 2015). The sites most involved in the current study were the buccal mucosa followed by the gingiva and the tongue, also similar to sporadic OLP (Carrozzo et al., 2019]. In comparison to our previous study (Carbone et al., 2009), familial OLP patients had more lesions on the dorsal tongue and gingiva, but because of the small cohort size these findings may not be indicative.

Dermatologic involvement in our study was 16%, which is comparable to the 15% reported in the literature for sporadic OLP (Wang et al., 2020).

In this study, one-third of the oral biopsies showed dysplasia (including from the smoker and one past smoker). In order to minimize interobserver differences among pathologists we compared the current results to our previous study conducted at the same institution with the same pathologist. 38.5% (79 of 205) lichenoid biopsies had dysplasia (Carbone et al., 2009), suggesting a similar rate in sporadic and familial OLP.

Limitations of the study include the fact that only one center was involved, which may limit the ability to generalize the results. As explained in the materials and methods section, this study was observational in nature and did not involve a matched control group. Statistical analysis was hindered by the small number of participants. To further investigate potential genetic causes, our next course of action involves conducting a prospective study. This future study will include HLA typing and genetic analyses of families, building upon the current findings.

5 | CONCLUSIONS

To the best of our knowledge, this study, with 20 OLP families, is the largest to date in the English literature. This may imply that familial OLP is more prevalent in specific ethnic groups, that is, has an ethnic tendency.

The high percentage of oral cancer among familial OLP patients in the absence of other risk factors might indicate a genetic predisposition to malignant transformation in this population. Identification of families with OLP may improve clinical management of high-risk patients, enabling early detection of malignant transformation. Therefore, we believe that inquiry about additional family members diagnosed with OLP should be part of the routine assessment of OLP patients. We therefore recommend that further studies of larger groups will be conducted in multiple centers, with genetic analysis of identified families.

AUTHOR CONTRIBUTIONS

Rakefet Czerninski: Conceptualization; funding acquisition; writing – original draft; methodology; supervision; writing – review and editing; formal analysis; resources; validation; data curation; project administration; software; investigation; visualization. **Zinat Awadieh:** Investigation; project administration; software; writing – original draft; formal analysis; visualization. **Svetlana Feldman:** Investigation; writing – original draft; software; project administration; formal analysis; validation. **Naama Keshet:** Investigation. **Abraham Zlotogorski:** Conceptualization; writing – review and editing; supervision; resources; methodology. **Yuval Ramot:** Conceptualization; investigation; funding acquisition; writing – review and editing; resources; validation; methodology; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author on reasonable request.

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