Melanoma

A small spot on the skin gone bad, melanoma strikes and too frequently kills young people; a seemingly innocuous primary lesion of sufficient depth can portent a dire prognosis. This year the American Cancer Society and the National Cancer Institute estimate 62, 480 U.S. citizens will be given the diagnosis, and 8,420 will die from it. Though melanoma rates have been rising in the U.S. for decades, a recent CDC analysis of U.S. cancer surveillance data shows that young women are being particularly hard-hit by the increasing incidence of the disorder – probably as a result of increased use of tanning booths and sun tanning. Indeed, numerous public health campaigns have focused on U.V. light exposure as a risk for melanoma. Many melanomas occur, however, in areas of the skin without high levels of sun exposure, and many arise outside of previously existing nevi. Risk factors seem to include a history of severe sunburns, numbers of nevi, pale skin with poor tanning, red or blonde hair, light colored eyes, freckles, prior history of dysplastic nevi or melanoma, exposure to sunny climates, age, gender – and as you might have already guessed – genetics.

If you are (un)lucky enough to be a fair-skinned male living in Australia your lifetime risk for developing melanoma may be as high as 4%. In the U.S., lifetime risk of melanoma is about 1%; this risk approximately doubles with a family history of the disorder. Begin to mix family history of melanoma with a personal history of the presence of dysplastic nevi and the risk skyrockets – an individual with dysplastic nevi and two relatives with melanoma has an estimated 500-fold risk of developing a melanoma. This is a distinct disorder, known as dysplastic nevus syndrome, and is inherited in an autosomal dominant manner. Fortunately, such families are rare – and only about 5% of all melanomas arise from such high-risk settings. Genetic testing in these high risk cases is available, but not routinely recommended. Four loci (CDKN2A, CDK, ARF and chromosome 1p22) have been associated with dysplastic nevus syndrome. The risk incurred by mutations in CDKN2A, which accounts for about 10-40% of families with dysplastic nevus syndrome, confers an impressive approximate 76% lifetime risk of developing melanoma. Recently, a study has demonstrated a potential value of genetic testing in these families – individuals with a positive test result were shown to boost their self screening to beyond recommended levels – of course this could lead to more false positive biopsies, but in this highly selected population this may be a reasonable trade-off. There is no indication to use this type of genetic testing in a screening setting, but taking a simple family history in routine care might pick out those individuals at need of specialized –and potentially life-saving – surveillance.

Over the last year, genome wide association studies have begun to shed some light on the underpinnings of sporadic cases of melanoma. Some of the associations are not terribly surprising – genes that seem to be related to traits such as fair skin or eye color (ASIP, TYR and TYRP1) turn up as melanoma risk factors. More recently, an area on chromosome 20q11.22 containing a number of potentially important genes has been identified. As with most results from genome wide association studies, the effect sizes are very small (odds ratio < 2) but are highly statistically significant. More interestingly, we are finding that seemingly unrelated disorders can share common genetic defects. A

most striking example of this is the shared association found for melanoma, diabetes, and heart disease with the CDKN2A/2B genes. What mechanistic relationship do these disorders share? Perhaps a link though immune function? It is increasingly likely that in a few years we will have these answers, and perhaps find a key to developing more effective treatments. In the meantime, ask your patients to cover up - especially when visiting Australia - and keep your eye out for those individuals whose relatives have more than their share of this serious disorder.