The Finnish Disease Heritage as a Product of the Population Structure

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Family welfare and medical genetics have much in common, at least in the field of genetic counseling. But the Finnish population and medical genetics also have a common denominator: the history and structure of the population are closely related to the scope of hereditary diseases in Finland.

The Finnish disease heritage

The concept of the Finnish disease heritage is over ten years old. This heritage consists of more than 20 rare hereditary diseases found to be unusually common in this country. These disorders extend over all branches of medicine and are mostly severe: they cause mental retardation, visual or hearing loss, skeletal, renal or neurological symptoms, severe congenital malformations, or disturbances of growth, metabolism, or blood formation. Some of these diseases were first described in Finland; in many of them the Finnish patients form the majority of all cases reported around the world. On the other hand, some hereditary diseases that are quite common elsewhere are extremely rare or absent in Finland. The most remarkable example of these disorders is phenylketonuria or PKU, a metabolic disease causing mental retardation (Norio, 1981).

Population as soil for hereditary disorders

The Finnish disease heritage is comprised mostly of autosomal recessively inherited diseases. This means that the affected individual must possess two genes of a given disease, one gene from each parent. The parents themselves are healthy because they have only one gene for the disorder while its pair is a normally functioning gene. All human individuals possess some, say 5, recessive genes for rare severe disorders. Affected children can be born only if both parents happen to have the same gene. Every child of such a couple has a risk of 1 in 4 of getting the disease and the possibility of 3 in 4 of being born healthy. How matters turn out in each case depends solely on chance. The fact that both parents of the affected child

happen to possess the same rare gene is often due to their consanguineous marriage: if parents are related to each other, they may both have received this rare common gene from a common ancestor.

The first traces of the Finnish disease heritage were discovered through a nationwide investigation of the congenital nephrotic syndrome (CNF), a lethal disorder of the kidneys (Norio, 1966). This disease had proved to be surprisingly common in Finland and its occurrence was often familial. Evidence in favor of the autosomal recessive inheritance of CNF was sought and found. The parents were always unaffected, the sex distribution of the patients was equal, the proportion of affected sibs was very close to 0.25, and the order of birth was of no consequence. The ancestors were traced in order to find consanguinities between the parents of the affected children. This is possible in Finland because the admirable population registers of the Lutheran Church go back six to ten generations. Twenty-nine percent of the parental marriages were shown to be consanguineous but in an unusual way. First cousin marriages were totally absent. Instead, most consanguinities were remote, going back five to eight generations. Many parents of the affected infants were consanguineous not only with their own spouses but also with two to ten parents of other infants with the same disease. The geographical distribution of the ancestors was uneven, being concentrated in more or less dense clusters in an extensive area of central, eastern and northern Finland. This area was — incredible as it may seem — not permanently settled until as late as the 16th century, i.e. less than 500 years ago (Figure 1). After this interdisciplinary discovery it was easy to predict that other rare recessive disorders might also be found to be overrepresented in Finland.

An overrepresentation of peculiar recessive disorders in a certain country needs two conditions: the existence of peculiar genes (and the absence of some others) and some mechanism that can easily lead two carriers of the same gene to marry each other. These prerequisites are the national and regional isolation of the Finnish population (Norio, 1981).

National isolation

Accurate data on the origin and composition of the ancient Finnish population, say 2000 years ago, are scanty. Written historical data are available only from 1100 A.D. onwards and archaeological theories have undergone a fundamental change during the last few years. However, the number of the »original» Finns must have been small. Thus they have not been able to bring to Finland the genes of every possible disorder but an assortment of them. Furthermore, Finland is situated on the margin of the inhabited world and between two contrasted cultures, that is, between Sweden and Russia. The Finnish language, for example, is completely different from both Swedish and Russian. Immigration from either side has thus remained minimal and therefore the original assortment of genes has been well preserved. This phenomenon undoubtedly applies to many isolated nations and tribes; the unique assortment of hereditary diseases among the Jews has been a well-known fact for a long time.

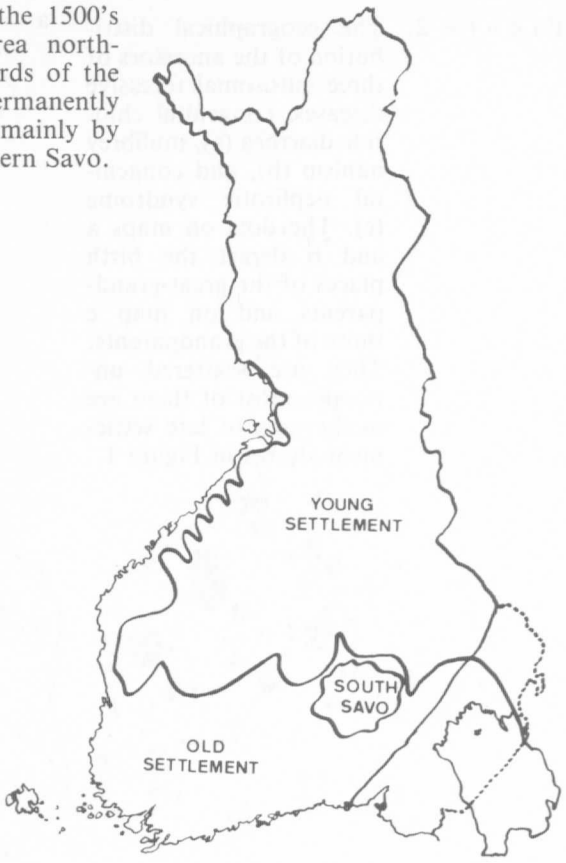


Figure 1. It was not until the 1500's that the large area northwards and eastwards of the curving line was permanently settled, and then mainly by people from southern Savo.

Regional isolation

Recessive genes as such cannot cause diseases. It is two of those genes together in one individual, viz. in a homozygous state, that makes the individual sick. For the overrepresentation of a given disease the carriers of identical genes — the heterozygotes — must have certain favorable circumstances to find and marry each other. In Finland this is due to an uneven geographical distribution of rare genes, viz. regional isolation.

Indeed, at the beginning of the 16th century A.D., only the western and southern coastal parts of today's Finland were permanently settled. In the 1500s the settlement of the central, eastern and northern parts of the country began. The immigrants mainly came from Southern Savo, an area in the mid-southeastern part of Finland (Figure 1). These newcomers brought into the wilds their individual recessive genes and distributed them in turn to their descendants. Clusters of rare genes were thus created by chance or genetic drift or founder effect (Figure 2). Since then these clusters have been maintained by the population structure. The popula-

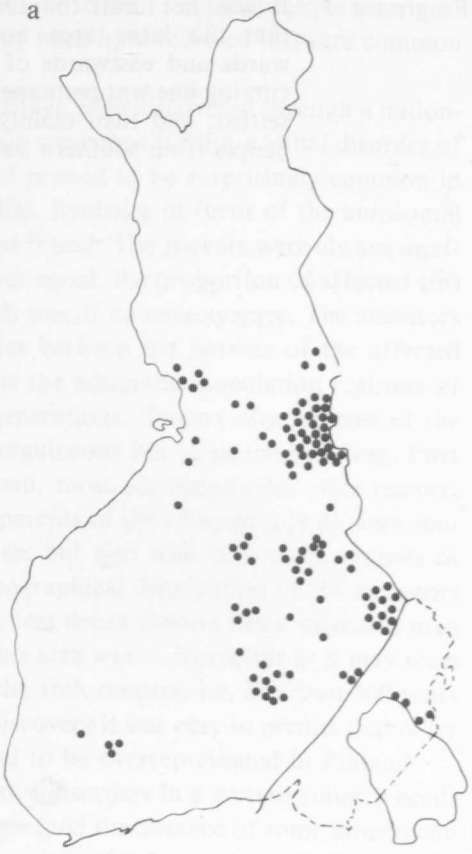
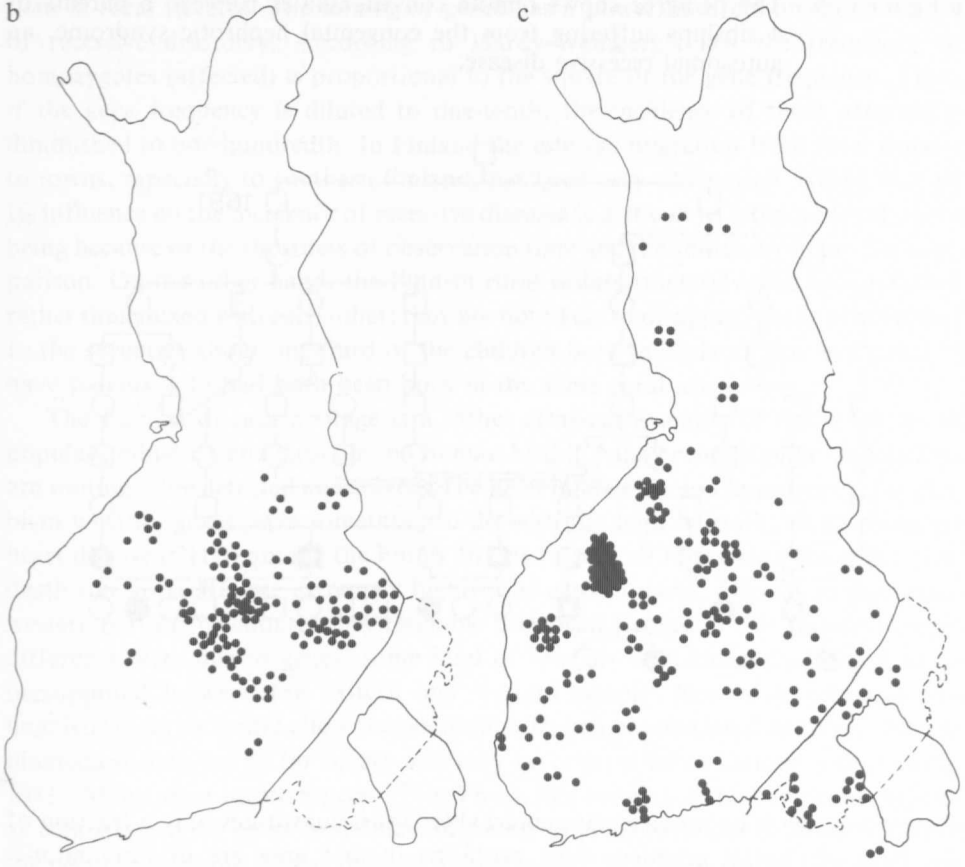


Figure 2. The geographical distribution of the ancestors of three autosomal recessive diseases: congenital chloride diarrhea (a), mulibrey nanism (b), and congenital nephrotic syndrome (c). The dots on maps a and b depict the birth places of the great-grandparents and on map c those of the grandparents. They are scattered unevenly; most of them are in the area of late settlement shown in Figure 1.

tion remained sparse (as compared to the large area of over 300.000 km^2 of the country) being 400.000 in the 17th century, 2.6 million in 1900 and nearly 5 million now. Long distances, vast forests and innumerable lakes separated the villages from each other. Most of the people lived in rural communes. Little need existed for internal migration. The afore-mentioned circumstances caused a population structure which is called isolation by distance or, better still, isolation by population density (Nevanlinna, 1972). These isolates have to a large extent been preserved up to now. Thus the native inhabitants in individual rural areas are even today descendants of those few immigrants from 15 to 20 generations back. The remote consanguinities found between parents of individuals suffering from recessively inherited diseases (Figure 3) are a manifestation of this phenomenon. In such areas marriage between two carriers of the same »rare» gene is not, after all, so rare an event. This explains the overrepresentation of homozygotes, i.e. affected individuals.

The same basic isolated structure of the rural population exists, although in a lesser degree, also in the older settlement area, excepting the southern and southwestern parts of the country.

The population density is greatest in the south and gradually decreases north-



wards, being especially sparse in Lapland. The distribution of the ancestors of the patients is inverse to the density of population: most ancestors originate from the areas settled later (Figure 2).

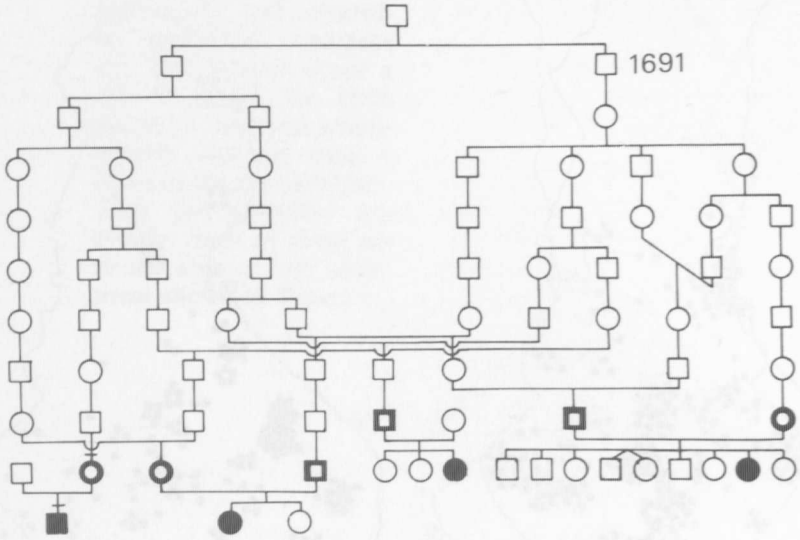
Systematic research on the structure of the Finnish population has been done by Nevanlinna (1972, 1973). He studied the frequencies of different blood groups, among others, and found enormous differences between neighboring villages, great differences between neighboring communes but only slight differences between neighboring provinces — all these due to the founder effect.

Marriages between first cousins are rare in Finland; they were prohibited by law until 1872.

Practical consequences

Of the 25 Finnish hereditary diseases about one-half are absolutely or potentially lethal, one-third cause mental retardation, one-third visual handicaps. Their incidence varies between 1:8000 to 1:60.000. About one newborn in a thousand suffers or is going to suffer from one of the Finnish disorders. Thus the load of the Finnish

Figure 3. The pedigree shows remote consanguinities between 6 parents of 4 sibships suffering from the congenital nephrotic syndrome, an autosomal recessive disease.



disease heritage is by no means unremarkable. Yet it constitutes only a fraction of the field of clinical genetics; most problems in that area are of international character also in Finland.

Because the geographical distribution of the Finnish genes is uneven, the diseases also more or less accumulate in certain areas of their own. That is why the local health care personnel should become acquainted with the rare disorders that occur abundantly particularly in their own area.

In contrast to the situation in medical knowledge and research in general, Finnish medicine should be self-supporting as regards its own hereditary diseases. Moreover, in that field Finnish medicine has a special challenge for international medicine: not only to help the few »international» patients but also to investigate the normal biological phenomena and details from which the diseases are aberrations. Another challenge is the obvious fact that all Finnish diseases are not yet known; up to now about one new disorder has been detected per year. Clinicians thus have to keep their eyes open for new diseases.

Perspectives for the future

Much-abused urbanization has at least one advantage: it shuffles genes. In big cities the chance of finding a spouse with a similar recessive gene is much smaller

than in rural isolates. The mixing of genes has a powerful effect on the incidence of recessive disorders. According to Hardy-Weinberg's law the frequency of homozygotes (affected) is proportional to the square of the gene frequency. Thus, if the gene frequency is diluted to one-tenth, the incidence of those affected is diminished to one-hundredth. In Finland the internal migration from rural isolates to towns, especially to southern Finland, has been very active after World War II. Its influence on the incidence of recessive diseases is difficult to estimate for the time being because of the shortness of observation time and the shortage of data for comparison. On the other hand, the Finnish rural isolates themselves have diminished rather than mixed with each other; they are not likely to disappear in the near future. In the seventies about one-third of the children born in Finland were estimated to have parents who had both been born in the same rural area.

The Finnish disease heritage is a rather clear-cut example of the influence of population history and structure on human health. Many other similar associations are waiting to be detected and solved. The most interesting and important is the problem whether genes have something to do with the high mortality from coronary heart disease (CHD) among the Finns. In this respect all Finns are not similar. The death rates of CHD are extremely high in the eastern parts, whereas in the southwestern part of the country they resemble European figures. If this eastern-western difference were due to genes, some kind of »racial» difference would have to be presupposed between the eastern and western people. New archaeological and linguistic theories would allow the possibility of such populational dualism, whereas biomedical data are so far scanty and may be interpreted in various ways (Norio, 1981). Many other health aspects of the Finns, like the various high mortality figures as compared to the other Scandinavian countries (Valkonen and Notkola, 1977) or the peculiar drinking habits, may, to a great extent, be due to the biocultural youth of this population.

Conclusion

In Finland national isolation due to many geopolitical and cultural factors has created and maintained a rare assortment of genes for recessive diseases. The sparseness of the population in a large nature-spattered area and especially the recentness of a great part of the permanent settlement have led to regional isolation. This has created clusters of recessive genes and thus an overrepresentation of the respective diseases.

The advanced level of medicine, despite the »primitive» population structure, and excellent population records have provided good resources for the investigation of these rare disorders and for the development of the concept of the Finnish disease heritage.

Many other interrelations between human health on the one hand and the structure and biological youth of the Finnish population on the other remain to be discovered in the future.

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