Health Effects of Human Population Isolation and Admixture

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There are occasions when, either by choice or by circumstances, human beings are driven to temporary or permanent isolation from other people. Some of the examples are working in a lighthouse, serving a prison sentence, or doing research in less populated areas. The same can happen to entire human populations, although this may seem quite improbable in an era which provides ever-increasing means of communication and transport. However, the gap between those who have access to these technological advancements and those who do not is increasingly widening. The number of people living in isolated communities, and whose isolation from other populations is constantly increasing, is largely underestimated.

Even in a highly economically developed part of the world, such as contemporary Europe, there are still many populations that live in the isolation from the others (Table 1). Within its research Framework Programme 6 (FP6), the European Commission (EC) recognized the large potential value of these populations as a model for studying the determinants of human health and disease, and also for preserving the genetic heritage of Europe. The Framework Programme has recently funded the proposal for the formation of the "European Special Population Research Network." Croatia became a welcomed partner within this network, as its island populations represent one of the best-characterized isolate resources in Europe. The human population biology of the Croatian islands has been thoroughly studied for decades, mainly by the Institute for Anthropological Research in Zagreb, while the consequences of island populations' isolation on health and disease have been studied more recently by several groups of researchers, mainly from the Rijeka and Split University Schools of Medicine and the Andrija Štampar School of Public Health in Zagreb.

This theme issue of the *Croatian Medical Journal* will systematically address the findings on health effects of population isolation and admixture on Croatian islands, resulting from the research undertaken within the past 4 years and funded by the Croatian Ministry of Science, Education, and Sports. This research was performed by a network of collaborating scientists from the Universities of Zagreb, Split, Osijek, and Rijeka, the Institute for Anthropological Research, and the Croatian Institute for Public Health.

Causes of human population isolation

There may be a number of possible reasons for isolation of a human population. The most obvious example is geographic isolation, which occurs

Table 1. An overview of isolated populations in contemporary Europe*

European country	Isolate population	Isolate type	Population size (estimated)	Geographical location
Austria	Croats	ethnic	100 000	Burgenland
	Slovenes	ethnic	50 000	Carinthia
	Hungarians	ethnic	70 000	Burgenland
	Alpine isolates	geographic	50 000	Tyrol
Belgium	Germans	ethnic	68 000	Southeastern border
Croatia	Adriatic islanders	geographic	100 000	15 eastern Adriatic islands
	Albanians	ethnic	20 000	Zadar city
	Roma	cultural	10 000	Pitomača town
Denmark	Faroese	geographic	46 000	Faroe islands
	Germans	ethnic	250 000	N. Schleswig, S. Jutland
France	Alsatians	linguistic	1 500 000	Alsace-Lorraine
	Basques	ethnic	730 000	Labourdin, lower Navarro
	Bretons	linguistic	300 000	Bretagne, northwest
	Calo (Gitano)	linguistic	20 000	South (Iberian Romani)
	Catalans	linguistic	150 000	Catalonian France
	Corsicans	geographic	280 000	Corsica island
	Flemish	ethnic	80 000	Westhoek, northeast
	Roma (Sinte, Vlax)	cultural	40 000	various
Germany	Roma (Sinti)	ethnic	60 000	various
	Sorbs (Slavs)	ethnic	120 000	Brandenburg, Saxony
	Danes	ethnic	60 000	Schleswig-Holstein
	Frisian speakers	linguistic	12 000	N. Friesland, Heligoland
	Jewish	ethnic	40 000	various
Finland	Saami	ethnic	2600	North, Inari, Skolt
Greece	Aroumanians/Vlachs	ethnic	40 000	Thessaly, Pindus, Ipiros
	Macedonians	ethnic	40 000	Prefectures drama, Castoria
	Pomaki	religious	27 000	Western Thrace
Holland	Frisian speakers	linguistic	700 000	Friesland
	Rucphen	religious	22 000	North Brabant province
Iceland	Icelanders	geographic	240 000	Iceland
Ireland	Gaelic	linguistic	260 000	various
Italy	Albanians	ethnic	100 000	Sicily, Puglia, Molise, Calabria
	Catalans	linguistic	20 000	Northwest Sardinia
	Croats	ethnic	2000	Molise, Camporabaso
	Friulians	linguistic	600 000	N. Friuli, Venezia, Giulia
	Greeks	ethnic	20 000	Reggio, Salento, Aspromonte
	Ladins	linguistic	35 000	Dolomites - Gardena, Atesino
	Sardinians	geographic	1 500 000	Southern Sardinia
	Walser	linguistic	3500	Valle d'Aosta
Malta	Maltese population	geographic	365 000	Malta island
Portugal	Mirandes	linguistic	15 000	Miranda do Duoro
Spain	Aragonese	linguistic	30 000	Pyrenean valleys
	Asturians	linguistic	450 000	Asturias principality
	Basques	ethnic	900 000	West Pyrenees ("Euskadi")
	Galego	linguistic	1 200 000	Galicia
Sweden	Finns	ethnic	30 000	Torne valley
	Saami	ethnic	20 000	Northwest region
UK	Cornish	linguistic	1000	Cornwall, southwest UK
	Orcadians	geographic	20 000	North of Scotland
	Shetlanders	geographic	25 000	North of Scotland
	Western isles population	geographic	30 000	Northwest of Scotland
	Welsh valleys	geographic	500 000	Wales
	Manx	geographic	75 000	Isle of Man

*This list is neither exhaustive nor complete; it has been compiled by internet-based search of official governmental information and reports on the ethnic, cultural, religious, linguistic or geographic minorities in respective European countries.

when a small group of founders inhabits a very inaccessible or hostile environment and manages to overcome the difficulties and procreate over a number of generations. However, populations do not have to be cut off from others geographically to be isolated. Sometimes, subpopulations remain isolated from the general population because of their cultural practices, language, tribal or national identity, or religion (1). Isolation has always an impact on the genetic structure of the isolated population, such as reduction of genetic diversity through genetic drift and increase in consanguinity due to limited mate choice (2). All these factors can have considerable effects on health and the burden of disease in isolated communities.

Health effects of geographic isolation

Health effects of geographic isolation can be observed at the local, regional, or even global scale. At a local scale, climate and available resources such as food, water, air, and shelter can have substantial impact on the leading health problems in an isolated population. For example, people living at very high altitudes, such as Sherpas in Asia, Alpine villagers in Europe, or several population groups in South and Central America have highly restricted dietary choices, while Tuareg and Bedouin tribes of Africa and Middle East have to adapt to scarce water resources, often infested by specific parasites and bacteria, which may determine their disease burden (3). Nomadic Saami of Finland and Sweden are believed to have extremely high rates of gastric cancer, as their diet in Arctic Circle is limited mainly to smoked food (4). On a larger scale, populations living in areas with high air pollution due to geographic configuration of their habitat will have increased burden of respiratory illnesses. Crowded tents in southeast Asian populations are an example how type of shelter can influence population health, since they were shown to substantially contribute to mortality from pneumonia in children during wet seasons and monsoons (5). On the global scale, there have been several dramatic examples of both benefits and dangers of living in isolation. Throughout history, isolation spared many communities from epidemics and pandemics. However, this led to the decreased herd immunity, and when the deadly pathogen was re-introduced after a long time, there were no immune individuals remaining and entire civilizations were simply wiped out. This may have caused the disappearance of the inhabitants of the Easter Island and the cultures of Mayas and Aztecs in central America, and the Cambodian Khmers in Angkor (3,6).

In this theme issue, several studies investigated the effects of geographical isolation. Smoljanović and colleagues investigated the role of CCR5del32 mutation as a potential marker of the effects of plague in two Croatian island communities in the medieval period, one that escaped plague and the other that was decimated by it (7). Bulayeva reports on the health problems encountered in her continuing research of isolated populations of Dagestan (8). Saftić and colleagues investigated the challenges of access to health care, in this case highly sophisticated surgery, in geographically isolated rural island communities (9).

Health effects of cultural, linguistic, tribal/national, religious, and social isolation

Populations sometimes adopt behaviors or identities that separate them from other populations. Isolated minorities, although they live in the same environment as larger general populations, sometimes show large differences in health risks due to different cultural practices. One of such practices is circumcision, which was found to lead to a decreased risk of cervical cancer (10). Similarly, boiling the water and exclusive tea drinking can decrease the risk of childhood diarrhea, as opposed to drinking biologically con-

taminated accessible water (3). Nomadic way of life still prevents the Roma populations from integrating into many European communities and using education and health care services, which would decrease the disease burden they experience (3). Differences that isolate populations, ethnic, or religious minorities exhibit are often a cause for violence, discrimination, or even genocide, as was observed recently in Rwanda, and historically in Europe (Jewish communities, Roma), North America (Indians), South America (Incas), and elsewhere (3). Large migrations of non-adapted individuals into new and very different habitats, such as the exportation of the convicts from the United Kingdom to Australia or New Zealand increased the risk of melanoma in those populations by an order of magnitude, in comparison with other populations (11). Dietary habits in Japan, which in itself is an isolate in global terms, are thought to be responsible for high rates of gastric cancer (12). On American Samoa, which adopted dietary practices from the USA, the rates of type 2 diabetes mellitus increased from among the lowest to among the highest in the world (13). Contrary to this example, Mediterranean diet, red wine, and a strong sense of community are thought to be very favorable for health and the leading reason for extreme longevity of some isolated populations of Sardinia (14).

In this issue, Pucarin-Cvetković and colleagues investigated the role of Mediterranean diet on health in Croatian island isolates (15), while Žuškin and colleagues investigated the benefits for respiratory health brought by living on the unpolluted islands (16). Kolčić, Polašek and their colleagues studied the main environmental and genetic risk factors to define the determinants of cardiovascular morbidity in these populations (17,18). Vuletić and Mujkić investigate how life in isolation reflects on the collective psychology and whether it has a positive or a negative effect for the sense of well-being in isolated island communities of Croatia (19).

Health effects of genetic isolation

Isolation in which no gene flow is allowed can have considerable effects on the population health (20). However, these effects have not been studied systematically to date. The first reason is that, at the time when an isolated population is founded, this is usually by a small group of people. Their allele frequencies may differ considerably from those in their population of origin because they represent a small and non-random sample of the general population. This provides an opportunity for extremely rare deleterious mutations to increase in frequency by several orders of magnitude in a resulting population and to represent a major health problem, although they would normally be of no importance in a large, general population. An example for this is the "Finnish disease complex," a distinctive set of Mendelian (monogenic) diseases found almost exclusively among the Finns, because by pure chance the Finnish founders carried those underlying mutations (21). In addition to the founder effect, deleterious mutations in isolate populations may continue to rise in frequency through "genetic drift," a random fluctuation in allele frequencies which occurs in small populations in absence of immigration and gene flow from the general population. Ashkenazi Jews are an example of a population with the highest recorded incidence of several such disorders (22). The situation in isolated populations is usually further aggravated by limited mate choice eventually leading to consanguinity, which further increases the chance of exposing a recessive deleterious mutation. All of these processes were probably involved in the occurrence of a rare disease known as *Mal-de-Meleda,* on the Croatian island of Mljet, which remained isolated as it was used as a quarantine for leprosy by the Dubrovnik Republic during the medieval period (23).

In this theme issue, Saftić and colleagues gave a historic perspective and review novel findings in relation to rare monogenic disorders found

in the Croatian islands (24), while Markić, Boraska and their colleagues sought for examples of single-gene frequencies and their associations with particular diseases in isolated populations (25,26).

Health effects of isolate break-up and population admixture

Throughout history, human population has been organized in small and sparsely scattered isolate communities tied to the land they harvested. However, dramatic changes that occurred in the way of life in the last 5-6 generations had affected the genetic structure as well. Measures to reduce childhood mortality have led to an unprecedented increase in population size, from about 1 billion (in 1850) to more than 6 billion (in 2000). Up to 1900, about 98% of the world's population lived in small rural communities which limited their mate choice, making consanguinity a relatively common phenomenon. Even today up to 2 billion people globally live in areas with a considerable prevalence of consanguineous marriages (27). The process of urbanization suddenly shifted a substantial proportion of human population from villages into the cities, which is predicted to cause massive outbreeding, gene flow, and admixture at the global scale. The World Health Organization has recently defined major disease risk factors that attribute most to the disease burden in the population, which include increases in body mass index, blood pressure, cholesterol levels, and blood glucose, all of them readily measurable biological quantitative traits (28). There is a plausible theoretical argument why inbreeding (decreased heterozygosity) and outbreeding (increased heterozygosity) should cause changes in mean population values of quantitative traits. However, in a recent review of this topic we could only identify a handful of studies in human populations that provided any data on these effects in post-reproductive age (29).

In this theme issue, Rudan and colleagues used a model of the metapopulation of Croatian island isolates to investigate the effects of inbreeding and outbreeding in the same population, and also to assess the applicability of the metapopulations for identifying genetic variants underlying human quantitative traits (30,31).

Isolated populations as popular model for biomedical research

Isolated populations often represent extremes in environmental exposures, behavioral practices, or genetic structure. Therefore, they can expose associations between environmental or genetic risk factors and human diseases that would otherwise not be easily observed in large, general populations (32). Furthermore, they are more easily studied because of their isolated nature, with low rates of migration, and reduced environmental and genetic diversity (33). This is what has rendered isolated populations a popular resource for biomedical research, ever since the days of predominant interest in measurable environmental exposures, to the present era of genomic revolution.

Studying these unique communities and living with them can be a truly rewarding experience for a researcher. However, the interest for them goes beyond biomedical research, as numerous examples from popular culture which dealt with the topic show. Oscar winning movie "*Witness,*" starring Harrison Ford, owed much of its success to gripping insights into the culture of the isolated Amish populations of Pennsylvania and Nebraska, USA. Similarly, TV-series "*Northern Exposure*," which showed adventures of a displaced New York physician among the Alaskan villagers gained immense popularity. The Croatians also have their favorites: an all-time classic TV-series "*Naše malo misto*" (*"Our small town"*) by Miljenko Smoje, or the more recent, award-winning novel "*Osmi povjerenik*" ("*The 8th delegate*") by Renato Baretić, which were both based

on unforgettable experiences with the unique islanders of Croatia.

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