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Polymorphisms of FAS and FAS Ligand Genes and Risk of Skin Cancer

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Skin cancer is the most common form of cancer in the United States among Caucasians. DNA damage induced by ultraviolet (UV) exposure has been shown to be involved in the etiology of melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) [1]. Under normal conditions, UV-induced DNA damage is repaired by DNA repair mechanisms, or cells with damaged DNA undergo apoptosis [2]. Apoptosis can be triggered by one of the two pathways: an intrinsic pathway or an extrinsic pathway. In the extrinsic pathway, a death-ligand binds a death-receptor that is displayed on the cell surface of the damaged cell. FAS ligand (FASL [also known as CD95LG and TNFSF6]) is one such death-ligand, and FAS (also known as CD95, APO-1, and TNFRSF6) is the corresponding death-receptor. Without the ability to undergo death-signal-induced apoptosis, mutations can rapidly accumulate, potentially leading to uncontrolled growth and tumor formation. Irregular FAS/FASL signaling has been implicated in the pathogenesis of skin cancer. High expression levels of the FAS receptor on melanoma cell surfaces inhibit tumor growth [3]. FASL is commonly expressed in high levels in SCCs and BCCs; one explanation for this is that FASL expression allows the neoplasms to escape attack from the immune system [4]. This evidence suggests a potential role of FAS and FASL in the development of skin cancers and the possibility that functional polymorphisms in these genes might be associated with skin cancer susceptibility.

Two known polymorphisms in the FAS gene promoter region (–1377 G>A, rs2234767; and –670 A>G, rs1800682), as well as two in the FASL gene (–844 C>T in the promoter region, rs763110; and –124A>G in the second intron, rs5030772), have been studied with regard to functional relevance or cancer susceptibility. Of these four polymorphisms, three (rs2234767, rs1800682, and rs763110) have known functional effects [5–7]. In this study, we performed a skin cancer case-control study of Caucasians nested within the Nurses' Health Study (NHS) to evaluate whether these four common polymorphisms in the FAS and FASL genes as well as their haplotypes are associated with the risks of melanoma, SCC and

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BCC. The nested case-control study consisted of 218 incident melanoma cases, 285 incident SCC cases, 300 incident BCC cases, and 870 age-matched controls. A detailed description of the characteristics of cases and controls has been reported in a previous publication [8].

There was no significant association between FAS -1377 genotype and either melanoma risk or SCC risk (Table 1). There was, however, a significant association between the FAS -1377 minor allele (A) and BCC risk (Table 1, additive OR = 1.34; 95% CI = 1.02–1.77; p for trend = 0.03). There was no association between FASL -844 genotype and either melanoma risk or SCC risk but the FASL -844 minor allele (T) was inversely associated with BCC (Table 1, additive OR = 0.81; 95% CI = 0.66–0.99; p for trend = 0.04). Genotype of FASL IVS2nt -124 was not associated with the risk of any type of skin cancer (Table 1). The results did not change materially after additionally controlling for skin cancer risk factors.

No haplotype in the FAS gene was associated with either melanoma or SCC risk. There was suggestive evidence that the FAS -1377A/-670G haplotype (i.e. minor alleles at both polymorphic sites) was associated with an increased risk of BCC (Table 2, OR = 1.30; 95% CI = 0.98–1.73; p for Global test = 0.08). No haplotype in the FASL gene was associated with the risk of any type of skin cancer (Table 2).

FASL is commonly expressed in high levels in SCCs and BCCs [4]. Consistently, we observed that the low-expression allele in the promoter region of FASL (i.e. FASL -844T) is associated with a reduced risk of BCC. We did not detect any associations between individual FAS or FASL polymorphisms and the risk of melanoma or SCC. To our knowledge, only two studies have reported results on FAS and/or FASL and skin cancer thus far. Nelson and colleagues reported no association between the FAS -670 polymorphism and risk of non-melanoma skin cancer [9]. Li and colleagues reported associations between the FAS -1377A and FAS -670G variants and a decreased risk of melanoma [10]. They also reported an association between the AG+GG genotypes of the FASL INV2nt -124A>G polymorphism and an increased risk of melanoma. Regional immunity may play a role in how FAS/FASL polymorphisms affect cancer susceptibility. It may be that with keratinocytic stem cells, which are more available to attack by immune cells that do not have to travel all the way through the basal layer of the epidermis where FASL is highly expressed [4], the effect of increased FAS receptor expression on deletion of lymphocytes is not large enough to outweigh the benefit for keratinocytic cells to be able to be signaled efficiently for apoptosis. For melanocytes, the effect of increased FAS receptor expression on hypersensitive lymphocyte deletion, especially because to reach melanocytes (or keratinocytes not in the basal layer), lymphocytes would have to travel through the FASL-dense basal layer of the epidermis, may override the benefit of melanocyte- (or non-basal-layer keratinocyte-) sensitivity to apoptosis. For keratinocytes not in the basal layer, the effects may be balancing, explaining the negative results with respect to SCC. Likewise, with FASL expression, it may be that keratinocytes in the basal layer of the epidermis are more harmed by the pro-inflammatory state that accompanies increased FASL expression than they would be by potential benefits to the immune system. For melanocytes or non-basal-layer keratinocytes, the effects may be balancing.

In summary, we evaluated four FAS and FASL polymorphisms in three skin cancers, and we did not detect any associations with the risk of SCC or melanoma. The limitation of this study is the modest sample size in each cancer type. Nonetheless, this is the first report of an association between the functional polymorphisms FAS -1377A and FASL -844C, and the FAS -1377A/-670G haplotype and an increased risk of BCC.

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Abbreviations

SCC	squamous cell carcinoma
BCC	basal cell carcinoma
NHS	Nurses' Health Study
FAS	FAS (the cell-surface death-receptor), a.k.a. CD95, APO-1, and TNFRSF6
FASL	FAS ligand (the death-ligand), a.k.a. CD95LG and TNFSF6
OR	odds ratio
CI	confidence interval

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Table 1

Four SNPs in the FAS and FASL genes and skin cancer risk

	Melanoma			SCC			BCC		
	Controls (%)	Cases (%)	OR ^a	Cases (%)	OR ^a	Cases (%)	Cases (%)	OR ^a	Cases (%)
<i>FAS</i> -1377 G>A									
GG	657 (78.7)	155 (74.5)	1	209 (76.3)	1	216 (73.0)	1		
AG	167 (20.0)	52 (25.0)	1.26 (0.88–1.81)	61 (22.3)	1.15 (0.82–1.61)	72 (24.3)	1.29 (0.94–1.78)		
AA	11 (1.3)	1 (0.5)	0.43 (0.05–3.33)	4 (1.5)	1.13 (0.36–3.59)	8 (2.7)	2.18 (0.86–5.50)		
Additive OR		1.14 (0.82–1.59)		1.13 (0.84–1.52)		1.34 (1.02–1.77)			
<i>p</i> for trend		0.43		0.42		0.03			
<i>FAS</i> -670 A>G									
AA	224 (26.6)	53 (25.0)	1	74 (27.3)	1	78 (26.4)	1		
AG	438 (52.0)	116 (54.7)	1.08 (0.75–1.55)	128 (47.2)	0.89 (0.64–1.24)	153 (51.7)	0.98 (0.72–1.35)		
GG	180 (21.4)	43 (20.3)	0.98 (0.63–1.54)	69 (25.5)	1.17 (0.80–1.72)	65 (22.0)	1.03 (0.70–1.51)		
Additive OR		1.00 (0.80–1.24)		1.08 (0.88–1.31)		1.01 (0.84–1.23)			
<i>p</i> for trend		0.98		0.46		0.90			
<i>FASL</i> -844 C>T									
CC	347 (40.7)	80 (36.9)	1	116 (41.7)	1	133 (46.5)	1		
CT	385 (45.2)	102 (47.0)	1.14 (0.82–1.58)	117 (42.1)	0.91 (0.68–1.23)	124 (43.4)	0.84 (0.63–1.12)		
TT	120 (14.1)	35 (16.1)	1.29 (0.82–2.02)	45 (16.2)	1.13 (0.75–1.69)	29 (10.1)	0.63 (0.40–0.99)		
Additive OR		1.13 (0.91–1.41)		1.03 (0.84–1.25)		0.81 (0.66–0.99)			
<i>p</i> for trend		0.25		0.80		0.04			
<i>FASL</i> IVS2nt -124 A>G									
AA	560 (67.1)	140 (70.0)	1	176 (66.2)	1	199 (68.2)	1		
AG	257 (30.8)	58 (29.0)	0.90 (0.64–1.27)	76 (28.6)	0.94 (0.69–1.28)	92 (31.5)	1.00 (0.75–1.34)		
GG	17 (2.0)	2 (1.0)	0.44 (0.10–1.94)	14 (5.3)	2.65 (1.28–5.48)	1 (0.3)	0.17 (0.02–1.26)		
Additive OR		0.85 (0.62–1.16)		1.16 (0.90–1.49)		0.90 (0.69–1.17)			

	Melanoma			SCC			BCC		
	Controls (%)	Cases (%)	OR ^a	Cases (%)	OR ^a		Cases (%)	OR ^a	
<i>p</i> for trend			0.31		0.25			0.43	

^aUnconditional logistic regression adjusted for age.

Table 2

Haplotypes in FAS and FASL genes and skin cancer risk (age-adjusted OR)

<i>FAS</i>		Melanoma				SCC				BCC			
		Controls		Cases		Cases		Cases					
A	B	n	%	n	%	n	%	n	%	n	%		
0	0	891	52.6	222	52.4	283	51.1	310	52.2				
		OR		1.00		1.00		1.00					
0	1	609	36.0	147	34.7	201	36.2	196	32.9				
		OR		0.96 (0.75–1.22)		1.04 (0.84–1.29)		0.92 (0.74–1.14)					
1	1	192	11.3	55	13.0	70	12.7	88	14.9				
		OR		1.12 (0.80–1.59)		1.16 (0.85–1.57)		1.30 (0.98–1.73)					
A: –1377 G>A; B: –670 A>G													
<i>FASL</i>		Melanoma				SCC				BCC			
		Controls		Cases		Cases		Cases					
A	B	n	%	n	%	n	%	n	%	n	%		
0	0	1054	60.6	260	59.4	346	60.5	383	64.3				
		OR		1.00		1.00		1.00					
1	0	382	22.0	108	24.6	117	20.5	115	19.3				
		OR		1.21 (0.78–1.91)		0.91 (0.71–1.17)		0.84 (0.65–1.09)					
1	1	256	14.7	66	15.0	95	16.5	76	12.8				
		OR		1.03 (0.75–1.43)		1.17 (0.89–1.55)		0.81 (0.60–1.09)					
0	1	48	2.7	4	0.9	14	2.5	22	3.6				
		OR		–		0.79 (0.38–1.66)		1.31 (0.71–2.43)					
A: –844 C>T; B: IVS2nt –124 A>G													

0, common allele; 1, rare allele.

The OR was calculated for the risk for one additional haplotype.