

***Null Results in Brief*****Fas/APO-1 Promoter Polymorphism Is Not Associated with Non-Melanoma Skin Cancer<sup>1</sup>****Heather H. Nelson,<sup>2</sup> Karl T. Kelsey, Megan H. Bronson, Leila A. Mott, and Margaret R. Karagas**

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**Introduction**

NMSC<sup>3</sup> incidence is increasing at an alarming rate (1), and the majority of NMSC is likely attributable to UV exposure. An important biological effector of UV exposure is the Fas receptor, which in cooperation with Fas ligand induces apoptosis in keratinocytes after UV exposure (2). The gene encoding Fas, *TNFRSF6*, contains a promoter single nucleotide polymorphism at position –670 that disrupts a GAS transcription factor binding sequence (3). Fas mRNA and protein are both induced after UV exposure (4), indicating that the regulation of this gene is important in the cellular response to UV. We tested the hypothesis that the –670 *G/A* promoter polymorphism of *TNFRSF6* was associated with NMSC.

**Materials and Methods**

Cases were identified through a state-wide incidence survey in New Hampshire as described previously (1). Cases were recruited from this incident survey, and population-based controls were frequency matched to cases on age and gender (5). All subjects were given an interviewer-administered questionnaire, and when possible a blood specimen was obtained. Genotyping was completed using a PCR-RFLP method as described by Huang *et al.* (3). ORs and 95% CIs were calculated using unconditional logistic regression; estimates were adjusted for age, gender, skin type (tendency to burn), and lifetime cumulative sun exposure. We used stratified analyses to determine whether the genotype-NMSC association varied by skin type, number of painful sunburns, or steroid use.

**Results**

The Fas promoter polymorphism was not associated with either basal cell carcinoma or squamous cell carcinoma. Allele frequencies did not vary significantly across case groups, and the associations remained null after adjustment for age, gender,

*Table 1* *TNFRSF6* polymorphism and NMSC risk

<i>TNFRSF6</i> genotype	Controls		BCC		SCC	
	<i>n</i> (%)	<i>n</i> (%)	OR <sup>a</sup> (95% CI)	<i>n</i> (%)	OR (95% CI)	
<i>G/G</i> (wild type)	101 (23.2)	120 (23.6)	Ref	53 (19.9)	Ref	
<i>G/A</i> (heterozygous)	200 (46.0)	234 (46.0)	0.99 (0.7–1.4)	155 (58.0)	1.39 (0.9–2.1)	
<i>A/A</i> (variant)	134 (30.8)	155 (30.4)	0.95 (0.7–1.4)	59 (22.1)	0.89 (0.6–1.4)	

<sup>a</sup>OR adjusted for age, gender, skin type (tendency to burn), and lifetime cumulative sun exposure.

skin type, and lifetime sun exposure (Table 1). There was no evidence of effect modification or interaction with known risk factors (data not shown).

**Statistical Power**

In comparing homozygote genotype groups, the study had >80% power to detect a statistically significant OR of 1.7 for basal cell carcinoma and 2.0 squamous cell carcinoma.

**Study Limitations**

Although this is a large study of NMSC, there are several potential limitations: (a) the study is geographically limited to New Hampshire and may not be representative of the disease outside this region; (b) although large, the study did not have sufficient power to detect ORs less than 1.7–2 and lacked power to detect modest interactions with exposure. Additional genetic variants in the Fas signaling pathway (*i.e.*, Fas ligand) have not been studied, and without such information, we cannot exclude the possibility that the –670 *TNFRSF6* polymorphism functionally interacts with other polymorphisms; and (c) we did not analyze the *Fas* gene for other single nucleotide polymorphisms and cannot rule out the possibility that additional variants exist and that they may impact NMSC risk.

**Conclusions**

The –670 *TNFRSF6* polymorphism has been reported to be associated with Alzheimer's disease and to interact with the APO-E variant (6), indicating that it has potential biological significance. Although Fas is an important mediator of the cellular UV response, this promoter polymorphism does not appear to impact NMSC risk.

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<sup>3</sup> The abbreviations used are: NMSC, non-melanoma skin cancer; OR, odds ratio; CI, confidence interval.

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