

# Iris Freckles a Potential Biomarker for Chronic Sun Damage

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**PURPOSE.** To investigate the role of sunlight exposure in iris freckles formation.

**METHODS.** We prospectively examined volunteers attending a skin cancer screening program conducted by ophthalmologists and dermatologists. Frequency and topographical variability of iris freckles were noted and associated with behavioral and dermatologic characteristics indicating high sun exposure.

**RESULTS.** Six hundred thirty-two participants ( $n = 360$ ; 57% female) were examined. Mean age of all participants was  $38.4 \pm 18.4$  years (range, 4–84 years). Of all individuals, 76.1% ( $n = 481$ ) exhibited at least one iris freckle. Most freckles were observed in the inferior temporal quadrant. The presence of iris freckles was associated with higher age (participants with iris freckles:  $41.8 \pm 16.8$  years versus participants without iris freckles:  $27.6 \pm 19.2$  years), a high number of sunburns during lifetime ( $>10$ : 31% vs. 19%), sunlight-damaged skin (26% vs. 11%), presence of actinic lentiginosities (72% vs. 45%), and a high total nevus body count ( $>10$ ; 78% vs. 67%).

**CONCLUSIONS.** The association of iris freckles, behavioral factors, and dermatologic findings, as well as the topographical distribution, indicate that sunlight exposure may trigger the formation of iris freckles. The evaluation of iris freckles offers an easily accessible potential biomarker, which might be helpful in indicating sun damage on the skin associated with cutaneous malignancies. Furthermore, the evaluation of iris freckles could also be helpful in understanding the role of sunlight in several ophthalmologic diseases.

**Keywords:** iris, freckles, sun exposure, iris nevus, iris neoplasms

Iris freckles; occurring in approximately 60% of all individuals, are the most common melanocytic iris lesions.<sup>1–3</sup> The term “iris freckle” is not comparable to the dermatologic definition of a “freckle,” which names a cluster of melanocytes that overproduce melanin granules. The number of melanocytes in a skin freckle is not increased. Iris freckles, in contrast, appear to be discrete, superficial colonies of atypical melanocytes at the iris surface that vary in their capability to synthesize pigment.<sup>1,4</sup>

Despite their frequent occurrence in adults, only little is currently known about the genesis of iris freckles. In contrast to iris nevi, which are thought to be of congenital origin caused by a melanocytic acceleration during embryogenesis, iris freckles are more commonly seen in elderly persons rather than in young adults.<sup>2,5</sup> Although iris freckles seem to have no malignant potential, pathways involved in the evolution of these melanocytic lesions might be interesting from a clinical point of view: in dermatology the appearance of hyperpigmented spots—especially in chronic sun-damaged skin—is linked to a high lifetime accumulation of sunlight. The UV-B spectrum of sunlight is a well-known promoter of melanogenesis.<sup>5–11</sup> The eyes are exposed to the light most of the time, and therefore it seems obvious that the iris is also affected by sunlight.

However, high cumulative doses of sunlight are also known risk factors for several dermatologic (e.g., nonmelanoma skin cancer) and ophthalmologic diseases (e.g., cataract or macular degeneration) and are mostly observed in elderly patients.<sup>11–17</sup> Thus we hypothesized that the formation of iris freckles might also be linked to sunlight exposure.

The aim of the present study was to investigate the frequency and topographical variability of iris freckles in a cohort of volunteers attending a skin cancer screening program and to associate them with behavioral and dermatologic characteristics in order to investigate the role of sunlight exposure in iris freckle formation.

## PATIENTS AND METHODS

During June 2012, we conducted a prospective, interdisciplinary study in which we examined nonhospitalized participants attending the skin cancer screening campaign .sun.watch., founded by the Austrian Cancer Aid/Styria, in a prospective setting. Screenings were performed in three different recreation areas in Styria.

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the local ethics committee (24-338 ex 11/12).



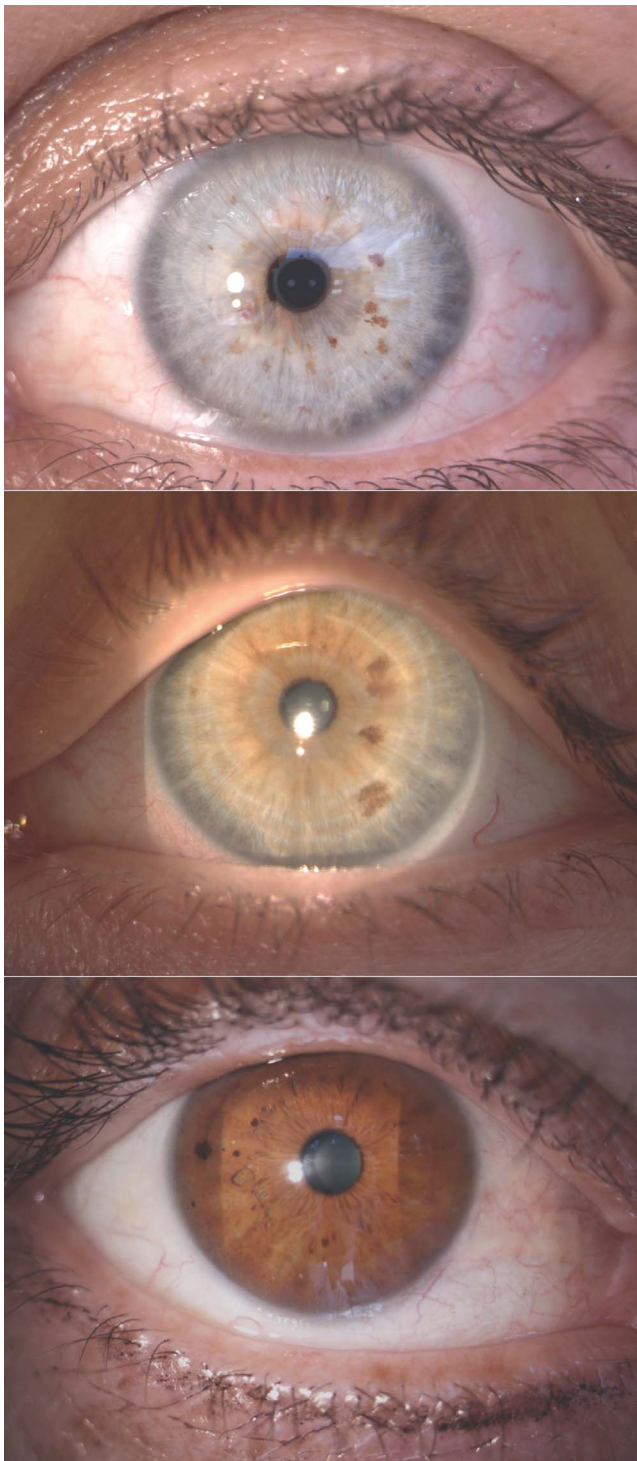


FIGURE 1. Examples of iris freckles and iris color stratification (*top*) light colored; (*middle*) medium colored; (*bottom*) dark colored.

Parts of these studies regarding the presence of iris nevi in this cohort have been published previously.<sup>18</sup>

Inclusion criterion was an age of 4 years or above to ensure compliance during slit lamp examination. Patients using prostaglandin eye drops were excluded.

After informed consent, all included patients filled out an anonymous questionnaire in which they were asked their age, sex, and factors indicating high amounts of sun exposure

TABLE 1. Presence of Iris Freckles With Regard To Sex and Iris Color

	Iris Freckles				P Value
	Absent		Present		
	n	%	n	%	
Iris color					
Light colored	78	51.7	259	53.8	0.030
Medium	26	17.2	118	24.5	
Dark	47	31.1	104	21.6	
Sex					
Female	86	57.0	274	57.0	1.000
Male	65	43.0	207	43.0	

(number of total sunburns and sunburns during childhood, the use of sun protection, and their outdoor behavior). For children <14 years, the legal guardian fulfilled the questionnaire.

Afterward, the participants were examined by experienced dermatologists for the following parameters: the total estimated body nevus count (scored as none, 1–10, 11–20, 21–50, 51–100, 101–200, and >200); the presence of atypical, congenital, acral, and facial nevi; actinic lentiginos (in accordance with the study of Garbe et al.<sup>19</sup> stratified into none, few, and many); as well as skin type (according to the Fitzpatrick classification<sup>20</sup>) and signs of chronic sun damage to the skin (dyspigmentation of skin commonly exposed to sun, spider veins, leathery and lax skin, and actinic keratosis).

After dermatologic examination, participants underwent a careful slit lamp examination performed by experienced ophthalmologists.

The presence, number, and location (upper nasal, upper temporal, lower nasal and lower temporal) of iris freckles were noted. An iris freckle was defined as small flecks of pigment, which range in color from yellow-tan to deep chocolate-brown on the anterior surface of the iris without involvement of the iris stroma. These criteria were chosen to distinguish iris freckles from iris nevi, which, in contrast, occupy and distort the iris stromal architecture.<sup>1,21,22</sup> All iris freckles were documented by an iris photo.

Iris color was recorded stratified into three groups: blue = light colored; green to gray = medium colored; brown = dark colored (Fig. 1).

For statistical analysis, the software SPSS (version 24.0; IBM Corp, Armonk, NY, USA) was used. Categorical data are presented as frequencies and percentages, and continuous data are described by means  $\pm$  standard deviations, medians, minimum, and maximum. Comparisons of participants with and without iris freckles were performed using Fisher's exact test for the categorical parameters presented in Tables 1 through 3. For the age comparison between the groups, a *t*-test was used. To evaluate the association between number of iris freckles (for both eyes) and age, the Spearman rank correlation coefficient was calculated. A *P* value <0.05 was considered to indicate statistical significance. All *P* values are regarded in an explorative sense.

## RESULTS

### Participants

Six hundred thirty-two participants (360 [57%] female) were examined dermatologically and ophthalmologically. The mean age of all persons was  $38.4 \pm 18.4$  years (range, 4–84 years). No sex-related age differences were observed (mean age female  $37.3$  years  $\pm 17.8$  versus male  $39.8$  years  $\pm 19.2$ ).

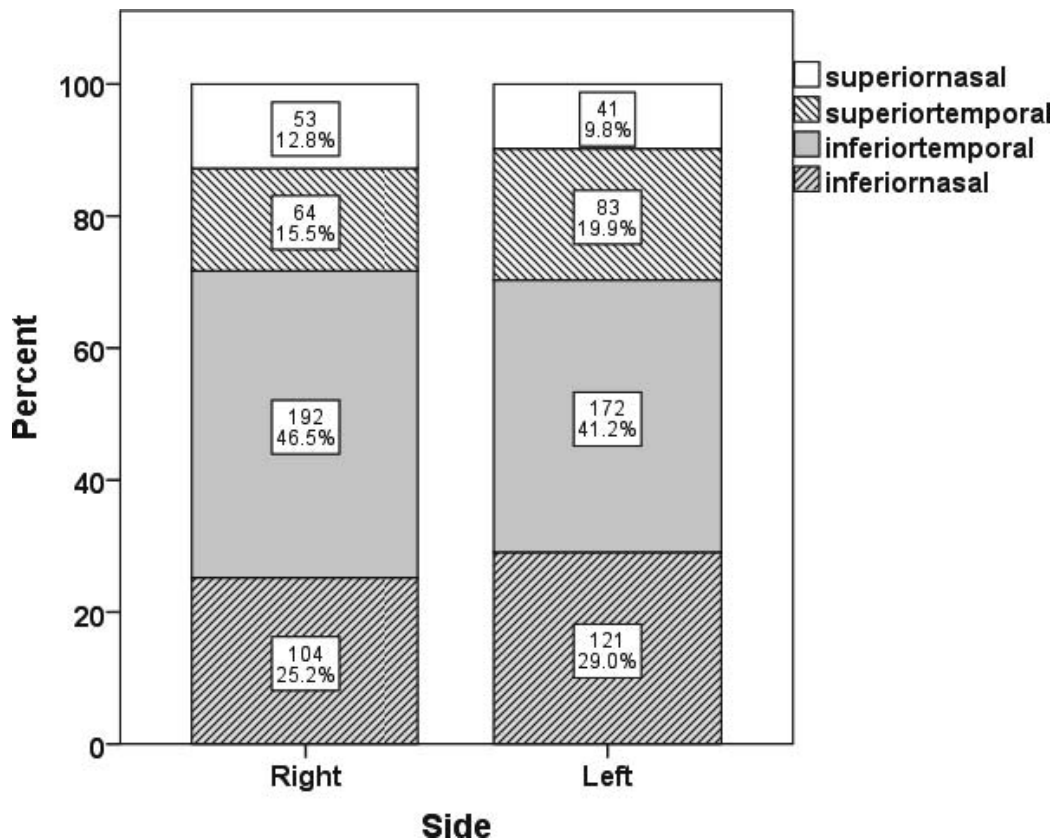


FIGURE 2. Sectorial distribution of iris freckles.

### Ophthalmologic Findings

Of all individuals, 76.1% ( $n = 481$ ) exhibited at least one iris freckle. The median number of iris freckles was five (range, 1–70) freckles. Most individuals exhibited bilateral lesions ( $n = 349$ ; 72.6%), but in 132 individuals, freckles were seen only unilaterally ( $n = 64$ , 13.3% right side, and  $n = 68$ , 14.1% left side).

For each individual, the iris sector exhibiting the highest number of iris freckles was noted, which in more than 70% of cases was the inferior iris quadrants (Fig. 2).

### Association of Iris Freckles With Demographics and Clinical Characteristics

Most participants had a light-colored iris ( $n = 337$ ; 53.3%), while medium ( $n = 144$ ; 22.8%) and dark color ( $n = 151$ ; 23.9%) were nearly equally distributed. Concerning participants with and without iris freckles, iris freckles were less present in individuals with a dark-colored iris. No sex-related differences were observed (Table 1).

The presence of iris freckles was statistically significant ( $t$ -test,  $P < 0.001$ ) related with older age: participants without iris freckles were  $27.6 \pm 19.2$  (median 26, range 4–77) years old, and participants with iris freckles were  $41.8 \pm 16.8$  (median 41, range 6–84) years old. Further statistical analysis revealed that the number of iris freckles correlated significantly with age (Spearman's  $\rho$  0.411;  $P < 0.001$ ).

### Questionnaire

A majority ( $n = 560$ ; 89.2%) of participants stated that they protect themselves from sun exposure, while only a minority

( $n = 46$ ; 7.4%) stated that they never experienced a sunburn. One hundred seventy (27.6%) individuals stated they had experienced a severe sunburn with blisters. Details about the questionnaire with regard to the presence of iris freckles are given in Table 2. Individuals with iris freckles were statistically significantly associated with an estimated higher number of lifetime sunburns (Fisher's exact test,  $P < 0.001$ ) and a history of severe sunburns with blisters (Fisher's exact test,  $P = 0.034$ ).

### Dermatologic Findings

Several dermatologic factors, especially those indicating high sun exposure, such as chronic light-damaged skin, actinic keratosis, or freckles on the skin, were carefully investigated and noted. Details about these indicators with regard to the presence of iris freckles are given in Table 3. Strong statistically significant associations were observed for actinic lentigines, sun-damaged skin, and the presence of freckles on the skin (Fisher's exact test,  $P < 0.001$ ).

### DISCUSSION

Our study adds further knowledge about the frequency and topographical variability of iris freckles as well as associated dermatologic findings, which allows for insights into the pathways involved in the development of iris freckles. In this study we observed statistically significant associations of iris freckles with factors well known to indicate high sun exposure.<sup>23,24</sup> The UV-B spectrum of the sunlight leads to direct damage of the DNA.<sup>25,26</sup> Several defense mechanisms are triggered by high amounts of UV-B radiation, including DNA repair to revert damage, apoptosis to remove irreparably damaged cells, and increased melanocytic stimulation to

**TABLE 2.** Results of the Questionnaire With Regard to the Presence of Iris Freckles

Parameters Questionnaire	Iris Freckles				P Value
	Absent		Present		
	n	%	n	%	
Spends most of the time indoors, <i>n</i> = 603					
Yes	83	57.6	300	65.4	0.112
No	61	42.4	159	34.6	
Uses sun protection, <i>n</i> = 628					
Yes	142	94.0	418	87.6	0.034
No	9	6.0	59	12.4	
Sun protection: use of clothing, <i>n</i> = 560					
Yes	58	40.8	178	42.6	0.768
No	84	59.2	240	57.4	
Sun protection: use of sun cream, <i>n</i> = 560					
Yes	120	84.5	336	80.4	0.318
No	22	15.5	82	19.6	
Sun protection: staying in the shade, <i>n</i> = 560					
Yes	42	29.6	162	38.8	0.055
No	100	70.4	256	61.2	
Estimated lifetime number of sunburns, <i>n</i> = 618					
None	25	17.0	21	4.5	<0.001
1-5	62	42.2	176	37.4	
6-10	32	21.8	130	27.6	
>10	28	19.0	144	30.6	
History of severe sunburns (with blisters), <i>n</i> = 615					
Yes	30	20.5	140	29.9	0.034
No	116	79.5	329	70.1	
History of sunburns during childhood, <i>n</i> = 520					
Yes	98	76.6	326	83.2	0.115
No	30	23.4	66	16.8	
Use of (refractive) glasses, <i>n</i> = 632					
Yes/sometimes	20	13.2	84	17.4	0.258
No	131	86.8	397	82.5	
Wears contact lenses, <i>n</i> = 632					
Yes	17	11.3	57	11.9	1.000
No	134	88.7	424	88.1	
Use of sunglasses, <i>n</i> = 632					
Yes/sometimes	120	79.5	404	84.0	0.215
No	31	20.5	77	16.0	

prevent future damage.<sup>10,11</sup> Melanocytes produce melanin that readily absorbs UV-wavelength light, acting as a photoprotectant. However, not only does melanocytic stimulation lead to increased melanin production but also, due to an acceleration of melanocytes, to the formation of melanocytic nevi and actinic lentigines.<sup>10,23,27,28</sup>

Iris freckles are also an acceleration of melanocytes containing large granules of melanin, at the superficial anterior iris surface, which is one of the most sun-exposed areas of the body.<sup>1-3</sup>

In our study we found that the presence of iris freckles is associated with a higher total nevus body count, suggesting a relationship of pathways involved in iris freckle formation and neovogenesis of the skin.<sup>23,29</sup>

The stated lifetime numbers of sunburns, an inflammatory reaction to acute DNA damage caused by excessive UV

**TABLE 3.** Iris Freckles and Dermatologic Findings

Dermatologic Findings	Iris Freckles				P Value
	Absent		Present		
	n	%	n	%	
Skin type					
I + II	112	74.2	360	74.8	0.915
III + IV	39	25.8	121	25.2	
Actinic lentigines					
None	83	55.0	136	28.3	<0.001
Few	47	31.1	203	42.2	
Many	21	13.9	142	29.5	
Actinic keratosis					
Yes	3	2.0	28	5.8	0.081
No	148	98.0	453	94.2	
Sun-damaged skin					
Yes	16	10.6	126	26.2	<0.001
No	135	89.4	355	73.8	
Number of melanocytic nevi on the skin					
0-10	50	33.1	106	22.0	0.027
11-20	50	33.1	207	43.0	
21-50	34	22.5	100	20.8	
>50	17	11.3	68	14.1	
Presence of dysplastic nevi on the skin					
Yes	37	24.5	142	29.5	0.256
No	114	75.5	339	70.5	
Presence of melanocytic nevi on the facial skin					
Yes	109	72.2	337	70.1	0.682
No	42	27.8	144	29.9	
Presence of freckles on the skin					
Yes	38	25.2	222	46.2	<0.001
No	113	74.8	259	53.8	
Presence of congenital nevi					
Yes	57	37.7	183	38.0	1.000
No	94	62.3	298	62.0	

exposure, as well as a history of severe sunburns with blisters, were both associated with the presence of iris freckles.<sup>10,14,25,30</sup>

The same association was seen for sun-damaged skin and solar lentigines, both well-known factors for an increased risk of nonmelanoma skin cancers.<sup>4,6,8,19,31,32</sup>

Interestingly, we found individuals with dark iris color to be less likely to exhibit iris freckles. This might indicate that a dark iris color is less photosensitive than a light iris color, comparable to dark skin.<sup>19,20</sup> This finding is in line with several other studies reporting that the development of nevi, freckles, and melanomas often depends on both the individual predisposition (e.g., light iris/skin color) and environmental factors (e.g., sunlight exposure).<sup>19,21,33</sup> However, another possible explanation for this finding could be that iris freckles are more difficult to notice in very dark irises.

Furthermore, iris freckles were also associated with higher age. The correlation of iris freckles with age and their association with the estimated number of sunburns, actinic lentigines, and sun-damaged skin seem to suggest that iris freckles indicate a high cumulative dose of lifetime sun exposure.

In line with those findings, we also found that individuals using sun protection in general exhibited fewer iris freckles than those who stated they did not do so. Differentiating sun protection strategies, we found that neither individuals stated to wear clothing nor those who use sun cream to protect themselves had a lower prevalence of iris freckles. Both clothing and sun cream are important and effective sunlight protectants of the skin, but they do not influence the light exposure of the eye.

Wearing glasses (for refractive reasons), contact lenses, or sunglasses did not influence the presence of iris freckles. However, a clear statement regarding the role of these devices in protecting the eyes from sunlight cannot be done. Qualities of glasses and contact lenses differ widely, and therefore further measurements of the UV blockage capability of the glasses/sunglasses/contact lenses used would be necessary.<sup>12,34,35</sup>

Another interesting finding, underlining the role of sunlight in iris freckle formation, was their inhomogeneous distribution: A possible explanation for this phenomenon might be that the superior orbital rim and the upper eyelid shield the superior nasal and the superior temporal iris quadrants while the nose shadows the superior and inferior nasal iris quadrants, leaving the inferior temporal quadrant the most sun exposed.<sup>3</sup>

Therefore, iris sun exposure also seems to be inhomogeneous with the most sunlight-exposed inferior temporal quadrant followed by the inferior nasal, the superior temporal, and the superior nasal quadrant, respectively, and indeed we found the highest number of iris freckles in the most exposed inferior temporal quadrant followed by the nasal inferior quadrant. The lowest number of iris freckles was found in the superior nasal quadrant, which is the less sun-exposed quadrant, shadowed by the nose and the orbital rim.

A limiting factor of our study is that the iris freckle prevalence that we observed was higher than that described in literature (76% vs. 60%).<sup>2,3</sup> As the study was conducted in a nonhospital setting, namely in three different, outdoor public swimming areas, participants recruited in these areas might have been more sun exposed during their lifetime due to individual behavioral characteristics.

Additionally, the assessment of sun exposure was based (besides clinically dermatologic findings) on a self-reported questionnaire. On the one hand, self-reports are important tools as they allow for the collection of individual data that is not interfered with by clinical observations. On the other hand, individuals might not report truthfully as an individual may not remember exactly (e.g., sunburns during childhood) or would like to present themselves in a socially accepted manner (e.g., the use of sun protection).

The role of sun exposure in the development of iris freckles seems to be obvious, but the (additional) influence of sun exposure in several ophthalmologic diseases (of the cornea, the retina, or the uvea, for instance) is not fully understood.<sup>35-39</sup> The presence of iris freckles is easily accessible, and their evaluation as a potential biomarker might be helpful in understanding the role of sunlight in this regard.<sup>36-40</sup> Based on our investigations, new recommendations regarding the use of eye-specific sunlight protection could be made.

Furthermore, from a clinical point of view, the presence of iris freckles also indicates sun damage to the skin, a risk factor for several different kinds of skin cancer. Within this context, there is certainly a need for further studies investigating the association between skin cancer and iris freckles.

In conclusion, our study confirms the hypothesis that the formation of iris freckles is induced by sunlight. Although iris freckles are believed to have no malignant potential, their presence might be indicative of a high cumulative dose of

sunlight (i.e., UV-B radiation) related to individual sun-exposure sensitivity. The evaluation of iris freckles offers an easily accessible potential biomarker that might be helpful in indicating chronic sun exposure. Therefore, the evaluation of iris freckles could be helpful in understanding the role of sunlight in several ophthalmologic diseases.

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