Genetics of Cutaneous Melanoma

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A portion of melanoma is familial and has been associated with atypical mole syndrome. This review outlines the current understanding of the genetics of melanoma and the relationship to cutaneous nevus phenotypes. A review of genetic studies of melanoma is presented, including linkage studies. Data from a linkage study of 12 Utah kindreds and one Texas kindred are detailed.

There is strong evidence both for a genetic component to melanoma and, to a lesser extent, for a genetic component to the atypical mole phenotype. Reports of linkage of melanoma/dysplastic nevus syndrome to chromosome 1p markers are now strongly in doubt. The Utah group has shown strong evidence of linkage of melanoma to chromosome 9p21 without evidence for heterogeneity. This is in the same region where chromosomal deletions are common in tumors of numerous tissues.

We conclude that there is a specific melanoma susceptibility locus located on chromosome 9p. The combination of the results of linkage in families with multiple cases of melanoma and the deletion of this chromosomal region in sporadic cases of melanoma strongly suggests that this melanoma susceptibility locus acts as a tumor suppressor. *Key words: nevus/ linkage/tumor suppressor. J Invest Dermatol 103:112S–116S, 1994*

There is strong evidence that melanoma has a familial and a genetic component [1,2]. Since the late 1970s, most research on the genetics of melanoma has focused on its association with an atypical pattern of moles, now commonly known as the dysplastic nevus syndrome [3–6]. Genetic studies using the combined cutaneous melanoma-dysplastic nevus syndrome trait have been highly controversial. We have recently localized a melanoma risk allele to the chromosomal region 9p21 using invasive melanoma as the clinical manifestation of the susceptibility locus [7]. This review discusses the evidence for a specific melanoma susceptibility locus and the different methods of clinical, epidemiologic, and genetic analysis used in the studies of melanoma and nevi.

HISTORY

The clinical observation of families having an excess of melanoma was first made in 1951 by Cawley [1]. He described several kindreds where multiple first degree relatives had cutaneous melanoma. Throughout the 1950s and 1960s occasional case reports or small series of families with multiple members who had melanoma appeared in the literature. In 1971, Anderson estimated that approximately 10% of all melanoma was due to a specific familial association [2]. This estimate, based on clinical observation, is still in common usage in the medical literature.

A population-based assessment of the familiality of cancer by site was performed by Cannon *et al* [8]. This analysis showed that melanoma cases were more closely related and showed closer familial clustering than most other cancer sites, including colon cancer and breast cancer, which have been long recognized to have a familial component, and for which susceptibility loci have been mapped **(Table I)**.

MELANOMA AND NEVI

Genetic studies using a combined melanoma-dysplastic nevus syndrome trait have been highly controversial. Because the genetics of melanoma has largely been intertwined with the study of nevi, it is necessary to review the relationship of nevi to melanoma.

Recently an NIH consensus panel focusing on early melanoma has suggested dropping the term dysplastic nevus, due to problems of definition [9]. In some previous reports, dysplastic nevi were diagnosed clinically [10] (although dysplastic is a histopathologic term) and differing histologic criteria for dysplasia have been used in other studies. In most studies, absence of dysplasia has been evaluated by clinical examination only. Similar problems exist with diagnosis of the dysplastic nevus syndrome, often based on clinical or histologic criteria [11]. In this discussion the terms dysplastic nevus syndrome and dysplastic nevus are used for historical reference only. We prefer the terms clinically atypical nevus, nevus with architectural and/or cytologic atypia, and atypical mole syndrome.

There are several types of associations between nevi and melanoma. First, there is an obvious association in that they are a related cell type. There is also the clinical observation that melanoma may evolve from various types of nevi [6]. Estimates of the percentage of melanomas that arise from nevi vary widely. Some families with a high incidence of melanoma also have an abnormal clinical nevus phenotype, discussed below [6]. Finally, case-control studies have demonstrated an association of excess number of nevi and clinically atypical and/or histologically dysplastic nevi with melanoma risk in multiple ethnic groups on multiple continents [12–15].

The dysplastic nevus syndrome (DNS) was first described in 1978 and was termed BK mole syndrome [3,5] or familial atypical multiple mole melanoma syndrome [4]. Since those initial descriptions, most genetic studies of melanoma have incorporated some measure of nevus phenotype, often considering the atypical mole to be a premalignant lesion which might be expressed in gene carriers prior

Table I. Sixteen Common Cancers Ranked By Degree of Kinship[a]

Rank	Cancer Site	ICD Code	Number of Cases	Mean kinship of Cases ($\times 10^{-5}$)
1	Lip	140.	486	3.82
2	Melanoma	172.	499	3.32
3	Ovary	183.	435	3.02
4	Prostate	185.	2824	2.57
5	Colon	153.	1638	2.08
6	Rectal/Anal	154.	736	2.04
7	Breast (male & female)	174., 175.	2525	2.02
8	Hematopoietic	169.	941	1.95
9	Brain/CNS	191., 192.	520	1.89
10	Stomach	151.	575	1.89
11	Cervix	180.	588	1.87
12	Lung	162.	1117	1.82
13	Pancreas	157.	441	1.75
14	Endometrial	182.	865	1.75
15	Bladder	188.	1182	1.68
16	Lymphoma	196.	721	1.27

[a] Modified from [8] with permission.

Table II. Demographic Data, Lod Score and Posterior Probability of Linkage By Kindred For 13 Kindreds in the Utah Data Set

Kindred	Number	Average Age at dx	Total Number Sampled	Posterior Probability	Max LOD
3364	22	60	53	1.00	5.34
1771	14	40	30	1.00	4.24
3137	16	44	41	1.00	2.02
3012	4	46	9	0.98	1.01
1764	4	38	21	0.95	0.70
3355	3	43	22	0.83	0.08
1763	2	24	7	0.80	−0.01
3106	2	47	6	0.80	−0.01
3157	4	57	14	0.80	−0.01
3348	7	73	5	0.80	0.00
3006	6	60	26	0.58	−0.46
3247	3	82	9	0.57	−0.49
3343	8	44	17	0.33	−0.91

to expression of melanoma [11,16,17]. Originally, DNS seemed promising as a premalignant trait that would be useful in mapping and cloning a melanoma susceptibility locus. Much basic research has also been done on dysplastic nevus syndrome melanocytes, looking for a biochemical or molecular genetic lesion that would explain their propensity towards transformation to cancer [18].*†

The usefulness of DNS as a clinical bridge to the melanoma susceptibility locus hinged on the ability to make accurate diagnoses. In practice this means one should be able to take members of a family and divide them into two groups, affected and unaffected. Clinical, histopathologic, and cell biologic parameters had been suggested for those divisions. Unfortunately, as the case control studies cited above demonstrate, a fair proportion (5-14%) [10,14,15,19] of the general population has clinically atypical nevi and/or an increased nevus number. Some of the studies have suggested a gradient of melanoma risk with increasing number of nevi. Studies of children have suggested that sun exposure also significantly affects nevus number [20]. Finally the Utah data demonstrate a continuum of nevus phenotype, rather than a binary division.

Histology has been suggested as a specific marker for genetic melanoma risk and for the diagnosis of DNS [21]. However, histologic analysis of nevi removed from controls shows that 5–54% of the general population have histologically dysplastic nevi [19,22–

24]. The studies with higher estimates have biopsied a higher number of unselected subjects. In our recent study of prevalence of dysplasia, random nevi were sampled from random members of our community and assessed by six separate pathologists [25]. Estimates of the prevalence of histologic dysplasia ranged from 9 to 32% with three of the six pathologists clustered in the 12 to 19% range. If over 10% of random nevi are judged to be dysplastic, clearly the proportion of persons bearing such dysplastic nevi is greater than 10%. The histopathologic presence of an isolated dysplastic nevus is therefore not specific for melanoma risk. These clinical and histologic diagnostic problems make genetic analysis of such a trait difficult.

The inheritance pattern for DNS was said to be autosomal dominant with a very high penetrance, based largely on the initial clinical observation of a few families [16]. Statistical evidence that dysplastic nevus syndrome behaves as an autosomal dominant trait has been difficult to generate, and hinged on the analysis of dysplastic nevus syndrome and melanoma as a combined trait [16,26]. Formal segregation analysis of the dysplastic nevus syndrome (using clinical and/or histologic diagnostic criteria) has demonstrated over-segregation [16,27]. That is, matings between affected and unaffected persons result in more than half their children being affected. Possible explanations of this over-segregation include a high phenocopy rate in the general population or misdiagnosis of the phenotype. A third explanation is that the trait is more complex, either involving more than one gene or involving more than one gene and an environmental factor (polygenic or multifactorial inheritance). The statistical analysis of a pattern of inheritance or linkage is dependent on assumptions used in the genetic model, such as gene frequency, penetrance, and phenocopy rate, and is especially dependent on correct diagnosis. Any of these issues can drastically affect the results

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* Kraemer KH, Seetharam S, Waters HL, Seidman MM: Hereditary dysplastic nevus syndrome: abnormal UV mutagenic spectrum in association with increased melanoma susceptibility (abstr). *Clin Res* 36:664A, 1988

† Yohn J, Robinson W, Norris D: Melanocytes and nevus cells from dysplastic nevus syndrome patients do not have increased sensitivity to ultraviolet B radiation (abstr). *Clin Res* 36:706A, 1988
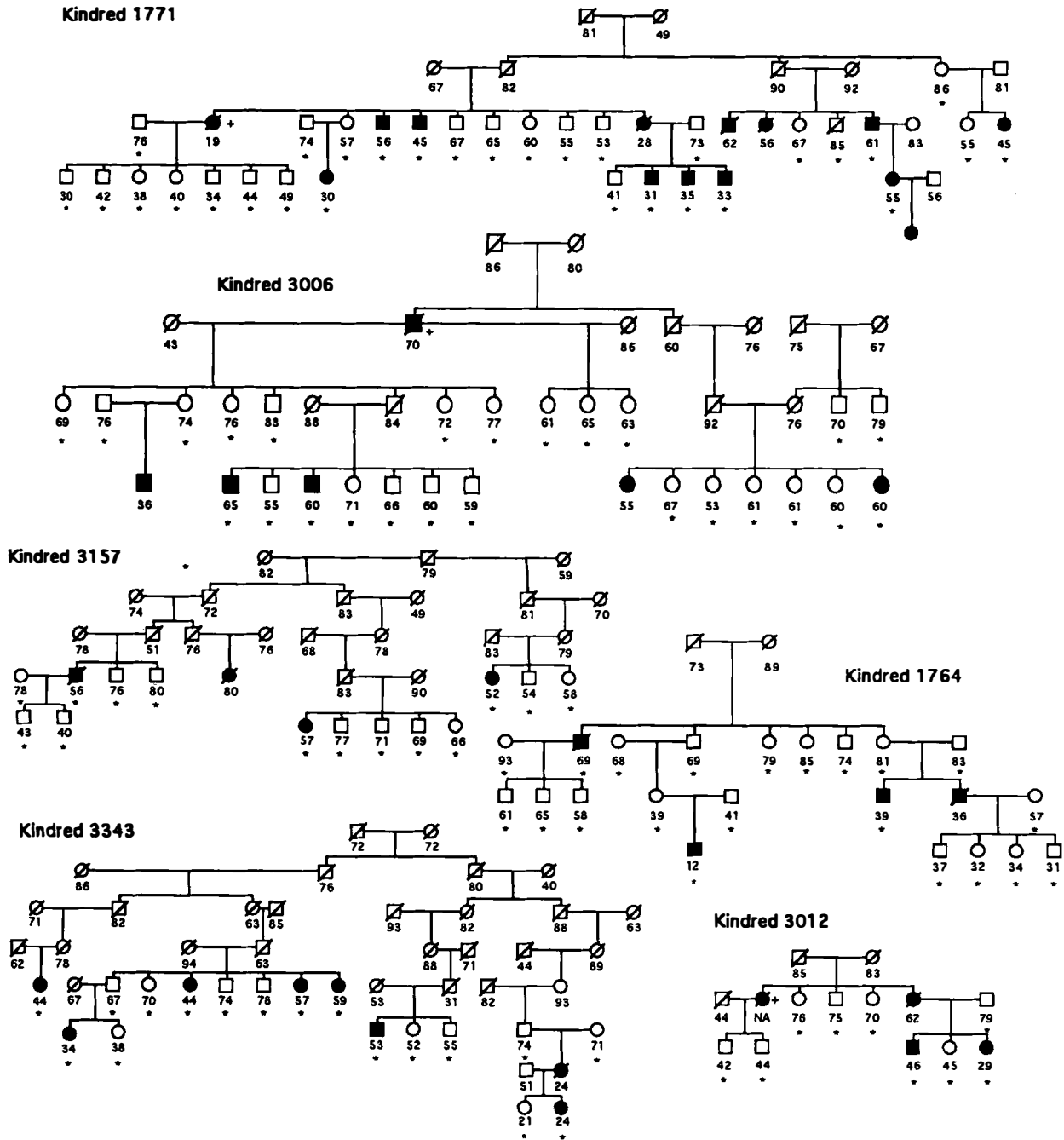
Figure 1. Pedigrees of six kindreds in the Utah data set. Individuals with melanoma have *solid circles*. The age of individuals at the time of the exam, at the time of melanoma occurrence, or at death is given below the symbol. Individuals with DNA samples available are indicated with an *asterisk*.

of genetic analysis. This may in part explain why different results have been reported. To avoid some of these problems, the Utah group chose to study the cutaneous melanoma phenotype only in studies looking for a susceptibility locus.

GENE LOCATION

Initial studies of "dysplastic nevus syndrome" and melanoma suggested loose linkage to the Rh locus on chromosome 1p [16]. A series of reports followed the initial linkage focusing first on dysplastic nevus syndrome and more recently on melanoma [11,28]. However, several groups have rejected linkage to 1p for either melanoma or for a combined melanoma and nevus phenotype trait [29–31].

Several other candidate regions have been suggested, largely based on cytogenetic studies of advanced tumors. Deletions in pre-

malignant tissue derived from dysplastic nevi suggested 9p as a possible site for a tumor-suppressor gene [32]. More recently the use of molecular probes involving conversion to homozygosity has refined the ability to study small deleted areas of chromosomes. The chromosome 9p location has emerged as a consistently deleted region in early melanomas [33]. Recently, a woman with multiple melanomas, multiple atypical nevi, and multiple congenital anomalies was identified as having a chromosomal abnormality. Cytogenetic chromosome analysis demonstrated a reciprocal translocation involving 5p and 9p, with the breakpoint being near 9p21 [34]. This supported 9p as a candidate for a melanoma risk gene.

LINKAGE EVIDENCE TO 9p

To avoid the problems with diagnosis and analysis of the dysplastic nevus syndrome as discussed above, we performed a linkage study
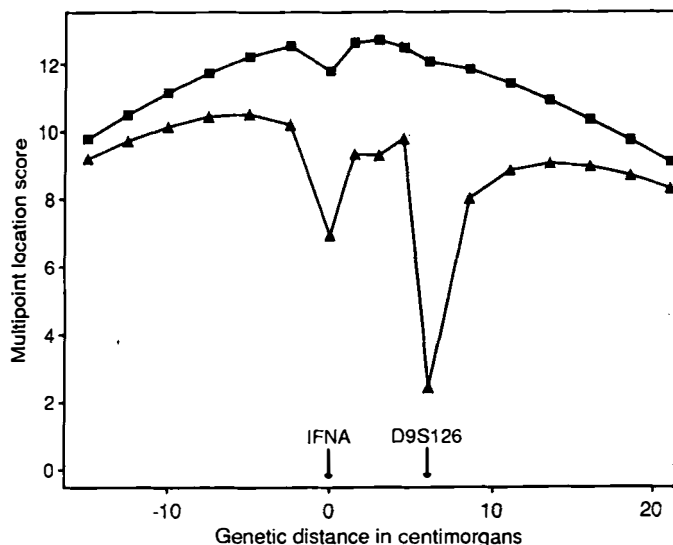
Figure 2. LOD score for various positions of the melanoma risk locus versus chromosome region on the short arm of chromosome 9 by multipoint linkage analysis [7]. *Solid squares* represents an age specific model that assumes melanoma is a rare autosomal dominant trait and allows sporadic cases of melanoma. The *triangles* represent an affected only model, which did not allow sporadic cases. For full details, see reference [7]. Reprinted from [7] with permission.

using invasive melanoma as the phenotype [7]. This requires a larger set of affected families than would a study of melanoma jointly with dysplastic nevus syndrome. We studied 13 families with multiple cases of melanoma (see **Table II**). Pedigrees of six of the Utah families are shown in **Fig 1**, with individuals affected with melanoma in solid symbols. Blood samples for DNA analysis were obtained from all available family members and, in several cases, DNA was extracted from the pathologic tissue blocks of melanoma patients who were deceased. In all cases, diagnosis of melanoma was confirmed, usually by examination of tissue slides, but where these were not available by pathologic report. Only invasive cutaneous melanoma was included; lentigo maligna melanoma, ocular melanoma, congenital neurocutaneous melanoma, and melanoma *in situ* were not considered part of the affected phenotype.

The linkage analysis used two probes from the region 9p21 near the interferon locus on chromosome 9p. Both probes are highly polymorphic in the general population, increasing their likelihood of providing information within each family. Linkage analysis tests the hypothesis that a particular polymorphism of one of the probes is co-inherited with the susceptibility to melanoma. If the melanoma susceptibility locus is in the same region of chromosome 9p as the probes, they will cosegregate within a family. The likelihood of a recombination between genetic loci varies, but is approximately 1% for every million base pairs. The statistical analysis of these data commonly uses a LOD score (which stands for logarithm of the odds) that allows this information to be pooled across families. A LOD score of 1 would correspond to odds of a physical association of the probe and the gene of 10 : 1, a LOD score of 3 would correspond to odds of 1,000 : 1, and a LOD score of 0 would indicate even odds or a 50 : 50 chance. Negative LOD scores indicate the odds are against linkage. These LOD scores can be computed for different locations of the gene relative to the probes used in the study, thus generating a probability curve that the gene in question would lie in the given region. Such a graph is shown in **Fig 2**, showing data from 10 of our Utah families and one Texas family [2]. As can be seen, the peak of the curve occurs at a LOD score of over 12, meaning the odds are 10^{12} to 1 in favor of a susceptibility locus for melanoma being in that region.

Many assumptions are made in calculating odds that the melanoma gene lies in a specific region. These analyses include estimates of the gene frequency in the general population, the sporadic rate

(the rate of melanoma occurring from non-genetic origins), and a penetrance probability, which is the probability of expression of the disease in a gene-carrier. Various sets of estimates were used in performing these calculations, covering different assumptions of the genetic component of melanoma, representing the upper and lower curves in **Fig 2** (for details see [7]). All analyses demonstrated strong evidence for linkage to a melanoma risk locus on chromosome 9p.

Our families gave no evidence of genetic heterogeneity. That is, no kindreds appear to show evidence against linkage to the 9p locus. Several of our small kindreds have slightly negative LOD scores or LOD scores very near zero. However, linkage calculations on small data sets are confounded by the presumed possibility of sporadic melanoma, that is, melanoma occurring in someone without inherited genetic susceptibility. Linkage studies of the 1p locus do show statistical evidence of heterogeneity between the families [28]. Analysis of the Utah data show no evidence for linkage of melanoma susceptibility to chromosome 1p. Further studies involving linkage to large families will be required to assess heterogeneity.

DISCUSSION

Conclusive evidence from conversion to homozygosity in random melanoma tumors and from our linkage studies indicated that a major melanoma risk allele is located on chromosome 9p. The most reasonable model would suggest that this functions as a tumor suppressor gene. We would predict that persons who carry this melanoma susceptibility gene have one abnormal copy; when the normal gene at 9p is either converted to the dysfunctional copy (conversion to homozygosity) or lost (conversion to hemizygosity) in peripheral tissue, a cancer develops. In patients who do not inherit any specific risk factor, it requires a genetic lesion in both copies, or loss of both copies (homozygous deletion). Recent studies have demonstrated conversion to homozygosity or homozygous deletion in this region of 9p in both lung cancer and glioma tumors [35,36]. This suggests that this tumor suppressor gene may act in other tissues. This would be analogous to loss of function of the retinoblastoma gene resulting in both retinoblastoma and osteosarcoma, or to the many cancers associated with the p53 gene product. These results suggest that there is a major gene that controls growth of melanocytes and other cell types in this region. Specific studies of the effect of this gene will be possible once this gene is cloned.

The relationship of the 9p melanoma risk locus to the atypical mole phenotype remains unclear. Previous studies on a subset of the families used in our linkage analysis demonstrated that total nevus density was inherited as an autosomal codominant trait in families with multiple cases of melanoma [37]. This explained roughly 60% of the variation in nevus density in these kindreds, several of which were selected for multiple cases of atypical mole phenotype. Other families in our linkage study were selected only for the presence of multiple cases of melanoma. Analysis of this data set may shed light on the relationship between atypical mole syndrome and the 9p chromosomal melanoma risk allele. Preliminary assessment of these data suggest that there may be an increased number of nevi in family members who carry the melanoma risk allele.‡

Nevus phenotype appears to be influenced by various genetic and environmental factors. The most reasonable model may be a multifactorial model where nevus phenotype is determined by a major locus for melanoma risk, by other genetic loci (including those that affect skin color), and by environmental influences.

We will learn much once the 9p melanoma susceptibility gene has been cloned. Although this appears to be an autosomal dominant locus that functions as a tumor-suppressor gene, the inference is based on indirect data. Cloning will allow direct tests for carrier status, thereby allowing calculations of the sex and age specific penetrance of melanoma within persons who carry the gene. This will also allow direct studies of the nevus phenotype of carriers and the interaction with environmental and other genetic risk factors.

Perhaps most interesting however, will be studies of the molecular mechanism of this tumor suppressor gene with the unusual propensity for homozygous deletion.

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