GENE MESSENGER

☆Topic: Familial Melanoma

☆Summary: Approximately one in 75 people in North America will develop melanoma. The presence of one or more of the following increases the risk tenfold: atypical moles, more than 100 typical moles or family history of two first-degree relatives with melanoma. Five to twelve percent of melanomas occur in individuals with a familial predisposition (two or more first-degree relatives with melanoma), but not all of these are part of a hereditary melanoma syndrome. Two genes, cyclin-dependent kinase inhibitor 2A (*CDKN2A)* and *CDK4*, account for up to half the cases of hereditary melanoma. Mutations in these genes are associated with a substantial lifetime risk of melanoma (typically with earlier age of onset) and, in some families, a predisposition to pancreatic cancer.

☆Bottom line: High-risk families can be offered referral for genetic counseling. *CDKN2A* and *CDK4* genetic testing is available but there is a lack of consensus on how results should alter clinical recommendations. The genetic basis for the majority of families with a predisposition to melanoma is not yet known. Melanoma prevention and surveillance recommendations should be based on the patient's personal and family history.

✓ The Disease

- The lifetime risk of melanoma is 1-2%.
- Risk factors: sun exposure, increased number of nevi (benign and dysplastic), fair complexion.
- Atypical nevi are defined as moles with asymmetry, variable pigmentation, irregular borders, or size > 6 mm.
- Highest incidence is in Australia, lowest incidence in individuals with African ancestry.
- Most predictive factor for long-term prognosis is the tumour thickness at the time of diagnosis.
  - Thin melanoma (<1.5mm in depth) = 5-year survival is greater than 90%.
  - Thick melanoma (>3.5mm) = 5-year survival is 54% in women and 42% in men.
  - Early diagnosis is key.
- 5-12% is familial but not all of these are part of a hereditary melanoma syndrome.
- Familial Atypical Mole-Malignant Melanoma (FAMMM) syndrome (also called the Dysplastic Nevus Syndrome) is an autosomal dominant hereditary melanoma syndrome associated with mutations in the *CDKN2A* gene.
- In general, familial melanoma cases have an earlier age at diagnosis (approximately 34 years compared to 54 years), thinner tumours, and a higher frequency of multiple lesions compared to sporadic melanoma cases.
- In individuals with familial melanoma, cancer risk is 50-90%. All suspicious moles should be excised.

✓ The Genes

- **P16 (*CDKN2A*)**
  - Tumour suppressor gene that regulates cell growth.
  - *CDKN2A* mutations have been observed in 20-50% of melanoma-prone families.
  - The chance of observing a mutation in *CDKN2A* increases with the number of affected family members.
    - > 50% if more than 6 relatives
    - < 5% if only 2 relatives
    - 10% when multiple melanomas are present in one individual with no family history

- Overall frequency of *CDKN2A* mutations in individuals with melanoma is estimated to be 0.2% in one Australian study and 1.2% in a more recent study.[1]
- Frequency of *CDKN2A* mutations varies across geographic areas.
- Multiple cutaneous malignant melanoma lesions and presence of pancreatic cancer in a family increase likelihood of detecting a *CDKN2A* mutation.
- Lifetime risk of melanoma in *CDKN2A* carriers from melanoma-prone families was estimated to be 67% to age 80 (Melanoma Genetics Consortium, 2002)[2]. Other environmental factors (geographic location, complexion, total number of nevi, sun exposures) influence the actual risk.
- Some mutations in CDKN2A confer an increased risk for pancreatic cancer, but the genotype-phenotype correlation is not clear.
- Relative risk of melanoma in individuals with a *CDKN2A* mutation in a population-based study was estimated to be 4.3 in a recent study, [1] which is much lower than was previously thought.

- ***CDK4***
  - Oncogene
  - Only found in 1% of melanoma-prone families
- Three variants recently identified in a large genome-wide study implicate *MC1R, TYR and MTAP* as additional susceptibility genes in melanoma-prone families.[3]

✓ Who should be considered at risk for familial melanoma?

Familial melanoma should be considered in any of the following:

(i) two first-degree relatives with melanoma

(ii) a single individual with multiple primary melanomas in the absence of a family history

(iii) a family history of melanoma, pancreatic cancer and astrocytoma (brain malignancy)

(iv) an individual with 10-100 dysplastic nevi (increased risk for melanoma, may have single gene-predisposition causing dysplastic nevus syndrome that may be distinct from a susceptibility to familial melanoma)

✓ Testing - for the faulty gene?

- Genetic testing for *CDKN2A* and *CDK4* is clinically available, but as *CDK4* mutations are rarely found in familial melanoma, it is questionable whether testing for this gene is helpful.
- Research studies are underway to evaluate new susceptibility genes and penetrance of known genes.

✓ Surveillance for individuals with familial melanoma

- All first-degree relatives (parents, siblings and children) of individuals with melanoma or multiple atypical nevi should be screened by detailed skin examination.
- Monthly skin self-exams (preferably after education from a dermatologist or dermatology nurse) and clinical examination by a skilled physician or dermatologist every 6 months in a brightly lit room (halogen light source ideal).
- Baseline photographs of atypical nevi with biopsy only of those that are changing.
- Total body photographs if there are multiple nevi which are difficult to track.
- Any suspicious lesions should be promptly excised (changes in moles/freckles, non-healing sore).
- Prevention
  - Avoidance of sunburn and sun exposure in peak hours
  - Use of sunscreens, protective clothing
  - Awareness of changes in shape, colour, elevation of nevi and surrounding skin

☆Web Resources: National Cancer Institute Melanoma homepage
http://www.cancer.gov/cancertopics/types/melanoma

☆References:

1. Berwick M, Orlow I, Hummer AJ, et al. The Prevalence of CDKN2A Germ-Line Mutations and Relative Risk for Cutaneous Malignant Melanoma: An International Population-Based Study. *Cancer Epidemiol Biomarkers Prev* 2006;15(8):1520-25.
2. Bishop DT, Demenais F, Goldstein AM, et al. Geographical variation in the penetrance of CDKN2A mutations for melanoma. *J Natl Cancer Inst* 2002;94:894-903.
3. Bishop DT, Bishop DT, Demenais F, Iles MM, et al. Genome-wide association study identifies three loci associated with melanoma risk. *Nature Genet* 2009;41(8):920-5.

☆Review Articles:

Santillan A, Cherpelis BS, Glass LF, et al. Management of Melanoma and Nonmelanoma Skin Cancer Syndromes. *Surg Oncol Clin N Am* 2009; 18:73-98.

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GenetiKit KNOWLEDGE IN TRANSLATION

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