The Finnish disease heritage

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The Finnish disease heritage (FDH) is the concept for nearly forty rare hereditary diseases which are overrepresented in Finland compared to the size of the population. They are rare diseases in Finland as well, because their incidence varies from 1: 10,000 to 1: 100,000. Thus, in a population of about 5 million inhabitants and 60,000 newborns per year, the annual number of new patients in one disease is perhaps ten, perhaps not even one. Excluded from the FDH are rare hereditary diseases that are as frequent in Finland as elsewhere and those common diseases in which genes act as predisposing factors in addition to environmental factors. This article provides an overview of the FDH and examines the connections between hereditary diseases and population history as well as geographic circumstances in Finland.

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Characteristics of the Finnish disease heritage

All branches of medicine are represented among the disorders of the Finnish disease heritage (FDH). Most diseases are severe, many even lethal. Some of them can be treated successfully if correctly diagnosed. They may appear as mental retardation, visual handicap, hearing disorders, congenital anomalies, skeletal or metabolic disturbances, neurological or renal diseases, or as many other kinds of symptoms and signs.

On the other hand, some diseases, such as cystic fibrosis or phenylketonuria, that can be called common among rare disorders elsewhere, are extremely rare or absent in Finland. The Finns cannot therefore be regarded as abnormally sick, but the assortment of their diseases is exceptional.

Most of the Finnish diseases show autosomal recessive inheritance. In other words, the affected individual must possess two disease genes, one from both unaffected parents who possess only one gene for the disease. The close relatives of the patients are usually healthy, because both parents in several couples of the kindred very rarely have the same rare gene. On the other hand, all individuals in all populations carry some rare single recessive genes. Fortunately, they seldom are the same genes as their spouses have. However, this situation may be more probable than in general if the parents are consanguineous, i.e., they share genes derived from a common ancestor.

The vast majority of all recessive disease genes in the population belong to healthy carriers of a single gene, the *heterozygotes*. The proportion of disease genes transmitted forward through the *homozygous* patients and their near relatives is minimal. That is why all preventive measures directed towards such individuals would be doomed to fail.

The background of the Finnish disease heritage

Two presuppositions are needed for the fact that one population has its own assortment of rare recessive diseases and an overrepresentation of those diseases. Firstly, the genes for those disorders must exist in this population. Yet bare genes cannot produce diseases. Affected individuals will not be born until two similar genes meet each other, first in the parents of one family and then in their child. Secondly, an overrepresentation of

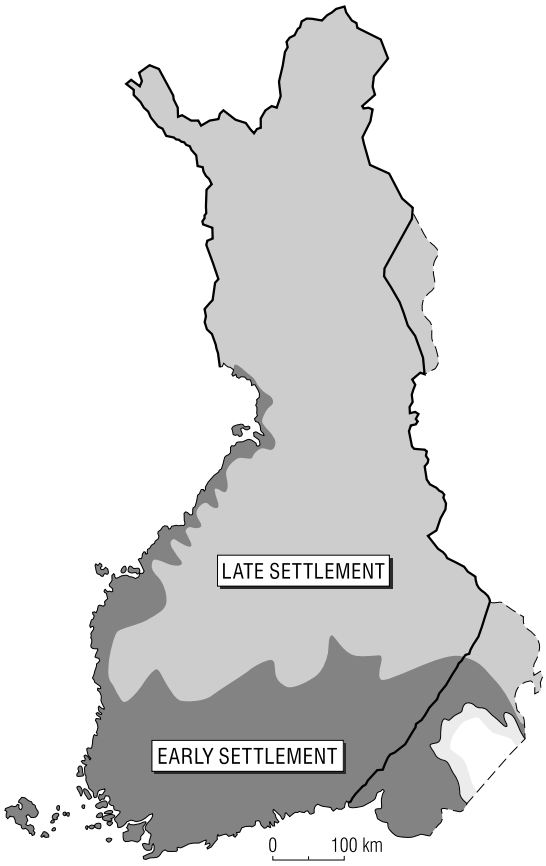


Fig. 1. The boundary of the stationary settlement in the beginning of the 1500s divides today's Finland into areas of early and late settlement (according to Jutikkala 1933).

rare recessive diseases in a population presupposes the existence of some factor that easily brings two carriers of the same rare gene into the same union.

In Finland, the above-defined two presuppositions materialize as the national and regional isolation of the Finnish population. The *national isolation* is due to Finland's geopolitical status. Finland is a small country near the northern edge of the inhabited world and between two different linguistic and cultural entities, Sweden and Russia. The small group of ancestors of the contemporary Finns has not brought to Finland all possible disease genes but a random assortment of genes. This assortment has remained quite unchanged at least during the historical era. Great migrations of peoples have not taken place in the north of Europe, contrary to the situation in central or southern Europe.

The primary conditions for the *regional isolation* have been Finland's large area and sparse population as well as the character of the terrain: vast forests and almost 190,000 lakes (Raatikainen & Kuusisto 1990). The most important factor is a strong wave of internal migration in the 1500s, supported and even pushed by the Swedish Crown. At that time, many individual families from the southern Savo region in the southeast moved to central, eastern and northern parts of today's Finland. This changed the way of living in these areas from hunting and fishing to stationary agricultural settlement. The settlers brought their genes from the *area of early settlement* (Fig. 1) to their new domiciles. Because of the limited need for continuous migrations some of these genes have remained clustered through generations. It is therefore not unusual in this *area of late settlement* that both parents, related to each other beyond six, ten, or twenty generations, happen to have the same disease gene and produce affected children (Norio 1981, 2000, 2002).

Genetic phenomena behind the FDH

The genetic phenomena that have influenced the development of the Finnish disease heritage are the *founder effect, genetic drift* and *bottleneck phenomenon.*

The *founder effect* means that when a new population originates from few individuals only, this new population gets no more than a small random sample from the genes of the primary population. The genes of different subpopulations originating from the same primary population thus differ greatly from each other.

The *genetic drift* influences the genetic pools of small subpopulations by chance. The children and grandchildren of a settler do not inherit from him or her the disease gene or its normal counterpart in similar proportions. One disease gene may have better luck in Nature's gamble than the chance one in two and may be transmitted to disproportionally many descendants of an individual settler. Another gene, correspondingly, may disappear more or less totally from the new population. This is how chance affects the genetic pool of a new population.

The *bottleneck phenomenon* is a special case of the founder effect and the genetic drift. A large population may diminish into a small fraction due to a war or an epidemic. In the remaining part of the population that has passed through this bottleneck, founder effect and genetic drift may act as in a freshly-formed small subpopulation. The bottlenecks may have been regional but sometimes more or less 'national', at least in the past times.

Where have the disease genes come from? Ancient immigrants have probably brought some of them. Perhaps a greater part has originated from new gene mutations in individuals within the Finnish population. Both alternatives have been greatly dependent on chance, so they do not reveal much about the roots of the Finns nor their genetic relationships to other populations (Norio 2000, 2002).

The geography of Finnish diseases

According to both the outlined pattern and empirical experience, the Finnish diseases are not evenly distributed in Finland. Investigations into these phenomena have created a geography of Finnish disorders. The birthplaces of the patients do not reveal any core areas of the disease genes because of the lively internal migration from the countryside to the cities after World War II. Instead, the birthplaces of the grandparents indicate the origins of the disease genes. The vast majority of the grandparents have been born in the countryside and nearly 80 percent of them in the described area of late settlement. In half of the families, both parents have been born in the same locality. In one-fourth of the families, all four grandparents have been born in the same or neighbouring community (Norio 2000, 2002).

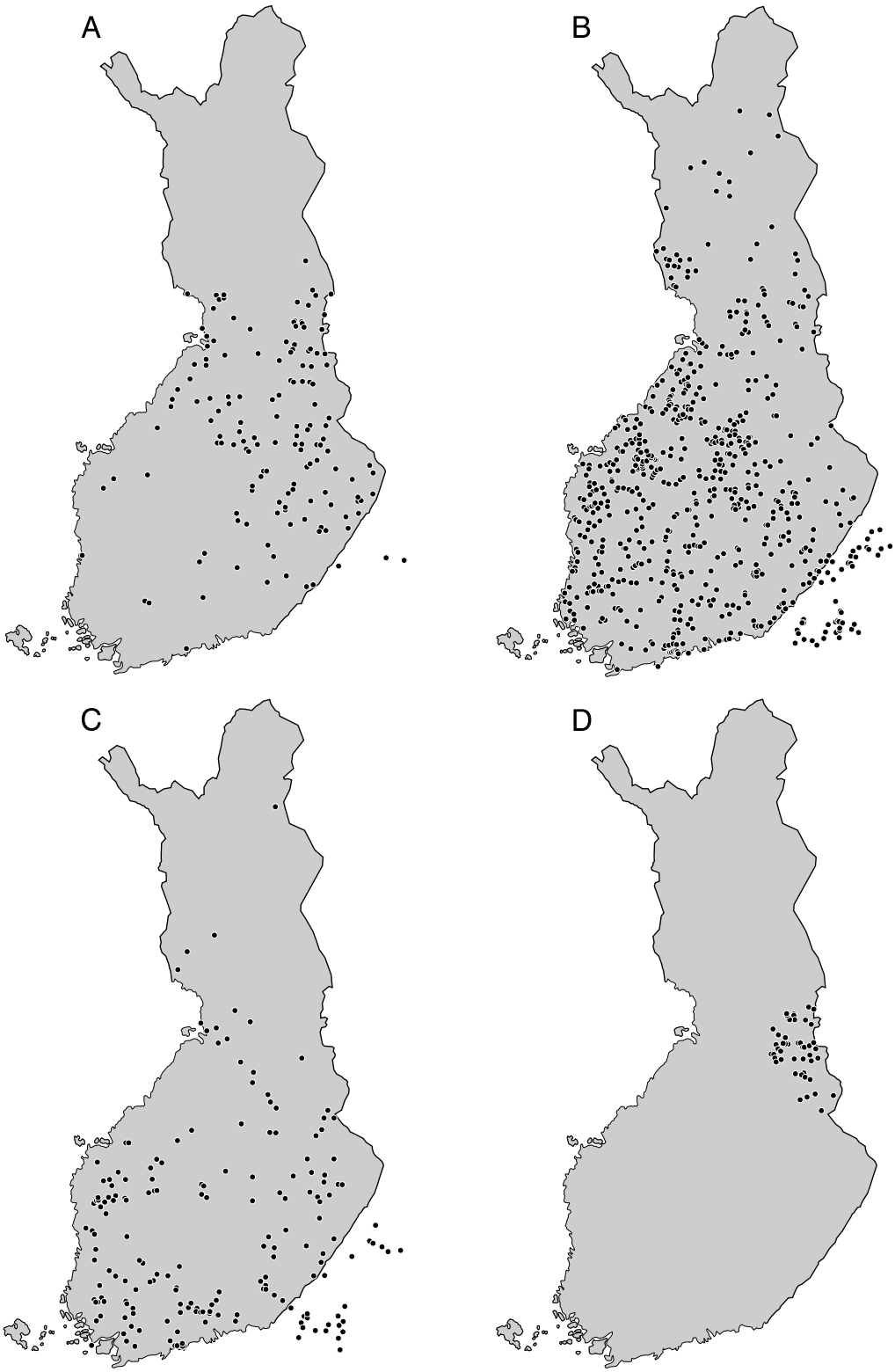
The disease maps in this article show some distributions of the disease genes (Fig. 2). Over one half of the maps of 30 investigated recessive diseases (Norio 2000, 2002) show a pattern inverse to the population density in Finland, whereas the disease genes are few in the densely and early populated southern and southwestern parts of the country. The majority of these disease genes are thus clustered in the area of late settlement since the 1500s. In this area, each map shows a distribution of its own.

The distribution patterns of some diseases differ from those described above. In six diseases, the genes are distributed almost everywhere in the country, although local clusters may appear in the area of late settlement. The genes of those diseases must be distinctly older than 500 years. Two diseases have maps congruent with Finland's population density. Strictly speaking, these diseases should perhaps not be called 'Finnish', because later on they have been found to be relatively frequent also in some other populations. These genes may descend from 'Indo-European' immigrants beyond several thousands of years. Two diseases, in turn, appear only in a very small area restricted to one historical province. These two are probably caused by a very recent gene mutation in an isolated subpopulation.

Investigations into particular diseases

How have the Finnish diseases become known, how have they been studied, and what are the benefits drawn from such investigations? The story of the first detected disease, the congenital nephrosis, may serve as an example (Jalanko et al. 2002). In the 1950s, at the University of Helsinki Children's Hospital, several newborn babies were admitted with an often familial and always fatal renal disease manifesting with edema and proteinuria (Hallman et al. 1956). The information on this condition provided in international textbooks was nonexistent. As data of more than 30 patients were sampled, extensive studies on the disease's clinical features and its Finnishness were started. Through Finnish church records, genealogical and genetic studies revealed recessive transmission of the disease, whereas several extrinsic factors could be excluded (Norio 1966). While the conventional treatment of nephrosis remained unsuccessful, renal transplantation – as soon as sufficient preoperative techniques were learnt – saved normal life and development for the patients (Holmberg et al. 1995). In the DNA-era of the 1990s, the gene of congenital nephrosis was first mapped to chromosome 19 (q13.1) and, subsequently, its structure was characterized (Kestilä 1995; Lenkkeri 1998). This led to the detection of the protein nephrin, which is encoded by the gene in question and is defective in the patients' kidneys. Nephrin, in turn, is probably a central component in the general filtration properties of the kidney and its faults may explain even many other mechanisms of renal diseases (Patrakka 2001).

The detection and studies of 'new' Finnish diseases usually start from observations of alert cli-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nicians. The nationwide sampling of patients and centralization of the studies into few hands has warranted an effective accumulation of knowledge for the physicians and the best possible aid for the patients and their families in the entire country. These investigations also help physicians elsewhere may they confront patients suffering from a 'Finnish' disease. Studying the pathogenesis of rare diseases also helps in understanding the normal mechanisms of the human body that are disturbed in genetic diseases.

Due to excellent study conditions and some internationally acknowledged research groups, the DNA structure of the majority of the Finnish disease genes is already known. This has given quick and reliable possibilities for diagnosing these disorders in children and adults as well as in fetuses. Population screening of the carriers, i.e., healthy possessors of one disease gene, is technically possible as well, but the practical and ethical problems of these procedures have not been solved yet.

The maps of diseases benefit not only genetic and epidemiological research but practicing physicians as well. The maps guide them to be aware of rare disorders that appear in their working areas – no physician can recognize forty rare disorders by heart.

Only some 60 newborns each year are, or will be, suffering from one of Finnish disorders. Thus the FDH is just one unique contribution in the whole of the medical genetic task, from the perspective of both the patients and the physicians. In this context it should not be forgotten that the bulk of medical genetics in Finland is of international character, i.e., the same conditions are found all over the world.

Future developments

In average one 'new' Finnish disease has been revealed annually up to these days. Now the frequency of new detections seems to be decreasing gradually. All Finnish diseases are not yet known, however.

The internal migration into cities reduces the size of the isolates although this movement does not intermingle the isolates. As an increasing number of couples will be formed in cities, this should diminish the probability that two similar rare genes meet. Due to this migratory shuffling of the rare genes, the incidence of Finnish diseases should decrease, although the amount of disease genes remains the same. Such a decrease has not yet been detected, not least because of the observation time has been too short so far.

What is the effect of today's foreign immigrants? Different migrant groups bring to Finland their own rare genes. Also some cases of rare recessive diseases not seen heretofore will be found if the immigrants intermarry frequently. Theoretically, the newcomers 'dilute' the Finnish gene pool. The practical diminishing effect of this on the incidence of 'Finnish' diseases may be imaginary, however, and at least very slow, if the number of foreign immigrants does not increase unexpectedly indeed.

Fig. 2. Four maps of Finnish autosomal recessive diseases depicted by the birthplaces of the patients' grandparents (one patient/family).

(A) Congenital chloride diarrhea: a congenital watery diarrhea due to an intestinal resorption defect of chloride. The disease is lethal if not treated properly, but allows normal life when diagnosed and treated with peroral mineral supplementation. The grandparents are concentrated in the area of late settlement populated in the 1500s and thereafter.

(B) Congenital nephrosis of Finnish type: a congenital renal disorder causing severe failure to thrive due to protein leakage in the urine. This otherwise lethal disorder can be successfully treated by renal transplantation. The grandparents spread over most parts of Finland forming clusters in the area of late settlement.

(C) Meckel syndrome: a perinatally lethal multiple malformation syndrome with severe brain anomaly, extra fingers and toes, and large cystic kidneys and liver. The western predomination of grandparents is congruent with Finland's population density.

(D) Northern epilepsy: An epileptic disorder beginning in childhood with later appearing psychic deterioration. The grandparents originate from a restricted area of one historical province.

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