Genetic Epidemiology of Melanoma: of Consortia and Conundrums

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With the explosion of hereditary cancer gene discoveries in the last decade, investigators have been presented with a variety of avenues by which to investigate the mechanisms and implications of genetic mutations. Genetic epidemiology, which has as its objective the elucidation of genetic and nongenetic contributions to disease, has risen to the challenge. Although now considered an established field of inquiry, genetic epidemiology continues to use the tools of genetics and epidemiology, reinterpreting their concepts in the context of novel analyses. In this issue, Bishop et al. (1) report the results of a study that estimates the penetrance of CDKN2A mutations using the resources of an international melanoma consortium. Their key finding is that the penetrance—that is, the probability that CDKN2A mutation carriers will manifest melanoma—appears to vary by the incidence of melanoma in the general population setting in which it is measured. Lifetime penetrance (by age 80 years) is estimated at 67% overall but is only 58% in Europe, compared with 91% in Australia and 76% in the United States. Multivariate analysis suggested that this variation in penetrance is best explained by the baseline population incidence of melanoma, potentially reflecting underlying ultraviolet (UV) exposure in those populations.

This finding is at first glance puzzling, because the long-held belief in the field is that the phenotype of hereditary cancer gene mutations should not be tied to the environment. For example, the incidence and high penetrance of familial adenomatous polyposis (presumably caused by truncating germline mutations in the APC gene) appear to be consistent across the world (2,3). However, there have been hints that the cancer phenotype encoded by hereditary mutations in cancer genes might be modifiable. For example, Brunet et al. (4) reported that cigarette smoking might reduce the risk of expressing breast cancer among BRCA1 or BRCA2 mutation carriers. Park et al. (5) have suggested that development of extracolonics cancers among mutation carriers of hereditary nonpolyposis colorectal cancer genes hMSH2, hMLH1, or hMSH6 might vary among countries.

Bishop et al. (1) have taken a more ambitious approach and, as a consequence, have uncovered a pattern that may not have been detected if performed by any single research center. Their study was performed in the context of a consortium (The Melanoma Genetics Consortium) that agreed to share pedigree and risk factor data and the results of genetic mutation analysis. In the process, this project has demonstrated both the strengths and the weaknesses of consortia. Certainly, comparability of methods and data as well as the large collection of multiple-case families are major advantages. However, weaknesses were also shown in sharp relief. The eight centers of this consortium employed a variety of modes of ascertainment (population based, clinic based, and referral) and eligibility criteria. For example, many, but not all, of the centers performed routine phenotypic skin examinations on all family members, which could potentially have resulted in reclassification of unaffected individuals as case patients in some centers but not others. Furthermore, the number of unaffected relatives per family tested for mutations varied significantly across the eight centers, from an average of 2.7 unaffected relatives per family in Italy to 16.7 per family in the United States and 23.2 in The Netherlands. Thus, the extent and manner in which family members were investigated could have influenced their probability of being included in the study. This could, in turn, have influenced the number of unaffected and affected individuals that were ultimately found to have CDKN2A mutations and consequently affected the penetrance estimate.

The authors used several strategies in an attempt to correct for these potential biases: first, they required that families included in the consortium contain at least two cases of melanoma in first-degree relatives and a proven germline mutation in CDKN2A; second, they verified melanoma in family members using pathology confirmation or medical record diagnoses; and finally, they computed the penetrances, taking into account their method of ascertainment, namely, conditioning the likelihood function on the family data as observed. Clearly, this study illustrates the problems of combining diverse data resources and underscores the value of forming a consortium before the initiation of data collection, but it also shows the strengths of well-coordinated consortal projects.

As is expected in any scientific endeavor, the study by Bishop et al. (1) answered one question but uncovered a conundrum that merits further investigation. Why and how do factors that affect geographic incidence rates of melanoma also affect the expression of melanoma among mutation carriers of a putative “high-penetrance” cancer-causing mutation? In trying to address this question, future investigations will have to examine whether environment (such as differing UV radiation levels between countries), genetic predisposition (such as presence of dysplastic nevi or modifier genes), or both underlie the variation seen in penetrance estimates. Recent evidence from two family studies (6,7) that are part of this consortium suggests that variants in the melanocortin-1 receptor gene (MC1R) can modify impact of the CDKN2A mutation on melanoma risk. In an Australian family study, Box et al. (6) showed an increase in penetrance of the CDKN2A mutation from 50% to 84% and a decrease in age at
onset of melanoma by approximately 20 years when at least one of eight MC1R variants examined was present; similar increases in penetrance (from 18% to 50%) were seen in a Dutch family study in association with the R151C variant (7). Some of these variant allele frequencies have also been found to differ by ethnicity (6). Data on pigmentation, ethnicity, UV exposure, and the presence of MC1R variants will help to elucidate whether these factors can explain the differential expression of the CDKN2A mutation by geographic region.

What does the future hold for family-based and population resources such as those developed by The Melanoma Genetics Consortium? It is very promising. The U.S. National Cancer Institute is sponsoring several initiatives to study the genetic epidemiology of major cancers (http://cancer.gov/research_funding/). Genetic epidemiology has developed a large toolkit of methodologies drawn from both epidemiology and genetics and has developed some of its own to design and execute studies that can take advantage of these valuable resources. The field, using maturing cancer population resources, is starting to hit its stride.

In conclusion, the discovery of cancer-causing mutations requires further investigation into their behavior and relevance in families and populations; large family consortia can provide one avenue for such investigation. The genetic epidemiologic approach is well prepared to handle the challenges of complex investigations and data sets, even across the globe.

REFERENCES