

Natural experiments in human genetics examples from Finland and the Korean Diaspora

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Most of our knowledge about the relationships between genetic variation and phenotypic variation in model organisms has resulted from designed experiments in which environmental and genetic manipulations as well as designed breeding experiments have been used. Obviously in studies of human beings, such approaches are not possible, so we have to be anthropologists and detectives and search for populations in which natural and historical circumstances have led to natural experiments that approximate some study design we might engineer in a model system. One of the most widely used such natural experiments for the study of rare Mendelian traits was the population of Finland, which has been culturally, linguistically, and geographically isolated for a couple thousand years, after having been settled by a small number of founders. This population structure led to certain rare disease-predisposing variants rising to appreciable frequency, making them much easier to identify. This is similar to how inbred rat strains artificially make rare variants fixed in an experimental population making their effects identifiable. Examples where this population structure helped in identification of some disease-predisposing factors will be presented along with others where it was not helpful, pointing out the rather obvious fact that any given experimental design is not optimal for answering all questions

In studies of plant genetics, a study design often used to try and identify evidence of interaction between genetic and environmental factors involves taking plants of a given set of strains and growing them in different fields, possibly with exposure to different insecticides, fertilizers, or climactic conditions to look at the contributions of the genetic differences between strains in different environmental conditions on phenotypic variation. Even with such extreme sampling, where both genetic and environmental conditions are controlled, it is notoriously difficult to demonstrate or identify G x E interactions, and without such designs it is essentially impossible in most cases, even when they do exist. To this end, perhaps the human population with greatest parallels to this design is the Korean diaspora. Because of historical events of the last 150 years, today there are numerous populations of Koreans living in very different parts of the world, with much reduced cultural continuity than other overseas ethnic populations. This is largely due to the circumstances in which they ended up outside the Korean peninsula being largely non-voluntary. Perhaps the most radically different overseas Korean populations are the Koreans of the former Soviet Union, who were stripped of their language and culture to a great degree, and live today as culturally Russian for the most part. To this end we have begun to do research on large families from this ethnically Korean population living in Kazakhstan. Another population of Koreans with

radical cultural changes after emigration is the group of roughly 150,000 Koreans who were adopted in Northern Europe and North American over the past 40 years. To this end we are studying ethnic Koreans adopted in Scandinavia, who are culturally Scandinavian, while being biologically Korean. Comparing phenotypic distributions and heritabilities among these populations for a variety of quantitative traits will provide a natural experiment in which it will hopefully be possible to examine the question of gene by environment interaction where sampling is on radical differences in environment and culture while controlling to some degree for genetic variation.