The genetics of melanoma

Melanoma is an increasingly common cancer and in order to direct preventative advice at those at risk, an understanding of susceptibility is crucial. This review summarizes what is known about common low-risk genes (such as those controlling red hair) and rare high-risk genes.

The primary genetic determinant of melanoma susceptibility is the genetic control of skin colour because the majority of melanomas occur in white-skinned peoples. The genes which control the normal variation in skin colour remain surprisingly poorly understood. Most is known about the role of the melanocortin receptor 1 gene (MC1R). Allelic variants of this gene have a major role in determining freckling, red hair and risk of skin cancer, and variants in this gene are therefore the best-established low-risk melanoma susceptibility genes. A number of other possible candidate genes have been explored as low-risk susceptibility genes but none have yet been firmly established.

The presence of numerous moles (known as the atypical mole syndrome phenotype) is the most potent phenotypic risk factor for melanoma, and moles are genetically determined. Mole genes are postulated to be low to medium penetrance susceptibility genes and individuals with this phenotype are at risk of melanoma and should be targeted for both primary and secondary prevention.

Rare families exist in which there are multiple cases of melanoma and these families are postulated to have inherited high-risk susceptibility genes. The genetic basis of a proportion of these families is known and much of the progress made has been as a result of work carried out by members of GenoMEL, the Melanoma Genetics Consortium, at www.genomel.org. Germline mutations at the CDKN2A locus on chromosome 9 impacting on the two alternative splice products at the locus (p16 and p14ARF) have been shown to be causal for melanoma as have the much rarer mutations in the gene coding for CDK4 which impact on the p16 binding site.

Variation in the proportion of families with these mutations is seen with number of cases of melanoma and latitude. The CDKN2A gene penetrance has been established, albeit in a biased set of families ascertained for large numbers of cases, so that improved penetrance estimates derived from less biased families are required. In some areas of the world (North America and some parts of Europe) carriers of CDKN2A mutations are also at increased risk of pancreatic cancer, although this has not been seen to date in the UK. The determinants of risk of pancreatic cancer are not established. The majority, but not all of families at risk of melanoma also have the atypical mole syndrome. The presence of the phenotype cannot, however, be used to predict gene carrier status therefore all family members require supervision. Gene testing for mutations at the CDKN2A locus is available in some areas of the world for families with clustering of melanoma in the family, but is held by GenoMEL to be premature. It is hoped that crucial data will shortly inform this process.

The descriptive epidemiology of melanoma

The age-standardized incidence rate of melanoma in the UK in men is around 5 per 100 000 per annum and 7 per 100 000 per annum for women (Quinn et al, 2004). For comparison, the rate in Australia is around 30 in men, and in the USA around 12 per 100 000 per annum (Quinn et al, 2004). The incidence has increased in Europe, the USA and Australia progressively since the 1970s. The incidence is higher in those with higher socioeconomic status, but survival is poorer in those with lower socioeconomic status (Quinn et al, 2004).

In the UK and internationally, the majority of melanomas occur in white-skinned peoples and therefore the major genetic determinants of risk are the genes determining skin colour. In hot countries such as Hawaii, the incidence of melanoma is much higher in residents of European origin than those of Polynesian origin (Chuang et al, 1999). Within Europe, the interplay between skin colour and the effect of the major environmental determinant of melanoma (sun exposure) is evident, so that the incidence is highest in white Swedish and Swiss peoples (Parkin et al, 1997) and lower in Mediterranean countries, even though these countries are at lower latitudes.

Family history is an important risk factor for melanoma. Familial melanoma was reported in the 19th century in the UK (Norris, 1820), and a strong family history of melanoma is the most potent risk factor for melanoma (Kefford et al, 1999). Any family history of melanoma is associated with a doubling of risk for close relatives. A study from the Utah population database

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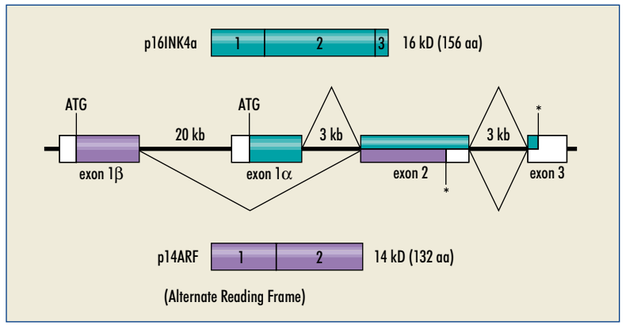


Figure 1. The two splice products at the CDKN2A locus: p14ARF (exon 1β) and p16 (exon 1α).

estimates risk to first-degree relatives of melanoma cases to be 2.1 (95% confidence interval (CI) = 1.4–2.9). A similar study from the Swedish Cancer Registry estimated the standardized incidence ratio for melanoma to be 2.40 (95% CI = 2.10–2.72) for offspring if one parent had a melanoma, 2.98 (95% CI = 2.54–3.47) for an affected sibling and 8.92 (95% CI = 4.25–15.31) if a parent and a sibling were both affected. The highest ratio was 61.78 (95% CI = 5.82–227.19) for offspring when a parent had multiple melanomas (Hemminki et al, 2003). Such patterns of risk are indicative of a significant hereditary component, which is most probably inherited as an autosomal dominant trait with incomplete penetrance. The most potent susceptibility gene is identified (CDKN2A) which is discussed below (*Figure 1*).

Table 1. Family cancer syndromes in which melanoma occurs

Family cancer syndromes	Cancers seen
Familial melanoma	Melanoma predominantly
	Pancreatic cancer in some pedigrees
Hereditary retinoblastoma	Retinoblastoma
	Cancers of the bone
	Soft tissues
	Nasal cavity
	Eye and orbit
	Pineoblastoma
	Melanoma
	Brain and CNS
	Buccal cavity
	Uterus (Kleinerman et al, 2005)
BRCA2	Breast cancer
	Prostate
	Stomach
	Melanoma
	Pancreas (Liede et al, 2004)
Li–Fraumeni syndrome	Breast cancer
	Sarcoma
	Brain tumours
	Melanoma

Rarely, melanoma occurs as part of family cancer syndromes which are well characterized and in which melanoma forms a small proportion of the cancers seen. Survivors of hereditary retinoblastoma, for example, are at increased risk of melanoma, especially in the radiation field (Kleinerman et al, 2005). In this study in which the cancer incidence was reported in a cohort of 1601 survivors of retinoblastoma, the standardized incidence ratio for melanoma in hereditary retinoblastoma patients treated with radiotherapy was 30 (95% CI = 20–45) (Kleinerman et al, 2005). Melanoma has also been reported to occur at increased levels in male carriers of BRCA2 mutations (Liede et al, 2004) and in the Li–Fraumeni syndrome (Potzsch et al, 2002; Cohen et al, 2005) (*Table 1*).

First, however, this article will discuss lower penetrance genes.

Pigmentation genes and susceptibility to melanoma

The genetic determination of skin colour is complex and controlled by many genes. In terms of risk of skin cancer most is known about a gene which codes for the MC1R receptor (Rees, 2003). This receptor is present on the surface of melanocytes and is reported to be expressed by other cells including those involved in inflammation (Rouzaud et al, 2005). MC1R plays a fundamental role both in quantitative aspects of melanin production but also qualitative, as allelic variants govern the ratio of types of melanin produced (the more protective brown/black pigment eumelanin to the red pigment phaeomelanin) (Naysmith et al, 2004).

Stimulation of the MC1R receptor by melanocyte-stimulating hormone (MSH) (Suzuki et al, 1996) results in increased eumelanin production and the agouti protein is the antagonist. Further variation in melanin production occurs because when MSH binds to some MC1R variants common in populations living at high latitudes, less eumelanin and more pheomelanin is produced (Sturm et al, 2001). The role of MC1R was reviewed by Rouzaud et al (2005). While the role of variation in the MC1R in determining skin type and melanoma risk (see below) is becoming clarified, much still remains to be understood about the biological basis of sun sensitivity and cancer risk in people with such variants. A small study from Scotland, for example, measured eumelanin and phenomelanin levels in irradiated Asian and white skin and confusingly showed that the Asian skin contained higher levels of pheomelanin than the white skin and furthermore that the eumelanin/pheomelanin ratios were the same in both skin types (Hennessy et al, 2005).

A simplistic view is therefore that there are skin cancer susceptibility genes which mediate their effects by governing the effectiveness of the protection afforded to melanocytes by melanin, which absorbs both ultraviolet and visible light, the quantity present and how it is organized in the skin. Phenotypically this is manifest as how pale the skin, eyes and hair are, so that these factors are risk factors for melanoma. Additional variation in risk results from the inheritance of MC1R which impacts on the ratio of pheomelanin to eumelanin produced. The phenotypic markers for this are red hair and freckles.

Gandini et al (2005) reviewed these in a meta-analysis of a large number of published case-control studies. They found that blue eyes (compared with dark eyes) are associated with a relative risk (RR) of 1.5 (95% CI = 1.3–1.7), (P<0.001). Within the white population, Gandini et al's meta-analysis showed that white skin compared with dark skin is associated with a RR of 2.1 (95% CI = 1.7–2.5) (P<0.001). There is some progress in understanding the genetic basis of this in that a polymorphism in the oculo-cutaneous albinism gene OCA2 has been shown to determine eye colour (Duffy et al, 2004) and also to be a risk factor for melanoma (Jannot et al, 2005). The presence of many freckles compared with few is associated with a RR of melanoma of 2.1 (95% CI = 1.8–2.5) (P<0.001), and red hair compared with dark a RR of melanoma of 3.6 (95% CI = 2.6–5.4) (P<0.001) (Gandini et al, 2005). There are data to support the view that the major determinant of this phenotype (red hair and freckles) is inheritance of allelic variants of MC1R (Valverde et al, 1995). Not surprisingly then, MC1R variants are identified as genetic risk factors for melanoma (Valverde et al, 1996); significantly also when they are found in dark-haired individuals (Palmer et al, 2000).

It is thought that natural selection of individuals with genetic variation in genes controlling skin colour occurred to favour the survival and therefore the reproduction of fair-skinned peoples in less sunny climates. There are some who feel that this was at least in part sexual selection (Aoki, 2002). There remains, however, a dominant but still somewhat controversial view that the drive to natural selection of fair skin in the north was the need for man to increase synthesis of vitamin D as a result of sun exposure where few foods contain much vitamin D. Most humans rely upon sun exposure to obtain sufficient for health and at high latitudes this may be impaired for long periods of the year (Ovesen et al, 2003). This is again of interest as the view has emerged that many European populations may have lower than optimal vitamin D levels (Ovesen et al, 2003).

Deficiency of vitamin D has great significance for bone health but possibly also for the prevention of auto-immune disease and cancer reviewed by Holick (2004). Natural selection in favour of individuals living in cold climates in previous centuries is therefore hypothesized to have been beneficial to them in terms of avoidance of clinical vitamin D deficiency. However, in times where sun exposure is hugely increased (and possibly to be increased still further as a result of cheap air fares and global warming), these people are at increased risk of skin cancer. It is the challenge to health educationalists now to assess the balance of risks to European populations of mixed skin type and then to convey those risks to the population in a way which can be understood.

Other putative low penetrance genes

There have been a number of studies reported in which groups have taken a candidate gene approach to identifying melanoma susceptibility genes, which have been reviewed (Newton Bishop and Bishop, 2005). They have looked at the inheritance of polymorphisms in genes they postulate may impact on the gene function sufficient to increase susceptibility to melanoma, by comparing the frequency of that polymorphism in melanoma patients with controls. There are limitations to many of these studies including limited sample size, weak choice of controls, and over-interpretation of results of marginal statistical significance (implying positive results are by chance). Ideally such studies should involve minimally 250 cases and controls; cases should be population-based meaning that they reflect the set of incident cases in a defined geographical region and in a defined time period. Controls should come from the same population (i.e. the same genetic 'pool' as the cases) minimizing concerns about bias of ascertainment of cases and controls (Goode et al, 2002). Convenience controls may or may not lead to spurious findings but always raise concerns about interpretability of findings.

There have been several studies looking at genes involved in DNA repair (Guptu Bertram et al, 2004; Han et al, 2005) which seems sensible given that sun exposure is causal and a mutagen, and that children with xeroderma pigmentosum (in which DNA repair is impaired) are prone to melanoma. The data currently remain unclear as they are for other cancers (Goode et al, 2002).

Other groups have looked at genes coding for detoxifying enzymes, with as yet no clear verdict (Strange et al, 1999; Kanetsky et al, 2001), and others at genes having effects on the immune system (Howell et al, 2001; Debniak et al, 2005b). There has been some interest in polymorphisms in genes concerned with vitamin D metabolism (Hutchinson et al, 2000) and p53 (Shen et al, 2003) but generally a history of an initial positive but often small study (Shahbazi et al, 2002; Meyer et al, 2003) is followed by a number of negative ones (McCarron et al, 2003; Bertram et al, 2004; Randerson-Moor et al, 2004). CDKN2A is identified as a potent

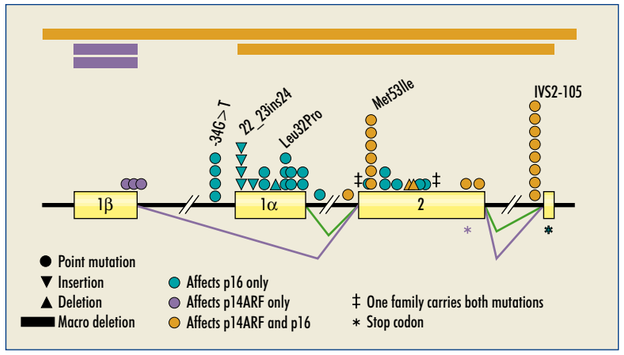


Figure 2. Mutations at the CDKN2A locus detected in UK melanoma families.

rare high penetrance gene which is discussed below. Polymorphisms in this gene have been studied as potential low penetrance susceptibility genes with as yet inconclusive results.

There is some evidence for inheritance of a polymorphism known as Nt500G in some populations (Kumar et al, 1998; Aitken et al, 1999) as a risk factor but not in others (Debniak et al, 2005a). There is similarly conflicting evidence for a similar role for A148T (Bertram et al, 2002; Debniak et al, 2005a). In summary then, pigment genes such as MC1R are low penetrance susceptibility genes but there are other low to medium penetrance melanoma susceptibility genes yet to be established. While there may be some clues identified as above, there are few data as yet.

Melanoma in families: high-risk genes

Melanoma patients may report a family history of melanoma. In a cohort of over 700 melanoma patients investigated by the authors' group, 7% reported that at least one other family member had had melanoma. Rare families, however, have multiple cases and where there are four or more cases in the family (in the UK) the majority have inherited mutations in a gene called CDKN2A (*Figure 1*). The CDKN2A locus on chromosome 9 is unusual in that it codes for two different proteins, both of which appear to predispose to melanoma. p16 is a cell cycle protein (Kamb et al, 1994) which also has a role in the induction of cell senescence (Bennett, 2003). The additional product p14ARF is part of the p53 pathway where it acts by blocking MDM2 binding of p53 (Chin et al, 1998). This gene therefore has functions impacting on the two major pathways RB and p53. Mutations at the locus may impact on the p16 product alone, p14ARF alone (*Figure 2*) (Randerson-Moor et al, 2001; Rizos et al, 2001; Hewitt et al, 2002; Harland et al, 2005) or both proteins. Curiously all seem to predispose the family members predominantly to melanoma alone.

Table 2. The proportion of UK families in which germline mutations at the CDKN2A locus have been detected by the Genetic Epidemiology Division of the CR-UK Clinical Centre at Leeds

Number of melanoma cases	Number of UK pedigrees screened by the Leeds group	Number of pedigrees with mutations	Percentage
7–10	3	3	100
6	5	3	60
5	14	10	71
4	26	17	65
3	45	10	25
2	99	14	14
Total	192	57	30

Mutations at the locus can be found in the majority of melanoma families with many cases in the UK (*Table 2*) but not all. For some cancers hereditary deletions removing one or more exons have been reported to 'explain' missing mutations but evidence supports the view that germline deletions are uncommon in melanoma families (*Figure 2*) (Mistry et al, 2005). There are therefore other susceptibility genes as yet to be identified. There is evidence for such a gene at 1p22 (Gillanders et al, 2003) but no gene has been identified there as yet. A new gene predisposing to ocular and skin melanoma has been mapped to chromosome 9q21.32 in families from Denmark (Jonsson et al, 2005). The gene has not yet been identified and as families with both ocular and cutaneous melanoma are extremely infrequent and so this gene may well reflect a rare syndrome. In families with fewer cases (less than four cutaneous lesions), the minority have identifiable mutations, which implies that in these families predisposition is related to the inheritance of other as yet unidentified genes. High and low penetrance susceptibility genes therefore remain to be identified.

These data imply that where there are four or more cases of melanoma in the family, the likelihood is that there is a high penetrance gene. In the majority of cases this is likely to be at the CDKN2A locus. A commercial test is available for germline mutations at this locus. It is the view of GenoMEL, the Melanoma Genetics Consortium (chaired by an author JNB), however, that it is premature to offer gene testing (Kefford and Mann, 2003) because of lack of information of great relevance to families and because currently a test result would not change management for the patient or the family. The data which currently remain lacking are accurate penetrance data and the risk of cancers other than melanoma. It is the intent of GenoMEL to remedy deficiencies in available data (www.genomel.org) so that fully informed genetic testing can be made available to those who wish it, as soon as possible.

The penetrance of a cancer susceptibility gene is the probability that a gene carrier will develop the cancer in their lifetime. GenoMEL has published the initial estimation of penetrance (Bishop et al, 2002) of CDKN2A and shown that there is geographical variation in penetrance (as expected) by latitude of residence (*Figure 3*). By the age of 50 years CDKN2A mutation penetrance reached 0.13 in Europe, 0.50 in the United States, and 0.32 in Australia; by the age of 80 years it was 0.58 in Europe, 0.76 in the United States, and 0.91 in Australia. These published data will be strengthened by continued data collection across GenoMEL groups in Europe, Australia and North America, in projects funded both by the National Institutes of Health and the European Commission. The data are collected from families selected on the basis of having large numbers of cases of melanoma and are therefore applicable to families ascertained for the presence of multiple cases.

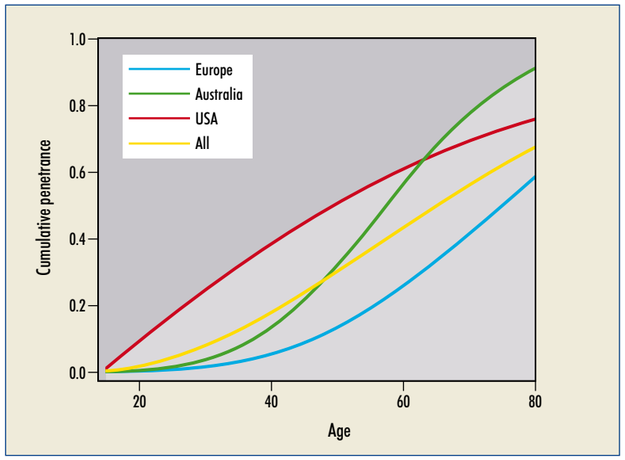
The Genetic Epidemiology of Melanoma (GEM) study group have published an estimate of penetrance which is lower (as expected but not statistically different from that obtained from multiple case families) as it is computed from CDKN2A mutations carriers ascertained in population-based studies (Begg et al, 2005). Overall the risk to carriers was 0.14 by the age of 50 years (95% CI = 0.08–0.22). While it might be expected that families with multiple cases of melanoma might have more risk factors than people without such a family history, it remains to be investigated whether the difference between the estimates is other than chance. GenoMEL will shortly report another estimate of gene penetrance based upon population-based ascertained cases.

Of great relevance to melanoma families is also the lack of clarity about the risk of cancers other than melanoma to mutation carriers. There is no doubt that in some centres families with germline CDKN2A mutations have an increased risk of pancreatic cancer. This is particularly obvious in those families in the Netherlands with the p16-Leiden mutation (Bergman et al, 1990) in which the mean age at diagnosis of pancreatic cancer was reported to be 58 years (range 38–77 years). The estimated cumulative risk of developing pancreatic cancer in putative mutation carriers by the age of 75 years was 17% (Vasen et al, 2000). An increased risk of pancreatic cancer is seen in the USA (Goldstein et al, 2004) and in Italy (Ghiorzo et al, 1999), but confusingly, not elsewhere, for example in the UK. Although there are theories to explain the difference between risks in different populations, the biological basis of this is not yet understood. GenoMEL is currently addressing this important issue. BJHM

Conflict of interest: none.

Aitken JJ, Welch D, Duffy D et al (1999) CDKN2A variants in a population-based sample of Queensland families with melanoma. *J Natl Cancer Inst* **91**(5): 446–52
Aoki K (2002) Sexual selection as a cause of human skin colour variation: Darwin's hypothesis revisited. *Ann Hum Biol* **29**(6): 589–608
Begg CBI, Orlow AJ, Hummer AJ et al (2005) Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample. *J Natl Cancer Inst* **97**(20): 1507–15
Bennett DC (2003) Human melanocyte senescence and melanoma susceptibility genes. *Oncogene* **22**(20): 3063–9
Bergman W, Watson P, de Jong J, Lynch HT, Fusaro RM (1990) Systemic cancer and the FAMMM syndrome. *Br J Cancer* **61:** 932–6
Bertram CG, Gaut RM, Barrett JH et al (2002) An assessment of the CDKN2A variant Ala148Thr as a nevus/melanoma susceptibility allele. *J Invest Dermatol* **119**(4): 961–5
Bertram CG, Gaut RM, Barrett JH et al (2004) An assessment of a variant of the DNA repair gene XRCC3 as a possible nevus or melanoma susceptibility genotype. *J Invest Dermatol* **122**(2): 429–32
Bishop DT, Demenais F, Goldstein AM et al (2002) Geographical variation in the penetrance of CDKN2A mutations for melanoma. *J Natl Cancer Inst* **94**(12): 894–903
Chin L, Pomerantz J, DePinho RA (1998) The INK4a/ARF tumor suppressor: one gene--two products--two pathways. *Trends Biochem SCI* = **23**(8): 291–6
Chuang TY, Charles J, Reizner GT, Elpern DJE, Farmer R (1999) Melanoma in Kauai, Hawaii, 1981-1990: the significance of in situ melanoma and the incidence trend. *Int J Dermatol* **38**(2): 101–7
Cohen RJ, Curtis RE, Inskip PDJ, Fraumeni Jr F (2005) The risk of developing second cancers among survivors of childhood soft tissue sarcoma. *Cancer* **103**(11): 2391–6
Debniak T, Gorski B, Huzarski T et al (2005a) A common variant of CDKN2A (p16) predisposes to breast cancer. *J Med Genet* **42**(10): 763–5

Figure 3. Penetrance of CDKN2A mutations by age and continent. Developed from Bishop et al (2002).



KEY POINTS

- Genes which determine skin colour and how the skin reacts to the sun 'explain' the greatest proportion of cases of melanoma.
- In families with multiple cases of melanoma in the UK, the majority with four or more cases have inherited mutations at the CDKN2A locus, and the greater the number of cases, then the higher the probability of finding a mutation.
- In the UK, families with mutations at the CDKN2A locus appear to be susceptible to melanoma alone, but in some other countries there is an additional susceptibility to pancreatic cancer.
- Other high and low risk melanoma susceptibility genes remain to be identified.

Debniak T, Kurzawski G, Huzarski T et al (2005b) NOD2 variants and the risk of malignant melanoma. *Eur J Cancer Prev* **14**(2): 143–6
Duffy DL, Box NF, Chen W et al (2004) Interactive effects of MC1R and OCA2 on melanoma risk phenotypes. *Hum Mol Genet* **13**(4): 447–61
Gandini S, Sera F, Cattaruzza MS et al (2005) Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer* **41**: 28–44
Ghiorzo P, Ciotti P, Mantelli M et al (1999) Characterization of ligurian melanoma families and risk of occurrence of other neoplasia. *Int J Cancer* **83**(4): 441–8
Gillanders E, Hank Juo SH, Holland EA et al (2003) Localization of a novel melanoma susceptibility locus to 1p22. *Am J Hum Genet* **73**(2): 301–13
Goldstein AM, Struewing JP, Fraser MC, Smith MW, Tucker MA (2004) Prospective risk of cancer in CDKN2A germline mutation carriers. *J Med Genet* **41**(6): 421–4
Goode EL, Ulrich CM, Potter JD (2002) Polymorphisms in DNA repair genes and associations with cancer risk. *Cancer Epidemiol Biomarkers Prev* **11**(12): 1513–30
Guptu Bertram C, Gaut RM, Barrett JH et al (2004) An assessment of a variant of the DNA repair gene xrcc3 as a possible nevus or melanoma susceptibility genotype. *J Invest Dermatol* **122**: 429–32
Han J, Colditz GA, Liu JS, Hunter DJ (2005) Genetic variation in XPD, sun exposure, and risk of skin cancer. *Cancer Epidemiol Biomarkers Prev* **14**(6): 1539–44
Harland M, Taylor CF, Chambers PA et al (2005) A mutation hotspot at the p14ARF splice site. *Oncogene* **24**(28): 4604–8
Hemminki K, Zhang H, Czene K (2003) Familial and attributable risks in cutaneous melanoma: effects of proband and age. *J Invest Dermatol* **120**(2): 217–23
Hennessy A, Oh C, Diffey B, Wakamatsu K, Ito S, Rees J (2005) Eumelanin and pheomelanin concentrations in human epidermis before and after UVB irradiation. *Pigment Cell Res* **18**(3): 220–3
Hewitt C, Lee Wu C, Evans G et al (2002) Germline mutation of ARF in a melanoma kindred. *Hum Mol Genet* **11**(11): 1273–9
Holick MF (2004) Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* **80**(6 Suppl): 1678S–88S
Howell WM, Turner SJ, Bateman AC, Theaker JM (2001) IL-10 promoter polymorphisms influence tumour development in cutaneous malignant melanoma. *Genes Immun* **2**(1): 25–31
Hutchinson PE, Osborne JE, Lear JT et al (2000) Vitamin D receptor polymorphisms are associated with altered prognosis in patients with malignant melanoma. *Clin Cancer Res* **6**(2): 498–504
Jannot AS, Meziani R, Bertrand G et al (2005) Allele variations in the OCA2 gene (pink-eyed-dilution locus) are associated with genetic susceptibility to melanoma. *Eur J Hum Genet* **13**(8): 913–20
Jonsson G, Bendahl PO, Sandberg T et al (2005) Mapping of a novel ocular and cutaneous malignant melanoma susceptibility locus to chromosome 9q21.32. *J Natl Cancer Inst* **97**(18): 1377–82
Kamb A, Gruis N, Weaver-Feldhaus J et al (1994) A cell cycle regulator potentially involved in genesis of many tumor types. *Science* **264:** 436–40
Kanetsky PA, Holmes R, Walker A et al (2001) Interaction of glutathione S-transferase M1 and T1 genotypes and malignant melanoma. *Cancer Epidemiol Biomarkers Prev* **10**(5): 509–13
Kefford RF, Mann GJ (2003) Is there a role for genetic testing in patients with melanoma? *Curr Opin Oncol* **15**(2): 157–61
Kefford RF, Newton Bishop JA, Bergman W, Tucker MA (1999) Counseling and DNA testing for individuals perceived to be genetically predisposed to melanoma: A consensus statement of the Melanoma Genetics Consortium. *J Clin Oncol* **17**(10): 3245–51
Kleinerman RA, Tucker MA, Tarone RE et al (2005) Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. *J Clin Oncol* **23**(10): 2272–9
Kumar R, Lundh Rozell B, Louhelainen J, Hemminki K (1998) Mutations in the CDKN2A (p16INK4a) gene in microdissected sporadic primary melanomas. *Int J Cancer* **75**(2): 193–8
Liede A, Karlan BY, Narod SA (2004) Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. *J Clin Oncol* **22**(4): 735–42
McCarron SL, Bateman AC, Theaker JM, Howell WM (2003) EGF +61 gene polymorphism and susceptibility to and prognostic markers in cutaneous malignant melanoma. *Int J Cancer* **107**(4): 673–5
Meyer P, Sergi C, Garbe C (2003) Polymorphisms of the BRAF gene predispose males to malignant melanoma. *J Carcinog* **2**(1): 7
Mistry SH,Taylor C, Randerson-Moor JA et al (2005) Prevalence of 9p21 deletions in UK melanoma families. *Genes Chromosomes Cancer* **44**(3): 292–300
Naysmith L, Waterston K, Ha T et al (2004) Quantitative measures of the effect of the melanocortin 1 receptor on human pigmentary status. *J Invest Dermatol* **122**(2): 423–8
Newton Bishop JA, Bishop DT (2005) The genetics of susceptibility to cutaneous melanoma. *Drugs Today (Barc)* **41**(3): 193–203
Norris W (1820) A case of fungoid disease. *Edinb Med Surg J* **16:** 562–5
Ovesen L, Andersen R, Jakobsen J (2003) Geographical differences in vitamin D status, with particular reference to European countries. *Proc Nutr Soc* **62**(4): 813–21
Palmer JS, Duffy DL, Box NF et al (2000) Melanocortin-1 receptor polymorphisms and risk of melanoma: is the association explained solely by pigmentation phenotype? *Am J Hum Genet* **66**(1): 176–86
Parkin D, Whelan S, Ferlay J, Raymond L, Young J (1997) *Cancer Incidence in Five Continents.* IARC Scientific Publications No 143. International Agency for Research on Cancer II, Lyon
Potzsch C, Voigtlander T, Lubbert M (2002) p53 Germline mutation in a patient with Li-Fraumeni Syndrome and three metachronous malignancies. *J Cancer Res Clin Oncol* **128**(8): 456–60
Quinn M, Babb P, Brock A, Kirby L, Jones J (2004) *Cancer Trends in England and Wales 1950-1999.* No 66. SMPS Office of National Statistics, London
Randerson-Moor JA, Harland M, Williams S et al (2001) A germline deletion of p14(ARF) but not CDKN2A in a melanoma-neural system tumour syndrome family. *Hum Mol Genet* **10**(1): 55–62
Randerson-Moor JA, Gaut R, Turner F et al (2004) The relationship between the epidermal growth factor (EGF) 5'UTR variant A61G and melanoma/nevus susceptibility. *J Invest Dermatol* **123**(4): 755–9
Rees JL (2003) Genetics of hair and skin color. *Annu Rev Genet* **37:** 67–90
Rizos H, Puig S, Badenas C et al (2001) A melanoma-associated germline mutation in exon 1beta inactivates p14ARF. *Oncogene* **20**(39): 5543–7
Rouzaud F, Kadekaro AL, Abdel-Malek ZA, Hearing VJ (2005) MC1R and the response of melanocytes to ultraviolet radiation. *Mutat Res* **571**(1-2): 133–52
Shahbazi M, Pravica V, Nasreen N et al (2002) Association between functional polymorphism in EGF gene and malignant melanoma. *Lancet* **359**(9304): 397–401
Shen H, Liu Z, Strom SS et al (2003) p53 codon 72 Arg homozygotes are associated with an increased risk of cutaneous melanoma. *J Invest Dermatol* **121**(6): 1510–4
Strange RC, Ellison T, Ichii-Jones F et al (1999) Cytochrome P450 CYP2D6 genotypes: association with hair colour, Breslow thickness and melanocyte stimulating hormone receptor alleles in patients with malignant melanoma. *Pharmacogenetics* **9**(3): 269–76
Sturm RA, Teasdale RD, Box NF (2001) Human pigmentation genes: identification, structure and consequences of polymorphic variation. *Gene* **277**(1-2): 49–62
Suzuki I, Cone RD, Im S, Nordlund J, Abdel-Malek ZA (1996) Binding of melanotropic hormones to the melanocortin receptor MC1R on human melanocytes stimulates proliferation and melanogenesis. *Endocrinology* **137**(5): 1627–33
Valverde P, Healy E, Jackson I, Rees J, Thody A (1995) Variants of the melanocyte stimulating hormone receptor gene are associated with red hair and fair skin in humans. *Nature Genet* **11:** 328–30
Valverde P, Healy E, Sikkink S et al (1996) The Asp84Glu variant of the melanocortin 1 receptor (MC1R) is associated with melanoma. *Human Molec Genet* **5**(10): 1663–6
Vasen HF, Gruis NA, Frants RR, van Der Velden PA, Hille ET, Bergman W (2000) Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). *Int J Cancer* **87**(6): 809–11