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Family History of Skin Cancer is Associated with Early-Onset Basal Cell Carcinoma Independent of *MC1R* Genotype

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Abstract

Background—As a marker of genetic susceptibility and shared lifestyle characteristics, family history of cancer is often used to evaluate an individual's risk for developing a particular malignancy. With comprehensive data on pigment characteristics, lifestyle factors, and melanocortin-1 receptor (*MC1R*) gene sequence, we sought to clarify the role of family history of skin cancer in early-onset basal cell carcinoma (BCC).

Materials and Methods—Early onset BCC cases (n=376) and controls with benign skin conditions (n=383) under age 40 were identified through Yale Dermatopathology. Self-report data on family history of skin cancer (melanoma and non-melanoma skin cancer), including age of onset in relatives, was available from a structured interview. Participants also provided saliva samples for sequencing of *MC1R*.

Results—A family history of skin cancer was associated with an increased risk of early-onset BCC (OR 2.49, 95% CI 1.80–3.45). In multivariate models, family history remained a strong risk factor for early-onset BCC after adjustment for pigment characteristics, UV exposure, and *MC1R* genotype (OR 2.41, 95% CI 1.74–3.35).

Conclusions—Risk for BCC varied based upon the type and age of onset of skin cancer among affected relatives; individuals with a first-degree relative diagnosed with skin cancer prior to age 50 were at highest risk for BCC (OR 4.79, 95% CI 2.90–7.90). Even after taking into account potential confounding effects of *MC1R* genotype and various lifestyle factors that close relatives may share, family history of skin cancer remained strongly associated with early-onset BCC.

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Keywords

Basal cell carcinoma; family history; skin cancer; epidemiology

1. INTRODUCTION

Basal cell carcinoma (BCC), which comprises the majority of non-melanoma skin cancers (NMSCs), is the most common cancer in humans and historically has been considered a disease of the elderly [1]. While the incidence of BCC in older individuals continues to rise [2– 6], there has also been a concurrent increase among individuals under age 40 [3, 6, 7]. This rapid increase in the incidence may indicate changes in lifestyle or environmental risk factors. However, genetic factors may also play an important role in the development of early-onset of BCC through gene-environment interactions.

Family history of cancer may be easily gathered through self-report and is often studied to evaluate an individual's risk for a particular malignancy. Importantly, family history is thought to be not only a marker of genetic susceptibility, but also to reflect shared lifestyle (environmental and behavioral) factors [8]. In several previous studies, a family history of skin cancer was shown to be an independent predictor of BCC without regard to the age at onset [9– 15], with a range of risk estimates from 2.0 to 17.0.

Although previous studies of BCC have evaluated family history of skin cancer in the context of host-related characteristics and lifestyle exposures, these evaluations have not assessed the impact of family history in the context of genetic risk factors. The melanocortin-1 receptor gene (*MC1R*), which codes for a protein that binds melanocyte-stimulating hormone and regulates skin and hair pigmentation, has been studied extensively in relation to BCC [16]. *MC1R* has been independently associated with BCC beyond pigment-related characteristics [17– 22]. It is currently unclear to what extent the risk for developing BCC associated with family history of skin cancer may be due to inherited variation in *MC1R*. Furthermore, previous studies have not assessed comprehensive data on NMSC and melanoma skin cancer family history separately, the degree of the affected relative, or the age of onset of skin cancer in relatives.

Our primary objective was to assess family history of skin cancer (melanoma and NMSC combined and separately, degree of relative with skin cancer, and age of onset of skin cancer in relative) in relation to risk of early-onset BCC. With additional data on *MC1R*, pigment characteristics, and lifestyle factors, we sought to evaluate how each of these variables might contribute to the observed association of family history of skin cancer with early-onset BCC, as well the independent association of family history after accounting for all of these factors.

2. MATERIAL AND METHODS

2.1 Study Population

The Yale Study of Skin Health in Young People is a case-control study of early-onset BCC described in detail elsewhere [23]. Individuals with BCC and controls with minor benign skin conditions were identified through the Yale University Dermatopathology database

between July 2006 and September 2010. To be eligible, participants must have been younger than 40 years at the time of skin biopsy, a Connecticut resident, and mentally and physically capable (or appropriate guardian for decisionally-impaired individuals or those age <18 years) of completing all study components. Study participants took part in an in-person structured interview, completed self-administered questionnaires, and provided a saliva sample with Oragene DNA 2- mL saliva collection kits (DNA Genotek Inc, Ottawa, Ontario, Canada). The Yale University Institutional Review Board approved this study and all participants (or guardians) provided written informed consent.

We enrolled a total of 389 BCC cases (participation rate: 72.8%) and 458 controls (participation rate: 60.7%). Cases were classified into single (only one BCC, n=242) or multiple (two or more BCCs, n=147) BCC under the age of 40 based on the Yale Dermatopathology database (data from 1990 on) and participant self-report. Controls were frequency matched to cases on age at biopsy (5-year age groups), gender, and biopsy site (head/neck, trunk, extremities). Among controls, the most common benign skin conditions were cyst (16.4%), seborrheic keratosis (16.2%), and wart (11.4%). All other skin conditions were present in <10% of controls.

During the structured interview, participants were asked about sociodemographics, outdoor UV exposure, indoor tanning, history of sunburns, sunscreen use, smoking status, and pigment-related characteristics (eye, skin, and hair color; skin reaction with first summer sun exposure; skin reaction to prolonged sun exposure; freckles on face; moles on back ≥5 mm). Interviewers were blinded to the case-control status until the end of the interview, when participants were asked about their personal history of cancer.

2.2 Assessment of Family History of Skin Cancer

An interviewer-administered structured interview was used to collect information about family history of skin cancer; separate response options were used for skin cancers other than melanoma, and for melanoma. Participants were asked to report family history of each of these for their grandparents, parents, siblings, and half-siblings individually. We also queried the age at which each skin cancer was diagnosed in each relative.

2.3 MC1R Sequencing and Variant Classification

DNA was isolated from saliva samples according to the manufacturer's protocol. Variants in *MC1R* were obtained via sequencing, with detailed methodology described elsewhere [23]. Sequencing was conducted at W. M. Keck Facility at Yale University using Applied Biosystems 3730 capillary instruments (Applied Biosystems, Carlsbad, CA). *MC1R* variants were classified into synonymous and nonsynonymous variants. All laboratory personnel were blinded to case-control status of study participants.

2.4 Statistical Analysis

The sample was limited to non-Hispanic white participants: 380 (97.7%) BCC cases and 390 (85.2%) controls. Three BCC cases were identified via a genetic sub-study on all cases as having Gorlin Syndrome and were excluded. Finally, 8 participants missing *MC1R* data were excluded. The total analytic population included 376 BCC cases and 383 controls.

We evaluated the univariate associations between baseline characteristics and early-onset BCC using χ^2 test for categorical variables and Wilcoxon rank sum or t-tests for continuous variables. Multivariate unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between family history of skin cancer and early-onset BCC. We also assessed family history of skin cancer in relation to multiple BCC and single BCC case status. We classified the family history of skin cancer exposure information in three ways. First, we evaluated family history of skin cancer (melanoma and/or NMSC) as a dichotomous variable. We then created a more detailed four-level categorical variable to assess family history: no family history; melanoma only; family history of NMSC only; and family history of both melanoma and non-melanoma skin cancer. Finally, we incorporated the degree of the relative with skin cancer (melanoma and/or NMSC) and the relative's age at diagnosis in another four-level categorical variable: no family history; skin cancer among grandparent(s) only; skin cancer among first-degree relative(s) with all being diagnosed at older ages (≥50 years); and skin cancer among any first-degree relative diagnosed at age <50 years old. First-degree relatives were defined as parents, children, siblings and half siblings. Fifty years of age was selected as the age threshold as it was the median age of skin cancer diagnosis for the youngest affected first degree relative.

Variables that altered the risk estimate by >10% or were significantly associated with disease status in the analytic population, except for *MC1R*, were included in the multivariate model. We then added *MC1R* to the multivariate model and evaluated the impact on the family history association in our fully adjusted model. We also assessed the impact of adding pigment-related characteristics (skin and hair color and skin reaction with first summer sun exposure), UV exposure variables (outdoor UV exposure, indoor tanning), and *MC1R* individually to a model only adjusted for study matching variables to determine the relative impact of each set of factors on the association of family history with BCC. Tests for trend were based on ordinal categorical variables.

All statistical tests were two-sided, with significance set *a priori* at P <0.05. Statistical analyses were performed using SAS version 9.3 (Cary, North Carolina).

3. RESULTS

The analytic population, comprised of 759 study participants, was 69.3% female with a median age at skin biopsy of 36.4 years. BCC cases had fairer pigment-related characteristics, were more likely to experience severe skin reactions to first summer sun exposure and prolonged sun exposure, and had a greater frequency of sunburns than controls (Table 1). BCC cases were more likely to have a family history of NMSC (62.2% vs. 33.7%, P<0.001); however, there was no significant difference between cases and controls with regard to a family history of melanoma (12.2% vs. 8.9%, P=0.13).

In the model accounting for sociodemographics, pigment characteristics, and outdoor and indoor UV exposure, individuals with any family history of skin cancer (melanoma and/or NMSC) had a greater risk of early-onset BCC compared to those without a family history of skin cancer (OR 2.49, 95% CI 1.80–3.45) (Table 2). Although family history of melanoma

only was not associated with early-onset BCC, individuals with a family history of both melanoma and non-melanoma skin cancer had a more than three–fold higher risk of early-onset BCC (OR 3.65, 95% CI 1.79–7.47). Among individuals with a family history of skin cancer in at least one first degree relative, the association with early-onset BCC varied based upon the affected relative's age at diagnosis (Table 2). Individuals with first degree relatives all diagnosed with skin cancer ≥50 years were nearly twice as likely to develop BCC (OR 1.88, 95% CI 1.25–2.84), whereas the likelihood of developing BCC was much greater for individuals with any first-degree relative diagnosed with skin cancer younger than 50 years (OR 4.79, 95% CI 2.90–7.90), as compared to individuals with no family history.

When we evaluated family history of skin cancer in relation to cases who had multiple BCCs compared to a single BCC, family history was more strongly related to multiple BCC (data not shown). For example, the association for family history of NMSC and/or melanoma was 2.80 (95% CI 1.74–4.52) for multiple BCC and 2.27 (95% CI 1.58–3.27) for single BCC.

The inclusion of *MC1R* nonsynonymous variants in the multivariate models slightly attenuated the association between family history of skin cancer and early-onset BCC; however, family history of skin cancer remained independently associated with early-onset BCC. After adjustment for *MC1R*, individuals with a family history of skin cancer were more than twice as likely to develop early-onset BCC (OR 2.41, 95% CI 1.74–3.35, as compared to OR 2.49, 95% CI 1.80–3.45 without adjustment for genotype) and those with a family history of NMSC and melanoma remained more than three times as likely to develop early-onset BCC (OR 3.54, 95% CI 1.72–7.26, as compared to OR 3.65, 95% CI 1.79–7.47 without adjustment for genotype) (Table 2). Individuals with a first-degree relative younger than 50 years at skin cancer diagnosis were still at the highest risk for developing early-onset BCC (OR 4.55, 95% CI 2.75–7.54, as compared to OR 4.79, 95% CI 2.90–7.90 without adjustment for genotype). *MC1R* was significantly associated with early-onset BCC in all multivariate models.

When we looked at the addition of pigment-related characteristics, UV exposure variables, and *MC1R* individually to the models, the greatest attenuation of risk in family history of skin cancer was due to the inclusion of pigment-related characteristics (skin and hair color and skin reaction with first summer sun exposure). For instance, the effect size of family history of skin cancer decreased from 3.10 (95% CI 2.29–4.20) in a model only adjusted for study frequency matching variables to 2.48 (95% CI 1.80–3.42) after adjusting for pigment-related characteristics. In comparison, the effect size of family history of skin cancer decreased from 3.10 (95% CI 2.29–4.20) in a model with study frequency matching variables to 2.78 (95% CI 2.04–3.79) following the addition of *MC1R*.

4. DISCUSSION

In our population, family history of skin cancer remained a strong risk factor for early-onset BCC after adjustment for pigment-related characteristics, UV exposure, and *MC1R* genotype. Adjustment for *MC1R* attenuated the effect size of family history of skin cancer modestly; notably pigment-related characteristics reduced the risk estimate for family

history more so than *MC1R* or UV exposure. Risk for BCC varied based on type of skin cancer in relatives, age of onset in relatives, and degree of affected relatives. Given that family history is a marker of genetic susceptibility and shared lifestyle factors, our findings suggest that unmeasured genetic and/or lifestyle factors underlie much of the association we have observed for family history.

In previous studies, a family history of skin cancer has been consistently shown as an independent predictor of BCC unselected for age at onset [9–15]. The effect size of this association has ranged broadly from 2.0 to 17.0. However, to the best of our knowledge prior studies have not evaluated the contribution to risk of BCC associated with NMSC and melanoma skin cancer history separately, the degree of relatedness of the affected relative, or the age of onset of skin cancer in relatives. Furthermore, previous studies had been limited by the absence of genetic data, such as *MC1R* sequencing, as well as the inclusion of family history of melanoma alone without information on NMSC. Our study includes *MC1R* and general skin cancer risk factor exposure data, which expands our understanding of the etiology and effect size of family history in development of early-onset BCC and addresses some of the limitations of previous studies of this risk factor.

Approximately 24% of cases had a first-degree relative diagnosed with skin cancer under age 50 in our study, and these individuals were more than four times as likely to develop early-onset BCC as compared with individuals with no family history. Earlier age at onset of cancer is generally associated with greater genetic risk. Thus, the high risk of BCC in those who had a first degree relative diagnosed with skin cancer under age 50 strongly supports the role of heritable factors, in addition to *MC1R* in the pathogenesis of early-onset BCC. Inherited variation in DNA repair genes may be an important hereditary factor, data for which were not available in our study. Associations between BCC and variants in genes for DNA repair pathways have been shown previously [24–26]. Other genetic factors may also play a role, as findings of recent genome-wide association studies for BCC include variants in the genes *TGM3* and *RGS22* [27–30].

When we evaluated pigment-related characteristics in our model, these variables explained more of the effect of family history than measures of UV exposure or *MC1R*. Heritability of pigment-related characteristics and risk for BCC are well known, and thus their role in explaining family history is not unexpected. However, the relative impact of pigment-related characteristics compared with measures of UV exposure or *MC1R* helps to elucidate the effect of phenotype in explaining risk due to family history more than other potentially shared risk factors between cases and affected relatives. While MC1R did not explain a significant proportion of the risk we observed with family history, our results and previous studies indicate an independent association of *MC1R* with BCC beyond pigment-related characteristics [17–22].

Shared lifestyle characteristics, such as environmental or behavioral factors, among family members may also contribute to the risk captured by family history of skin cancer. It is likely that individuals in our population shared UV-related activities, such as outdoor activities and family vacations, or UV protective behaviors such as sunscreen use, with family members. While we did assess UV exposure through multiple questions in our

interview, past UV exposure is challenging to measure. The addition of UV exposure variables to the model did attenuate the effect of family history, although a general question about an individual's family history of skin cancer may be an easier and complementary method to capture the composite of shared lifestyle factors above and beyond the individual questions on these topics.

Our study was strengthened by having full sequencing of *MC1R* to most accurately assess risk from this gene, as well as phenotype and lifestyle information, which enabled us to evaluate family history of skin cancer, in the context of a diverse set of known skin cancer risk factors. In addition, we comprehensively assessed family history of skin cancer during our interview using interviewers blinded to case-control status, such that we had data on type of skin cancer, degree of affected relative, and age of onset of disease in relatives.

Some limitations of this evaluation included that family history of skin cancer was not verified through objective methods, so it is possible some of the self-report family history data are inaccurate. In addition to the potential for overall inaccuracies, it is important to note that our findings may be susceptible to recall bias and an overestimate of the association due to BCC cases knowing more about their family's skin cancer history [31, 32]. However, controls were selected from a sample of individuals who had undergone a skin biopsy for benign skin conditions, and thus, were theoretically more similar to cases with regard to possible recall bias than controls selected from the general population. Other limitations of our study include the observational study design and the absence of genetic information beyond *MC1R*.

5. CONCLUSIONS

Our findings demonstrate that variants in the pigment-related gene, *MC1R*, account for a minor amount of the risk and that pigment-related phenotype explains a greater amount of risk for early-onset BCC due to family history of skin cancer. It is likely that other lifestyle factors also explain the risk of early-onset BCC associated with family history of skin cancer given the strong association of family history that remained following adjustment for pigment characteristics, measures of UV exposure, and *MC1R*. Individuals with a first-degree relative diagnosed with skin cancer prior to age 50 and those with a family history of both melanoma and NMSC are at highest risk for early-onset BCC. As the incidence of early-onset BCC continues to increase and young patients who have had skin cancer face decades of skin cancer risk, it is important that we continue to develop our understanding of risk factors for this malignancy. It is also notable that while many studies in this genomic era focus on the role of DNA genotype, a few simple questions about family history of skin cancer may be a strikingly predictive tool for assessing risk of early-onset BCC [8].

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Abbreviations

BCC	basal cell carcinoma
CI	confidence interval
NMSC	non-melanoma skin cancer
MC1R	melanocortin 1 receptor gene
OR	odds ratio
UV	ultraviolet

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Highlights

- Studies of familial skin cancer and basal cell carcinoma (BCC) are limited
- BCC risk varied by cancer type and age of onset of familial skin cancer
- The family history association was not explained by lifestyle or behavioral factors
- Evaluating family history may aid in assessing risk of early-onset BCC

Table 1

Selected characteristics among Non-Hispanic white early-onset BCC cases and control (n=759)

Characteristic	Cases, n (%) (n=376)	Controls, n (%) (n=383)	*P*-value[1]
Age (y), median (IQR)	36.3 (33.2–38.5)	36.6 (32.6–38.5)	0.864
Female	256 (68.1)	270 (70.5)	0.472
Body site of skin biopsy			<0.001
Head	204 (54.3)	161 (42.1)	
Extremity	72 (19.2)	125 (32.6)	
Trunk	100 (26.6)	97 (25.3)	
Education			<0.010
≤ Some college	105 (28.0)	143 (37.5)	
College graduate	112 (29.9)	111 (29.1)	
≥Some graduate school	158 (42.1)	127 (33.4)	
Hair color			<0.001
Black/dark brown	100 (26.7)	157 (50.0)	
Light brown	136 (36.3)	152 (39.7)	
Blonde/fair	100 (26.7)	63 (16.4)	
Red	39 (10.4)	11 (2.9)	
Skin color (inner upper arm)			<0.001
Olive	15 (4.0)	74 (19.3)	
Fair	212 (56.4)	233 (60.9)	
Very fair	149 (39.6)	76 (19.8)	
Skin reaction with first summer sun exposure			<0.001
Turn brown, no sunburn	6 (1.6)	31 (8.1)	
Mild sunburn followed by tan	142 (37.8)	196 (51.3)	
Painful sunburn peeling	198 (52.6)	142 (37.2)	
Severe sunburn blistering	30 (8.0)	13 (3.4)	
Skin reaction with prolonged sun exposure			<0.001
Very brown, deeply tanned	39 (10.4)	69 (18.0)	
Moderately tanned	168 (44.7)	220 (57.5)	
Mildly tanned peeling tendency	123 (32.7)	76 (19.8)	
Freckled, no suntan	46 (12.2)	18 (4.7)	
Moles ≥ 5 mm on back (n), median (IQR)	1 (0–3)	0 (0–2)	0.005
MC1R nonsynonymous variants			<0.001
0	65 (17.3)	131 (34.2)	
1	173 (46.0)	175 (45.7)	
≥ 2	138 (36.7)	77 (20.1)	
Outdoor sun exposure in warm months (h), mean ± SD	8946 ± 3426	8286 ± 3231	0.011[2]
Sunburns (n), median (IQR)	6 (1–16)	3 (1–9)	<0.001
Family history of skin cancer			
Family history of non-melanoma skin cancer	234 (62.2)	129 (33.7)	<0.001

Characteristic	Cases, n (%) (n=376)	Controls, n (%) (n=383)	*P*-value[1]
Family history of melanoma	46 (12.2)	34 (8.9)	0.132

IQR, Interquartile range; *MC1R*, melanocortin 1 receptor gene.

[1] X^2 for categorical variables, Wilcoxon rank sum for continuous variables

[2] *t* Test

Table 2

Multivariate association between family history of skin cancer and early onset basal cell carcinoma with and without *MC1R*

Characteristic	Cases/Controls	Multivariate model OR (95% CI)[1]	*P*-value	Cases/Controls	Multivariate model plus *MC1R* OR (95% CI)[2]	*P*-value
Family History of Skin Cancer						
No family history of skin cancer	130/233	1.00		130/233	1.00	
Family history of skin cancer	244/149	2.49 (1.80–3.45)	<0.001	244/149	2.41 (1.74–3.35)	<0.001
Type of Skin Cancer Family History						
No family history of skin cancer	130/233	1.00		130/233	1.00	
Family history of melanoma only	12/20	0.99 (0.43–2.25)	0.976	12/20	0.93 (0.41–2.13)	0.859
Family history of NMSC only	198/115	2.61 (1.85–3.68)	<0.001	198/115	2.53 (1.79–3.58)	<0.001
Family history of melanoma and NMSC	34/14	3.65 (1.79–7.47)	<0.001	34/14	3.54 (1.72–7.26)	<0.001
P trend[3]			<0.001			<0.001
Degree and Age of Onset Family History						
No family history of skin cancer	130/233	1.00		130/233	1.00	
Skin cancer among grandparents only	48/47	1.97 (1.19–3.25)	0.008	48/47	1.99 (1.20–3.30)	0.007
Skin cancer among 1st degree relative ≥50 years	96/73	1.88 (1.25–2.84)	0.003	96/73	1.80 (1.19–2.73)	0.005
Skin cancer among 1st degree relative <50 years	92/27	4.79 (2.90–7.90)	<0.001	92/27	4.55 (2.75–7.54)	<0.001
P trend[3]			<0.001			<0.001

OR, odds ratio; CI, confidence interval.

[1] Adjusted for age at diagnosis, body site, gender, skin color, hair color, first exposure of season to 1 hour of summer sun (turn brown with no sunburn, mild sunburn with some degree of tanning, painful sunburn for a few days following by peeling, severe sunburn with blistering), history of ever indoor tanning, and outdoor sun exposure in warm months (hours)

[2] Adjusted for variables in multivariate model plus MC1R nonsynonymous variants (0 variants, 1 variants, ≥ 2 variants).

[3] Based on ordinal categorical variables.