Commentary: Migrant study designs for epigenetic studies of disease risk

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Comparisons of migrant, native and host populations are particularly useful in elucidating the balance between genetic and environmental influences on disease risk. In this issue of IJE, Campanella and colleagues have conducted a novel study of epigenetics in Italian migrants and non-migrants from the European Prospective Investigation
into Cancer and Nutrition (EPIC-Italy). Differences in DNA methylation were identified at several CpG sites when comparing migrant and host populations, including after adjustment for available dietary and lifestyle factors. The authors hypothesized that patterns they observed fit with an adaptive mechanism to counter the mismatch between early-life exposures and later-life environment experienced in the migrant population.

The role of epigenetics and its interaction with the genome to mediate the changing health outcomes observed in many migrant groups is clearly important. However, migrant studies are complex. The effects of changing environments on health outcomes vary not only according to ethnicity and regions of origin and destination, but also according to who is migrating, why and when they migrate and what health outcome is being measured over what period. We discuss a small selection of historic migrant studies in order to illustrate their utility and interpretation, alongside aspects of the new epigenetic study by Campanella et al.1

Selective migration

Migrants tend to be selected groups, usually healthier and wealthier than those who remain in the home region. This is often known as the ‘healthy migrant’ phenomenon and was observed in older African Americans who migrated from the southern USA to the north. African Americans who migrated had better health than those who stayed in the south, whereas there was no difference in health between White Americans who migrated and those who stayed in the south. This suggests that selective migration and selective survival contribute to the complex patterns of ethnic and racial differences in regional variations in health.2

Selective migration is also likely to affect Campanella and colleagues’ study.1 However, they do not report measures which enable comparisons of general health or socioeconomic position in the migrant and native populations. It is a challenge for future studies to address these aspects, including whether differences between migrant and native populations reflect acculturation or reflect differences that were present before migration.

Critical periods

The concept of critical periods during the life course, when environmental or genetic risk factors may exert particularly strong influences, is familiar in epidemiological studies3 and particularly pertains to migrant studies. When migrants retain the disease risk of their place of birth, it suggests a dominant causal role for early-life exposures or genetic factors, whereas when they acquire the disease risk of the host population, it is likely that later-life exposures exert the major influence.

Campanella and colleagues acknowledge the absence of information on age at migration as a key limitation of their study. South to north migration within Italy peaked in the late 1950s to early 1960s,4 a time when the study population would, on average, have been in early adulthood. The authors hypothesize that DNA hypermethylation in migrants compared with the host population, across a large pericentric area on the long arm of chromosome 7, reflects environmental effects from two different critical periods. These perhaps indicate an adaptive mechanism to cope with mismatches between the periods of early-life programming in the home (southern Italian) environment and later-life (north-west Italian) environments. Longitudinal studies with known age of migration would be ideally placed to answer these questions more fully in future research.

Speed of change in disease risk following migration

First-generation migrants of Japanese descent to Honolulu and California experienced a doubling of coronary heart disease mortality compared with those observed in Japan, but not reaching levels experienced by the host US population.5 In contrast, the protection from coronary disease observed in people of Black African descent in West Africa, the Caribbean and the UK, has been slowly lost across generations in US African Americans.6

The lack of information on health outcomes in Campanella and colleagues’ study1 is another important limitation, and future studies should include frequent epigenetic sampling in order to establish aetiological pathways, given that the effects of environmental factors act at various speeds depending on the population under study.

Epigenetic analysis of migration

Batch effects and differences between probe types are now routinely addressed in studies using 450k array data. In addition to these considerations, it is now well established that differences in cellular composition between samples can cause observed differences between groups. Of note, at least some of the CpG sites identified by Campanella et al. appear on the list of CpG sites associated with cell composition, recently published by Jaffe and Irizarry.7 Furthermore, as studies begin to accumulate genetic and epigenetic data in tandem, it is increasingly important to
investigate the effect of the genome on the epigenome. For example, in EPIC-Italy more than half of the southern individuals originated from Sicily which, being an island, is likely to have a subtly different genetic make-up compared with the rest of Italy.

**Conclusion**

Epigenetics is well placed to elucidate mechanisms by which change in environment impacts on disease risks, by comparing differences in the epigenome that are associated with specific environmental risk factors, genetic make-up and health outcomes. Interactions and modulation between the epigenome and genome may explain the differential patterns of risk retention or protection following migration.

Although generating interesting hypotheses, the reported cross-sectional migrant study can neither inform on directions of causality, nor determine which aspects of lifestyle and environment affect the epigenome. It cannot distinguish whether change in methylation has occurred over time or if the migrant group were also distinct from other southern Italians in early life. Most importantly, it is unable to determine the role of epigenetic modifications in determining future disease risk. However, it is a promising first foray into the study of epigenetic changes associated with migration—a field which has the potential to provide fascinating aetiological insights into environmental effects on disease risk. Future studies should include careful phenotypic characterization of native, migrant and host populations, detailed data on health behaviours (ideally supported by objective biomarkers), collection of data on age at migration, acculturation and repeated assessments of epigenetic responses to changes in environmental risk factors, linked to changing disease risks.

Notwithstanding their analytical complexities, such migrant studies will be key to further understanding the role of environmental risk factors across the life course for current and future generations.

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**References**