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REVIEW ARTICLE

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# Finnish Disease Heritage I: characteristics, causes, background

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**Abstract** This review of the Finnish Disease Heritage (FDH), a group of rare hereditary diseases that are overrepresented in Finland, includes the following topics: FDH characteristics, causes and background, primary theory, revis(it)ed theory, consanguineous marriages in Finland, internal migration of the 1500s, family series for further FDH studies, geography and population structure as a basis for FDH, geography of individual diseases, the structure of FDH families, family structure in individual diseases, Finnish gene mutations, linkage disequilibrium and haplotypes, age of gene mutations, frequencies of disease genes and carriers, and a short description of the possible future of FDH.

## Introduction

According to the shortest possible definition, the Finnish Disease Heritage (FDH) is a group of rare hereditary diseases that are overrepresented in Finland. Many people both in Finland and abroad are aware of this peculiarity only to this limited extent.

The purpose of this article is to describe this phenomenon more precisely and to explain why it exists and what type of rules it follows. Instead of mathematical applications and exhaustive molecular genetic details, every effort has been made to elucidate the historical, prehistorical, demographic, political, and cultural background of this medical singularity. Knowledge of these topics is needed for understanding this phenomenon, especially for those who describe new disorders or apply mathematical and molecular genetic theories to explain detected details, and for further scientific progress.

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This report is presented in three parts. In the second part (Norio 2002a), the population prehistory and the genetic roots of the Finns are described. In the third part (Norio 2002b), details of the relevant individual diseases are described. This also shows the way in which this heritage has been and can be retained.

Finland is situated in northern Europe, between Sweden and Russia (Fig. 1). It is a long country extending from latitude 60 ° to 70 °. A narrow strip of northern Norway separates Finland from the Arctic Ocean, whereas in


**Fig. 1** Finland and its surrounding countries in northern Europe

the south, the nearest neighbor Estonia lies behind the Gulf of Finland, a part of the Baltic Sea. The north–south length of the country is about 1100 km, its greatest width over 500 km. Because the map of Finland resembles a young woman with a wide flaring skirt, this country has a pet name, Maiden Finland. Its area is 338,000 $km^2$, of which 68% is covered by forest and 10% by water, including over 180,000 lakes (Raatikainen and Kuusisto 1990). The number of inhabitants exceeds 5 million. Thanks to the Gulf Stream, the mean temperature is 6°C higher than the average at corresponding latitudes.

Finland belonged to the Kingdom of Sweden from about 1100 to 1809 and to Czarist Russia from 1809 to 1917. Since then, it has been an independent republic that has never been occupied. Finland has been a member of the European Union since 1995, and the monetary unit has been the Euro since 2002.

As an illustration of the medical niveau, the infant mortality is one of lowest in the world (4 per 1000 live births). The mean expectation of life at birth is 74 years for men and 81 years for women.

## On the trail of FDH

In the 1950s, the doctors at the Children's Hospital, University of Helsinki, were faced with a large problem. Over and over again, they received newborn patients with a form of nephrosis that, despite all treatment, always ended fatally within months or a couple of years at the longest. Unfortunately, the disease was distinctly familial, contrary to nephrosis in general. Suggestions given by textbooks were scanty.

A nationwide study was started in order to solve the etiology of this discouraging disease. We wanted to determine some particularly Finnish causative factor, possibly related to the place of domicile, sauna habits, maternal disease, or tapeworm, which was common in the fish-eating Finnish population at that time. The possibility of hereditary etiology was taken into consideration from the beginning (Nevanlinna and Kantero 1962), although this was by no means regarded as self-evident. For this reason, the ancestry and near relatives of all the known 57 families were traced.

Soon, it was evident that the etiology of congenital nephrosis (CNF) had to be genetic. Several parents of the CNF patients proved to be consanguineous not only with their spouses, but also with other CNF parents. Most consanguinities were remote and concentrated on an area settled as late as the 1500s. The proportion of affected sibs was, properly corrected, almost "too exactly" one fourth (0.250). Among the near relatives (first and second cousins) of the patients, only a few CNF cases were found, as was expected. The completed study (Norio 1966) established the recessive transmission of CNF. Because the abundant occurrence of this recessive disorder was found to be associated with the population structure of the Finns, it was easy to predict that other rare recessive disorders would also be found to be overrepresented in Finland.

## Description and definition of FDH

Today, FDH comprises at least 36 disorders: 32 being autosomal recessive, two being autosomal dominant, and two being X-chromosomal. The disease spectrum extends to all branches of medicine but is most distinctly visible in pediatrics. Almost one third of the diseases cause mental retardation, and as many show visual handicap. Congenital malformations, bone disorders, hearing loss, metabolic disturbances, epileptic or deteriorating neurological diseases, blood disorders, and multisystemic syndromes are represented. Most of the diseases cause severe handicap and a heavy burden to the patient and the family. A half of the diseases are lethal sooner or later. Some disorders, in turn, can be effectively treated, provided that the correct diagnosis has been made.

Even if overrepresented, the disorders are nevertheless rare also in Finland. The incidence varies mostly between 1:10,000 and 1:100,000. As about 60,000 babies are born per year in Finland, the number of new patients with one of the relevant diseases is perhaps six a year, perhaps not even one. As a whole, yearly about 60 newborn babies, viz. 1 in 1000, suffer or will suffer from one of the Finnish recessive disorders.

FDH was presented in print for the first time in Finnish in 1972 (Perheentupa 1972) and for an English speaking readership in 1973 (Norio et al. 1973). Now the individual diseases will be described in detail and a table with numerical data will be given in Part III of this review (Norio 2002b). In this Part I, the names of the diseases are discernible in Fig. 2, which presents the so-called Perheentupa's steps. They are named as such after Jaakko Perheentupa, Emeritus Professor of Pediatrics, who has detected and described more of the Finnish disorders than anyone else. In the manner described in the legend to Fig. 2, the steps show that about one new disorder has been detected yearly in Finland. Every possible Finnish disorder is still not known.

What is included in FDH? Certainly not all hereditary disorders affecting the Finns are included; the bulk of these disorders is of an international character. Neither are monogenic disorders included that are quite common in Finland but also elsewhere. An example of such a disorder is Willebrand disease, despite it being first published by the Finnish hematologist, E.A. von Willebrand (1926). As a further restriction, the term does not include multifactorial disorders, even if they are common in Finland, such as insulin-dependent diabetes mellitus (Podar et al. 2001; Åkerblom et al. 1997) or coronary heart disease (Vuorio et al. 2001). Also excluded from this article are Finnish genetic investigations of ordinary disorders, no matter how unique the results are (Juvonen et al. 2002; Sarantaus et al. 2000).

Thus, FDH comprises monogenic, mostly autosomal recessive disorders, which are markedly overrepresented in Finland. Some of them have been detected in Finland, and later some scattered cases have been reported elsewhere. In some, the number of known cases is greater in

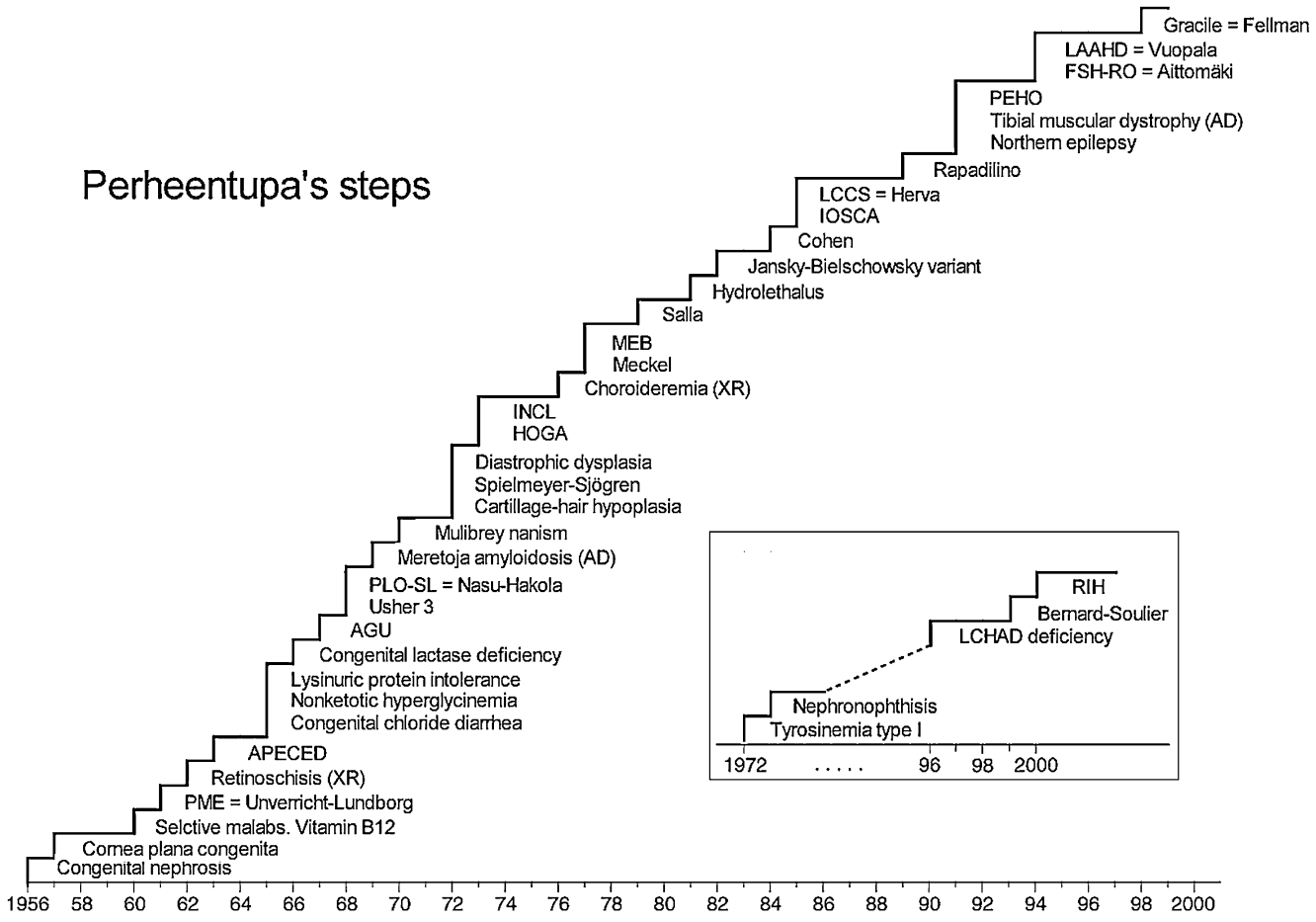


**Fig. 2** Perheentupa's steps. (Perheentupa means "family cottage"). The *vertical line* of each FDH disease shows the year of its first Finnish publication. The steps have risen by about one step per year; the upper plateau has not been reached as yet. The five diseases *underneath* the steps (*inset*) are candidates for being lifted onto the steps

Finland than in all other parts of the world put together. But even 10% of all known patients can be considered as overrepresentation bearing in mind that the number of the Finns is less than one thousandth of the world´s population and only about 0.5% of the summed populations of Europe and North America.

One prerequisite for a disease to be included in FDH is that a minimum of ten families must be known. Any new disorder must be studied properly so as to be sure that it is a homogeneous clinical entity. In many cases, the Finnish clinical genetic community has, by quiet mutual agreement, accepted the disorder into FDH.

The reverse side is also relevant to the definition of FDH: many rare hereditary disorders that are relatively common in other countries are very rare or practically nonexistent in Finland. The most striking example is phenylketonuria: fewer than 10 Finnish patients are known, despite energetic searching, and carrier frequencies are smaller than 1:180 (Pastinen et al. 2001). The incidence of cystic fibrosis is one tenth that in other parts of Europe. Thus Finland is not an uncommonly sick country, but the assortment of diseases is uncommon. Perhaps the old saying according to which the sum of all sins is constant must be accepted as being true in this regard.

## The primary theory

In the 1970s, after several Finnish disorders had been studied genetically and genealogically, a primary theory for FDH took shape (Norio 1981). According to this theory, the causes of FDH are national isolation and regional isolation.

The first presupposition for an exceptional assortment of recessive disorders is, of course, an exceptional assortment of recessive genes. This has been produced by national isolation because of the geopolitical status of this country. Finland is a small nation near the northern edge of the inhabited world and between two different languages and cultures, viz., Swedish and Russian. The small number of ancient ancestors of the Finns did not bring to Finland all possible disease genes but rather a random assortment of them. This assortment remained unchanged, at least during the historical era. Great migrations of peoples did not take place in the north, unlike the situation in central or southern Europe.

Odd genes cannot create an overrepresentation of odd disorders unless some factor favors the formation of ho-

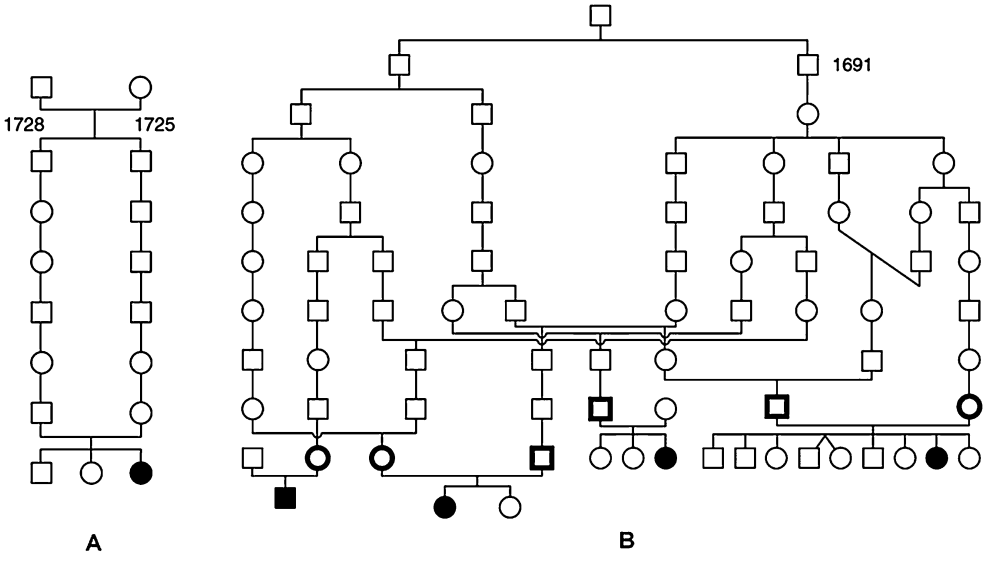


**Fig. 3A, B** Two Finnish pedigrees. **A** The parents of an affected child are often remotely consanguineous (here "fifth cousins"). **B** A typical Finnish consanguinity pedigree shows six parents (*bold*) of four affected children (*black*) being remotely consanguineous through a forefather lived in the 1600s

mozygosity of the disease genes. This factor is regional isolation. The primary condition for this in Finland was its large area and sparse population and the nature of the terrain with its vast forests and immense number of lakes. The decisive role belonged to a strong wave of internal migration in the 1500s, when many individual families from southern Savo in the southeastern part of the country moved into the unsettled middle, eastern, and northern parts of today's Finland. Aided by the founder effect and genetic drift, the genes of the settlers formed clusters, which, with little further mixing, have remained to the present day.

This crucial insight to the significance of population history was initiated through genealogical studies of CNF families. In Finland, almost the whole population has historically belonged to the Lutheran Church, which has kept reliable population registers since the 1600s. With the aid of these church records, it is possible, but laborious, to trace ancestors of today's individuals beyond ten generations. Having done so with CNF families (Norio 1966), 28% of parental marriages were shown to be remotely consanguineous. Additionally, several (up to 10) parents of different CNF families were revealed to be consanguineous beyond 6–10 generations (Fig. 3). The most important message obtained from such pedigrees was the revelation of the structure of the Finnish population in the late-settled area.

These findings have also established the geography of the diseases. Because of the lively migration to the south and into the cities in the last few decades, the birthplaces of the patients do not display the "home" of disease genes, but the birthplaces of grandparents do so excellently. These are concentrated to the area of late settlement and form clusters here and there (Fig. 4). Each disease map shows a distribution of its own but with concentrations mainly within the area of the late settlement. As further diseases became known and their recessive inheritance was to be proved, the tracing of laborious pedigrees could be replaced by drawing a map of the birthplaces of the grandparents.

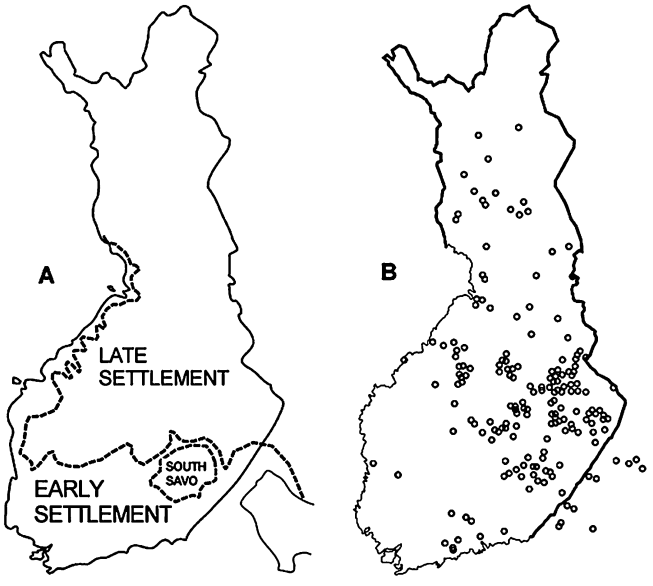


**Fig. 4A, B** Area of late settlement in Finland. **A** The area was permanently populated by immigrants from southern Savo in the 1500s and onwards (according to Jutikkala1933). **B** The grandparents of affected children (here mulibrey nanism) are typically concentrated on the area of late settlement

## The revis(it)ed theory

Over the course of time, a suspicion has arisen that the primary theory for FDH is too simplified. Many details were originally based on assumptions or were entirely lacking, and many unproved statements have been waiting for evidence or disproof. The data regarding especially the genetic roots of the Finns have been referred to by different authors in different ways, and all of them cannot simultaneously be true. Thus, new multidisciplinary studies seemed necessary to me. These are reported in the following subsections.

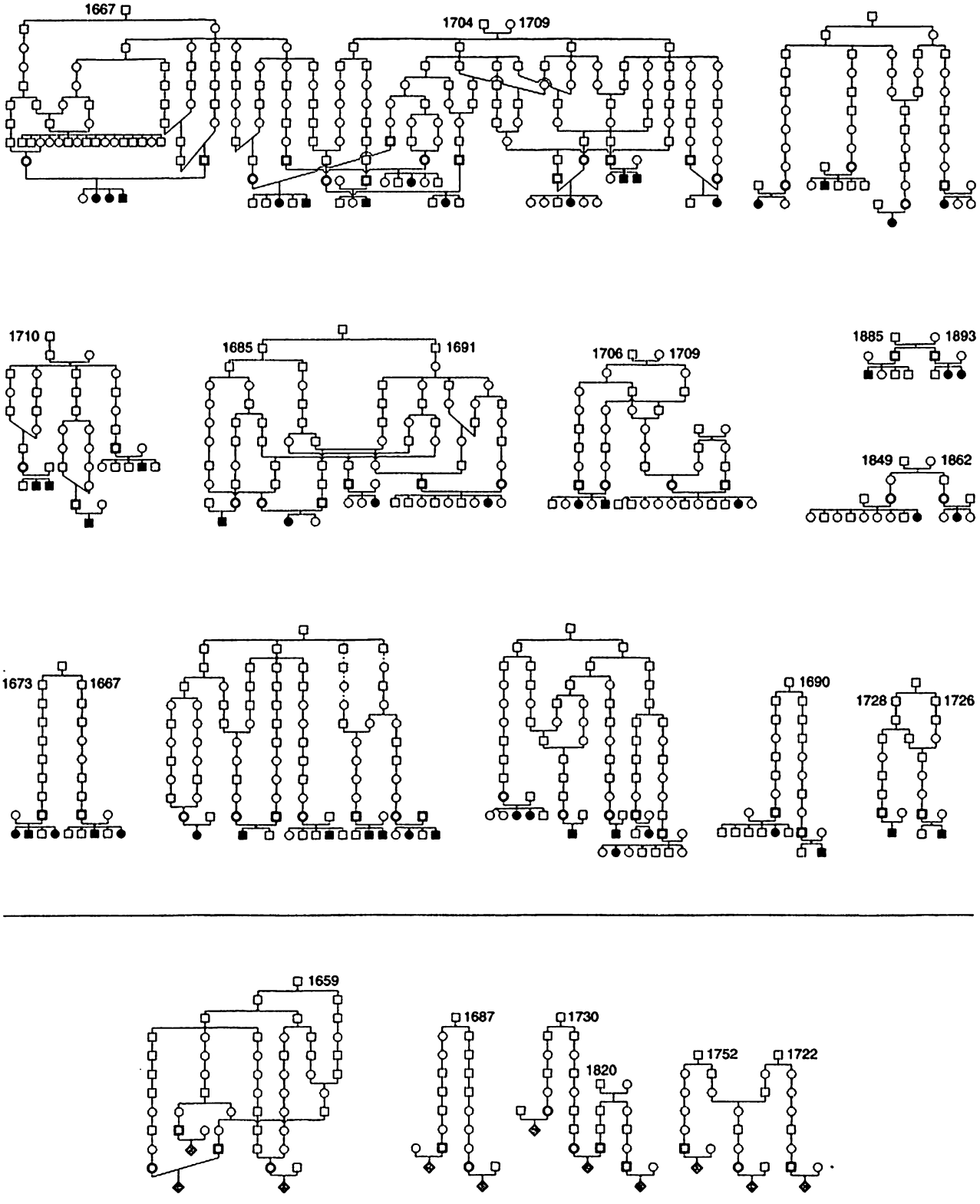


**Fig. 5** *Top* Consanguinities in the series of 57 congenital nephrosis families (Norio 1966). *Bottom* The scant consanguinities traceable for the parents of 57 age-matched control families

## Consanguineous marriages in Finland

Close consanguinities between parents of recessive patients are surely not the cause of FDH. They are rare in Finland. Marriages between first cousins were prohibited by law up to 1872. In CNF, among the 57 families in my study (Norio 1966), there were no first cousin marriages, although one has subsequently taken place. One could imagine that closely consanguineous marriages would be more frequent among the nobility than others. However, I have never encountered a titled family during my genealogical studies of rare recessive disorders.

According to Jorde and Pitkänen (1991), 0.17% of Finnish marriages during the period 1878–1929 involved first cousins. Official population statistics at the turn of the century 1800–1900 gave similar numbers (0.1–0.2%). Today, these numbers must be even smaller. Most European numbers are of a similar magnitude: over 0.2% in Norway (Magnus et al. 1985) and France (Tchen et al. 1977) and nearly 0.3% in Hungary (Czeizel et al. 1976). Larger figures are reported from outside Europe: 4% from Japan, over 20% from northern Africa and the Middle East, and even 37% for Punjab in Pakistan (Bittles 1994).

As can be expected, inbreeding coefficients reported from Finland are small: 0.0001 in the general Finnish population (Jorde and Pitkänen 1991), 0.0006 for CNF patients, 0.002 for CNF parents (Norio 1966), and 0.009 in a rural southeastern population one century ago (Nevanlinna 1972). Values of 0.0002 from Norway and France (Magnus et al. 1985; Tchen et al. 1977), of 0.0007 from a 300-year-old immigrant population from Canada, and of 0.002 from French-Canadian patients with recessive disorders (De Braekeleer and Gauthier 1996) serve as values for comparison. In Japan, the order of magnitude of the inbreeding coefficient is 0.001, whereas that in the Near East and India is 0.01 (Bittles 1994).

Ignatius (1994–1995) studied the frequency of first cousin marriages among the families of 24 FDH diseases. Of the marriages between patients' parents, 1.6% were between first cousins. This number is nearly 10 times greater than average. However, in 14 out of the 24 diseases, there was no parental marriage between first cousins. This result establishes that, even in Finland, the parents of patients with rare recessive disorders are closely consanguineous more often than others but that close consanguinities cannot be the cause of FDH.

Remote consanguinities, in turn, are important for FDH. Genealogical church record studies have given a rule of thumb: if the parents of a patient were born in the same commune, they can often be shown to be remotely consanguineous (Fig. 3a). Usually the common ancestor couple was born in the 1700s, beyond 6 to 8 generations, or perhaps even further back. This rule holds better in the eastern and northern parts of the country rather than in the early settled areas. Obtaining this result presupposes that the church records have been preserved in the particular congregation and that the investigator has spared no trouble. If several parents of different patients were born in the same locality, most of these parents can usually be shown to be descendants of one pair of ancestors (Fig. 3b). The mathematical power of the evidence from such pedigrees is not great. The pedigrees may not even establish that the disease gene really has descended to the patients along the drawn paths. Instead, the pedigrees can be considered as a convincing picture of the Finnish rural population structure.

It is easy to ask whether consanguinity pedigrees are evidence of recessive inheritance or whether all Finns are remotely related to other Finns. These questions can now be answered. For all of the 57 CNF families (Norio 1966), a control family was chosen from the population register so that the birth date of the control child matched that of the first affected sib of the affected family. A professional genealogist traced the ancestry of these families in the same diligent manner that I had done for the CNF families. My hypothesis was that, if the parents of a control family were born in the same rural locality, they might be consanguineous, but that group consanguinities would be rarer between the controls than among the CNF parents.

The first part of the hypothesis was not fully correct, whereas the second part proved to be true. The CNF parent pairs were born in the same or neighboring commune in 42% of cases and the control pairs in 39%. However, 28% of the CNF parent pairs but only 14% of the control pairs could be shown to be remotely consanguineous. If both parents were born in the same or neighboring commune, then 16/24 or 67% were shown to be consanguineous in CNF families and 7/22 or 32% in control families.

The result of the study of the group consanguinities can be seen in Fig. 5. As consanguinities in the CNF series were abundant, only a few tiny interrelationships could be found between control parents. Thus, this study showed convincingly that group pedigrees of remote consanguinities between several parents of patients can be taken as evidence for the recessive inheritance of the Finnish diseases.

## Internal migration of the 1500s

The population structure of the area of late settlement is a consequence of the internal migration movement of the Savo people initiated in the 1500s. At that time, the boundary drawn between the areas of early and late settlement (Fig. 4) separated two cultures. The settlement of the southern and western "coastal zone" relied on farming. The remaining area was not totally empty of people, but the different regions were distributed to serve as hunting and fishing grounds for the people of the southern counties.

A strong man in favor of population reform was King Gustavus Vasa (1523–1560). He had freed Sweden-Finland from the supremacy of Denmark and so had to arrange the affairs of the newly independent state in a novel fashion (Jutikkala and Pirinen 1996). The farmers of southern and western Finland cultivated their clay soil in the customary way. On the other hand, the Savo people of southeastern Finland had to clear fields by slashing and burning trees. Such fields did not yield harvest for long, and hence the Savo people often needed new ground for new fields. The interests of the King and the Savo people had much in common. The Savo people wanted new areas for living. For the Crown, it was profitable for the eastern woodlands near the uninhabited Russian border to have a Finnish population. Secondly, every farm had to pay tax, which was very important for the heavily indebted King, and so the King abolished the hunting rights of the southern counties and allowed the Savo people to move into the wilderness.

The Savo people started on their way northwards willingly but were partly coerced into doing so by the Crown by means of various incentives. However, individual families went on into the wilderness in the eastern, middle, and northern parts of today's Finland. Wherever they went, they founded new villages and began "to be fruitful, and multiply, and replenish the earth" (*Genesis* 1:28). When the new village became crowded, some people moved further on and set up a new village. This population movement continued onwards like a fan and lasted, at least in Lapland, for more than 200 years. The sparseness of population, vast forests, and numerous lakes created isolation by distance or, according to Nevanlinna (1972), isolation by population density. Further migrations were mainly directed to empty regions, not to other previously populated centers. Even in the late 1800s, the Finnish community was mainly rural with a small amount of industry and little need for mixing. Thus, the rural isolates remained preserved even up to modern times. Because of the lively industrialization during the last few decades, many people have recently moved from the countryside to the towns but not to any great extent from one isolate to another.

In many areas of the early settlement southwards and westwards of the boundary line, the population structure during the last few centuries was similar to that in the area of the late settlement. The exceptions were the most southwestern and southern districts with the oldest settlements, communes of small areas, and the lively internal migration through the centuries. In these areas, most of the diseases of FDH are rare. If, for some disease, several parents were born there, it is difficult or impossible, even with an energetic effort, to find noteworthy consanguinities between them. In such an area, the gene frequency of the disease must be high for some unknown reason.

For a geneticist, it is obvious how favorable the population structure of the area of late settlement is for the founder effect and genetic drift. These have created clusters of some of those rare genes that the migrating people of southern Savo happened to possess and bring with them in the heterozygous state. In these clusters, homozygosity of a rare gene need not be a rare event. Reciprocally, some of the disease genes may have vanished with drift. The Savo people did not have all possible disease genes, not even all those that existed in other parts of Finland. Compared with the recessive diseases of some villages in isolated valleys of a mountain region, the Finnish isolates have formed systematically and serially. Many different genes have been taken along in the spreading movement. One gene is not restricted into one isolate but is distributed through many branches of migration onto a greater area, such as displayed by the individual disease maps. The isolation has not been strict: it was not too difficult to look for a spouse through the forests and beyond the lakes. Thus, one isolate may comprise neighboring communes.

An important concept for understanding the power of remote relationships is the loss of ancestors. Imagine a Finnish individual born in middle Finland in 1950. His temporal distance to a founder from southern Savo born in 1525 is 17 generations. Thus, beyond 17 generations, he must have $2^{17}$ (over 130,000) ancestors. If the majority of his ancestry comes from the same village founded in the 1500s, then, say, 10 founders at fertile age represent the majority of those 130,000 ancestors. Thus, every founder appears as ancestor more than 10,000 times on average. This extreme example shows that if we could draw a pedigree of ancestors 17 generations back, the amount of traced consanguinities would be endlessly great.

In many isolated areas in Finland, it is not unusual that all four grandparents (and in such a case, also the majority of further ancestors) were born in the same locality. An example of a situation approaching the example above is the region of Lake Lappajärvi. Group consanguinities traced for several disorders of FDH lead in fact to this region. Actually, pedigrees showing these consanguinities are the youngest branches of the huge imaginary ancestry pedigree traced back to 17 generations. This example also gives an explanation for a surprising phenomenon in the control study of CNF parents (Fig. 5). In the biggest control pedigree on the left, four control parents were shown to be consanguineous with each other. This pedigree comes from Lappajärvi. Whenever any people happen to be born in this region, they can be shown to be consanguineous, even though they do not carry any disease gene.

## Family series for further FDH studies

For subsequent studies, a series was compiled of all known families with a recessive FDH disease found in Finland by 1990 (exceptionally, a few patients born in the 1990s were also included). The two newest disorders out of the 32, viz., GRACILE syndrome and Vuopala disease, were omitted, because their data were not complete. The lists of families were obtained from the principal consultant doctors for each disease. The number of families in one disease varied between 178 and 9, with a mean of 50.7. The birth dates and places of patients, parents, and grandparents were ascertained from population registers. The total number of families was 1520. Out of the theoretical number of 9120 of the parents and grandparents, 8828 (96.8%) could be traced, whereas 217 (2.4%) remained untraced because of illegitimacy and 75 (0.8%) because of other causes.

To obtain a control series, a random family was chosen from the central population register for every diseased family for four disorders (CNF, hydrolethalus, Meckel, mulibrey) as described above. The number of control families was 324. Their parents and grandparents were traced in the same manner as in the disease series.

The only data used in the study were the birth year and birth place of the patients/controls, their parents and grandparents. Permission for the study was obtained from the Finnish Ministry of Social Affairs and Health.

*Geography and population structure as basis for FDH*

Two maps were drawn of all the 30 diseases. In them, birth places of patients (1/family) and grandparents were depicted by dots. Similar maps were drawn of the control series. The birthplaces of the grandparents represent the "domiciles" of the disease genes, whereas in the maps of the patients and parents, the migration during the last decades to towns and to the south disturbs the original geography.

Figure 6 presents the birth places of the grandparents in all of the 30 diseases. Compared with the population density of Finland (Fig. 7), the dots are underrepresented in the south and southwest but overrepresented in other, sparsely populated parts of the country. In the last named area, several clusters are seen but also a couple of light areas. Their exact naming and analysis are not significant for the international readership; all the details have however been presented for interested Finnish readers in Finnish (Norio 2000). Less than 4% of the grandparents were born in the five biggest cities, in which 30% of Finns lived in 2000.

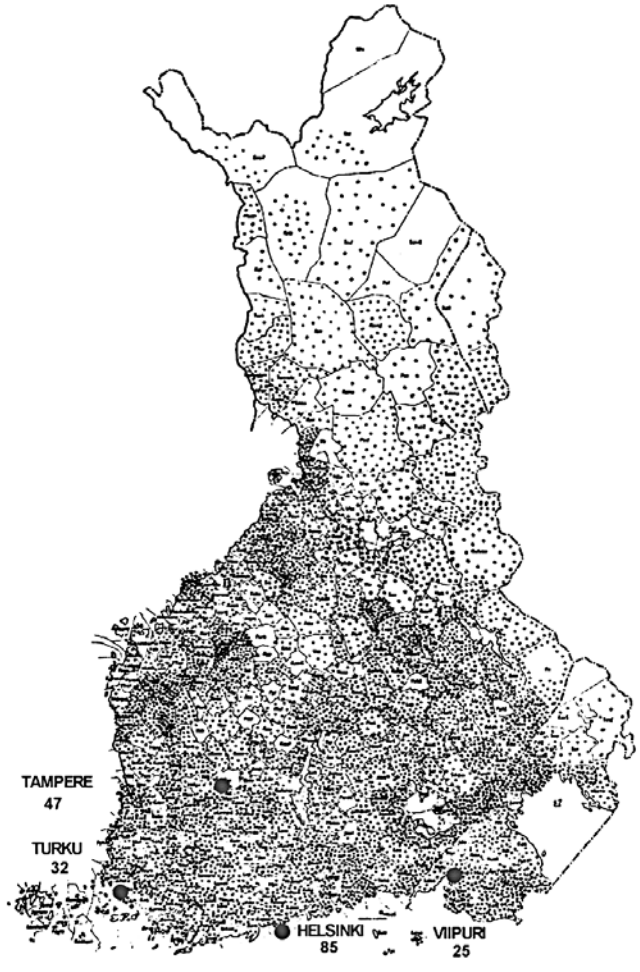


**Fig. 6** Birth places of the nearly 6000 grandparents in 30 FDH disease families are marked by dots. The numbers of grandparents born in the four largest towns are marked with numbers

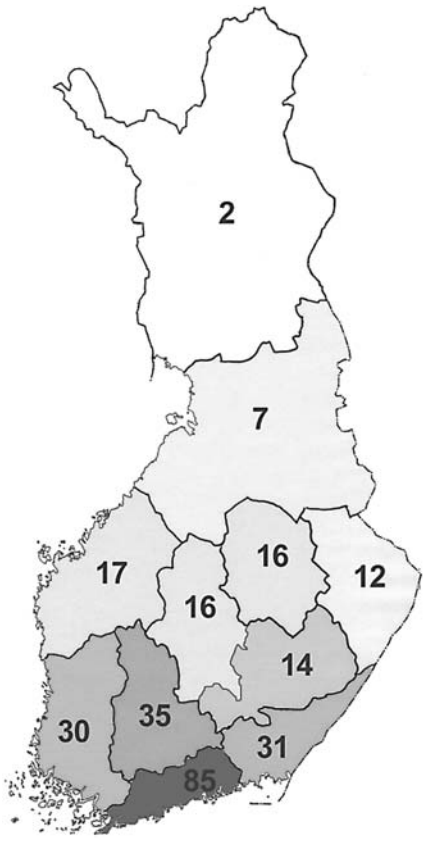


**Fig. 7** Density of the population of Finland by counties in 1960 (inhabitants per km$^2$ land area)

In the map of patients (not shown), the clusters of Fig. 6 or at least their buds can be discerned, although as many as 19% of the patients were born in the five biggest cities.

The control grandparents (not shown) were disseminated seemingly at random. They followed the population density of Finland, except that the most southern county of Uusimaa was underrepresented, because most grandparents of most of the present people of that area were born elsewhere. For the same reason, only 5% of the grandparents were born in the five biggest cities, whereas the corresponding proportion of the control children was 25%.

The distribution of the birth places of the grandparents in FDH is inverse in comparison to the population density of the country. This finding presents itself well when Finland is divided in two parts. The densely populated southern part comprises three counties (Uusimaa, Turku and Pori, Häme) and is called here Dense Finland. The remaining counties, which also represent mainly the area of late settlement, will be called Sparse Finland. The area of Dense Finland is 16% of the country, but its population in the last 50 years has been about 50% of the whole population. Of the control children, a similar proportion, viz., 49%, was born in Dense Finland; of the control grandparents, this value was 31%. Of the FDH patients, 35% and, of the grandparents, only 22% were born in Dense Finland, or in other words, the majority was born in Sparse Finland.

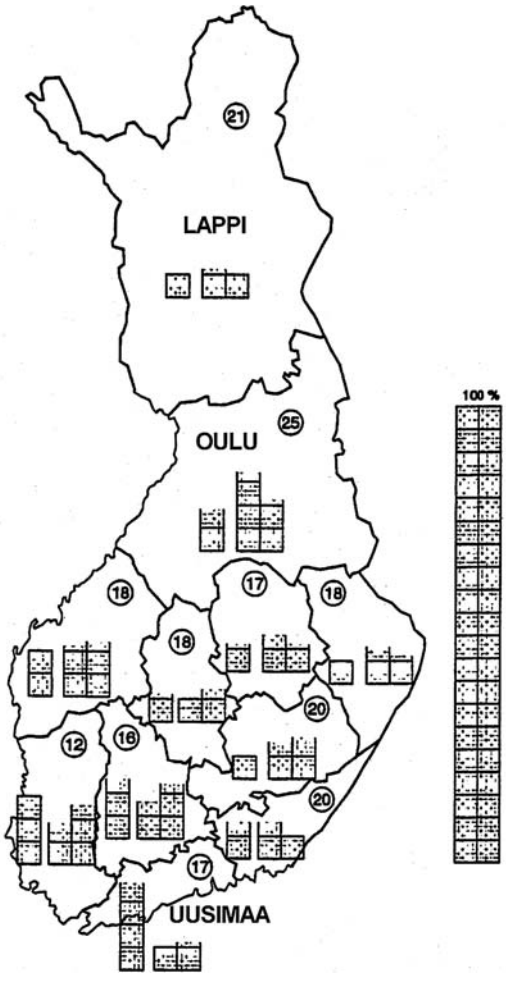


**Fig. 8** The distribution (%) of FDH and control grandparents compared with the proportion of the population in 1960, by counties (*extreme right* 100%). *Left column* Proportion of population in the county compared with the population of the country, *middle column* proportion of FDH grandparents in the county compared with the total number of FDH grandparents, *right column* proportion of control grandparents in the county compared with the total number of control grandparents, *circled numbers* indices of the risk of being affected by FDH disorder (proportion of FDH families compared with the number of children born in the county in 1960, per thousand)

Figure 8 displays the distributions of grandparents of the patients and controls compared with the proportion of inhabitants in various counties. In Dense Finland, there are plenty of inhabitants but few FDH grandparents. The proportion of those affected by FDH is greatest in the county of Oulu. Perhaps the isolation has remained most effective just there. The settlement has been more recent than in the more southern counties, and recurrent wars have created several bottlenecks. Because of religious reasons, the number of children in the families is great, which means that marriages of two heterozygotes are easier to reveal than average.

I predicted that the northernmost and extremely sparsely populated county of Lappi would have been affected the most by FDH, but that was not the case. Apparently, proportionally few disease genes reached Lapland with the last remnants of the migration movement of the Savo people. In the maps of some individual disorders, however, Lapland is abundantly represented. Any disease gene that has reached Lapland has had very favorable possibilities for homozygosity.

In Fig. 8, there are also indexes about the proportion of affected families compared with the number of children born in the county. They show that the risk figure of having a Finnish disease is about double in the county of Oulu (25) compared with the southwestern county of Turku and Pori (12).

## Geography of individual diseases

For every disease, a map was drawn depicting the birth places of the grandparents. Only four of them are presented here as examples (Fig. 9). In Part III (Norio 2002b), a map of every disease is shown. The names of the diseases are expressed here in the shortest possible way; they are explained and provided with MIM numbers in Part III (Norio 2002b).

The maps could be divided into five groups. The biggest group comprised 16 out of 30 disorders: APECED, CCD, CLD, Cohen, CPC, FSH-RO, Herva, HOGA, hydrolethalus, IOSCA, LPI, mulibrey, NKH, PLO-SL, Salla, and Ush3. In all of them, the birth places concentrate on the area of late settlement (southern Savo included), whereas other parts of the country are mostly empty. These disorders follow precisely the primary theory of FDH showing the importance of the population movement in the 1500s.

The second group included six disorders: AGU, CHH, CNF, INCL, PME, and SS. They are the most common of all. The birth places of the grandparents cover most parts of the country. However, the area of late settlement is overrepresented, and clusters are seen here and there, as in the first group. Apparently, these genes had dispersed before the population movement of the Savo people.

The third group was composed of only two diseases, viz., Meckel syndrome and diastrophic dysplasia. For them, the distribution of dots is predominantly western and follows the population density of Finland. These genes may have arrived in Finland with the western Indo-European immigrants (Part II; Norio 2002a) and may have spread around in the country without the contribution of the southern Savo people. Indeed, these disorders are not very rare even elsewhere in Europe. It is questionable whether these two diseases should be called Finnish at all.

The fourth group also consisted of two disorders that, contrary to the former two, are extremely Finnish. They are northern epilepsy and the Finnish variant of Jansky-Bielschowsky disease. They are strictly local: the latter in Southern Ostrobothnia, the former in Kainuu at the waist of Maiden Finland near the eastern border. Their genes must be very young, having been brought by one individual or originating from a fresh mutation several hundreds of years ago. Indeed, another disorder, viz., tyrosinemia

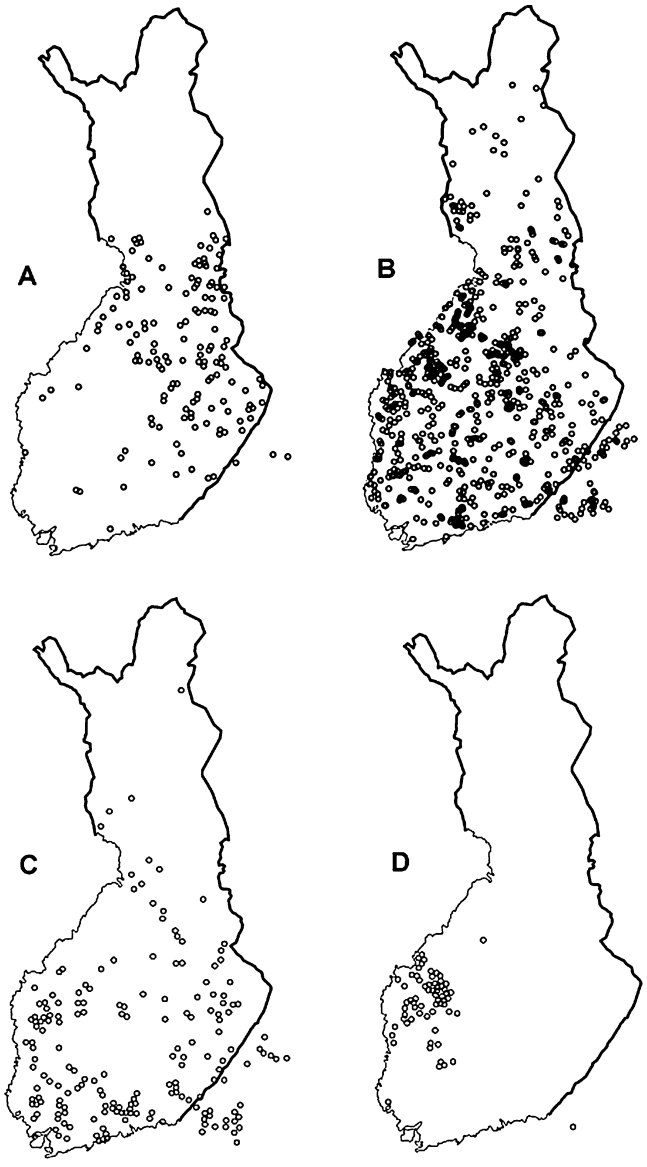


**Fig. 9A–D** Examples of four different types of FDH diseases depicted by the birth places of grandparents. **A** Congenital chloride diarrhea: the grandparents are concentrated in the area of late settlement populated in the 1500s and thereafter. **B** Congenital nephrosis of the Finnish type: the grandparents are spread over most parts of the country and form clusters in the area of the late settlement. **C** Meckel syndrome: the western predominance of the grandparents is congruent with the population density of Finland. **D** Finnish variant of late infantile neuronal ceroid lipofuscinosis: the grandparents originate from a restricted area of about one county

type I, shows a distribution similar to the Jansky-Bielschowsky variant. Tyrosinemia has not been included in the FDH because it has been considered a classical disease with an global distribution (cf. Part III, Norio 2002b).

The age dimensions of these four groups are dealt with in a later subsection.

Four disorders (MEB, PEHO, rapadilino, $SMB_{12}$) were placed into the fifth group. Their maps are atypical and cannot be connected with any other maps. In all these disorders, the number of families is less than 20.

The two dominant (Meretoja, TMD) and two X-chromosomal (choroideremia, retinoschisis) diseases of FDH did not belong to my study. Maps of earlier investigations are, however, available for them (Part III, Norio 2002b). These maps also show regional concentrations, although these diseases, being caused by one gene only, do not need isolation for their occurrence. These local concentrations are another sign of the limited internal mobility of the Finnish population.

Although the maps of disorders can be grouped, each of them certainly has its individual history of origin. Some paths of the disease genes from southern Savo to their present areas of prevalence could perhaps be traceable with great effort by the aid of local population histories or even of studies of names. Most histories, however, may remain forever veiled in the darkness of the past. Nevertheless, I find it difficult to agree with Nevanlinna's opinion that the diseases have spread over the country randomly like a smooth patchwork quilt.

## Structure of the FDH families

Information regarding the interdependence of birth places of patients, parents and grandparents is essential, because the birth places disclose the way in which the homozygosity of rare genes may have been produced. All studied combinations are presented in the legend of Fig. 10, whereas some of the most important results from all 30 diseases are given here.

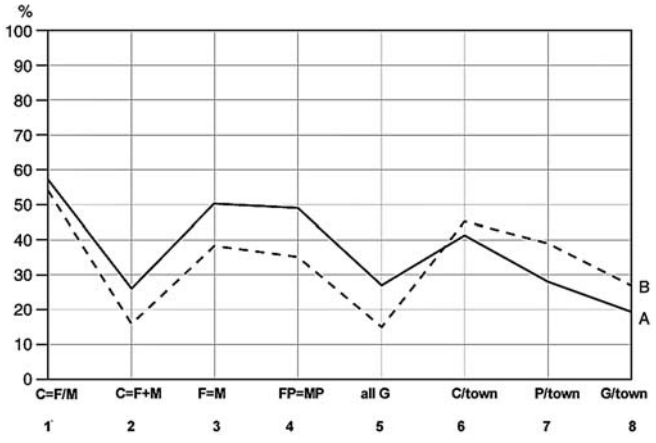


**Fig. 10** Mean curve of family structures in 30 FDH diseases (*solid line*) and four control series (*broken line*). *Points 1–8* depict the following items (%):*1* the patient (control) and one of the parents were born in the same commune; *2* the patient (control) and both parents were born in the same commune; *3* both parents were born in the same or neighboring communes; *4* at least one of the paternal (*FP*) and one of the maternal grandparents (*MP*) were born in the same or neighboring communes; *5* all four grandparents were born in the same or neighboring communes; *6* the patient (control) was born in a town; *7* at least one of the parents was born in a town; *8* at least one of the grandparents was born in a town (*C* child, *F* father, *M* mother, *P* parent, *G* grandparent)

Both parents of the patient were born in the same commune or neighboring communes in 50% of the families. Just as often (49%), at least one of both the paternal and the maternal grandparents was born in the same commune or neighboring communes. Thus, the patients probably received both of their disease genes from the same region.

The patient and both parents were all born in the same commune in one fourth (26%) of the families. All four grandparents were born in the same commune or neighboring communes also in one fourth (27%) of the families. Both these figures reflect the isolate origin of the family.

The figures of the control families (Fig. 10) are somewhat smaller than those of FDH families. Most distinct is the difference concerning the common birth place of all four grandparents (15% instead of 27%). This indicates that, in general, Finnish families are not as often from isolates as are the affected families.

In 38% of the control families, the parents were born in the same commune or in neighboring communes. This figure is in accordance with the estimate of Nevanlinna that one third of Finnish children born in 1971 had parents who were both born in the same locality. The number of FDH parents here was, as previously mentioned, considerably higher (50%).

The figures indicating possibilities for remote consanguinity of the FDH parents are high. However, in about half of the families, the parents were not from the same locality. Thus, the disease gene can be received from a larger area than one isolate. This result fits in well with the step-like or fan-like structure of the Savo-born populations. A considerable number of parents have, after all, received their disease gene from different parts of the country, perhaps entirely by chance. As described earlier, in a half dozen disorders, the gene has spread throughout the country.

Of the patients, 41% were born in towns, whereas with regard to healthy Finnish children, 38% in 1960 and 63% in 1997 were born in towns. Out of the FDH parents in 28% of the families, and out of the grandparents in 19% of the families, at least one was born in a town. Many Finnish families have moved into towns during the last few decades; couples may have married in the countryside but moved to cities before the birth of the affected child.

## Family structure in individual diseases

The individual disorders were also characterized by the same parameters presented above from the whole series. Mean values for these eight parameters were depicted by a curve. The curves of different diseases were compared and diseases were grouped according to the similarity of the curves.

High values of the first five points indicate the rural or isolate character of the disease, whereas high values of the three last points represent townmanship. The fifth point indicating that all four grandparents are from the same region is the best sign for the isolate character of the disease and is called here the isolate value. The curves of the disease groups are presented in Fig. 11.

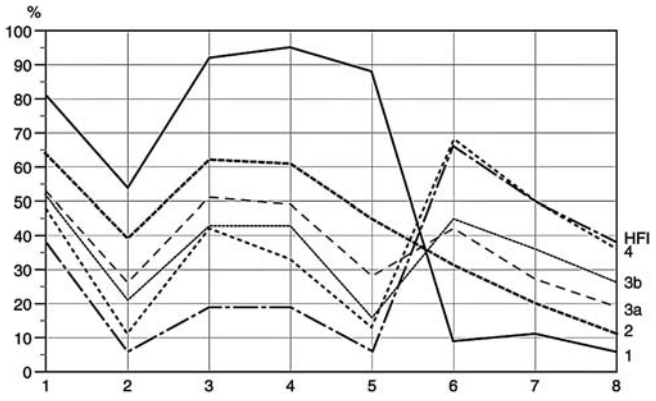


**Fig. 11** Family structure curves of individual diseases have been grouped according to the similarity of their form. Mean curves 1–4 have been drawn for each group. The groups are described and interpreted in the text. *Points 1–8* as in Fig. 10

The most prominent is curve 1, which is composed of the two strictly local disorders, Northern epilepsy and the Jansky-Bielschowsky variant. The "rural end" of the curve is extremely high, the isolate value being 90% and "city end" only about 10%.

Curve 2, which was formed by eight disorders (Cohen, FSH-RO, HOGA, IOSCA, LPI, PLO-SL, Salla, Ush3) has a considerably high rural beginning. The isolate value is over 40%, and the right end slopes gently. The maps of these disorders are of the type of late settlement. The disorders are rare, which is why homozygotes appear mostly in the population of the rural isolate type.

Curve 3a with ten diseases has a moderately high rural beginning. The isolate value is lower than that in the former two curves, and the curve rises toward the point of patients born in towns. The curve comprises five "common" disorders (AGU, CHH, CNF, PME, SS) with an overall distribution. Their genes are so common that they do not need isolation for homozygosity but also appear in towns. The other five (CCD, CLD, CPC, Herva, NKH) are concentrated in northern Finland, where gene frequencies in the whole region may be high enough for homozygosity. Curve 3b is otherwise similar, but the isolate value is still lower. Out of these three disorders (APECED, DD, INCL), the two last ones are also common in southern Finland: the gene frequency must be high even there, although consanguinities are rare.

The fourth group (curve 4) consists of three diseases (hydrolethalus, Meckel, PEHO). The rural beginning of the curve is lower than the city end, and the isolate value is low (under 20%). These disorders have been detected recently and manifest themselves perinatally. Therefore, the majority of patients were born in the last few years in a population that had moved into towns. Their gene frequencies may be quite high.

The curves of four diseases (MEB, mulibrey, rapadilino, $SMB_{12}$) deviated from others and could not be interpreted.

For comparison, the curve of hereditary fructose intolerance is shown. In the 1970s, this disease was thought to belong to the FDH. Later, we realized that the disease was

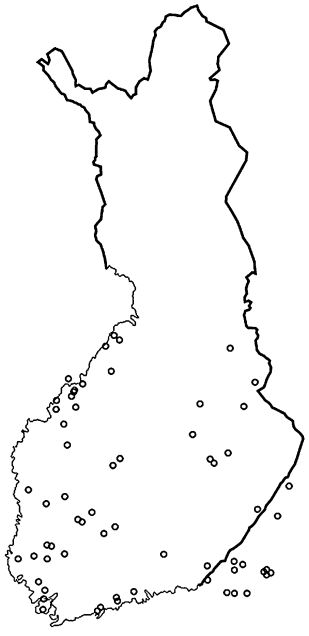

**Fig. 12** Western distribution of grandparents in a "non-FDH disease", viz., hereditary fructose intolerance, follows the area of the early settlement

no more common in Finland than elsewhere. Moreover, its map is atypical, being accentuated toward the western coast (Fig. 12). Carrier frequencies determined by the microchip technique (Pastinen et al. 2001) varied between 1:130 and 1:390. The curve is a "contradiction" of the Finnish diseases: the isolate value is only 6%, and over 65% of the patients were born in towns.

## Finnish gene mutations

Because of the favorable prerequisites for molecular genetic studies, a great proportion of the genes of FDH are known. Thus, out of the 36 diseases, the gene has been mapped in 33 (92%) and characterized in 27 (75%). In the three non-mapped disorders, the number of known families is still small.

Earlier, as the genetics of a new Finnish disease was being studied, regular questions were: from where, when, and by how great a group of people was the gene brought to Finland? Usually, it was very difficult to produce any answers. Today, the trend is to assume that the main mutation in most diseases originated in a single individual, often even within the Finnish borders.

When the first attempts at characterizing gene mutations were successful, the finding of several mutations in one disease of FDH was an unexpected result and even caused confusion. However, one main mutation was (and still is) responsible for the majority of disease genes. Today, it is understood that Finnishness does not protect the Finns from several mutations, even though they are mostly very rare. These rare mutations would never become exposed without the main mutation that has spread as clusters into isolates and thus easily creates affected homozygotes. The rare mutations are usually found as compound heterozygotes together with the main mutation.

Out of the 27 characterized FDH genes, the main mutation is found in 100% of the chromosomes in eight disorders. In most of the others, the main mutation is represented in more than 90% of the chromosomes. In two disorders, the corresponding percentage is "only" 70 (Peltonen et al. 1999; Part III, Norio 2002b).

In most of the few patients found near the Finnish border in northern Sweden and northern Norway, the Finnish main mutation is present. On the contrary, in most FDH disorders elsewhere outside Finland, the mutations differ from the Finnish ones. Detailed information concerning the mutations in individual diseases is given in Part III (Norio 2002b).

## Linkage disequilibrium and haplotypes

Strong evidence of the descent of many Finnish disease genes from a single founding ancestor, who existed not too far back in the past, has been obtained from linkage disequilibrium and haplotype data. Strong linkage disequilibrium between disease genes and nearby markers is a rule in FDH. Indeed, in 1980s together with Albert de la Chapelle, we planned to map Finnish genes by searching for pairs of similar homozygous markers among restriction fragment length polymorphism panels of patients. It soon turned out that Lander and Botstein (1987) in USA had come up with the same idea to be used in patient series from closely consanguineous marriages. They published it under the name of homozygosity mapping (Lander and Botstein 1987). The idea was then developed further, but technical obstacles were unsurmountable at that time. Later, Leena Peltonen's group (Nikali et al. 1995) succeeded in mapping the gene of IOSCA very elegantly with a similar technique by using a series comprising only four families.

Long haplotypes of markers up to 13 cM (Peltonen et al. 1999) around a particular disease gene, common to the majority of parents, are an especially Finnish phenomenon. They also predict the existence of a main mutation long before it is characterized. An instructive example taken from Cohen syndrome (Kolehmainen et al. 1997) is presented in Fig. 13. A different example is given by a dominant gene mutation 1 in the gene MCH1 of hereditary non-polyposis colorectal cancer (HNPCC). According to the investigations of de la Chapelle's group (Moisio et al. 1996), this mutation was present in 17 kindreds in middle Finland but only in two kindreds near the eastern boundary. In the former group, the common haplotype was long, whereas in the latter, it was very short. It is tempting to suggest that the mutation came to eastern Finland a long time ago, so that the haplotype in common has shortened greatly because of many recombinations. From eastern Finland, the gene may have been transported only recently to middle Finland. Here, the transported random haplotype has remained largely unchanged across the few generations that have elapsed since the movement of the gene.

| 30 chromosomes of 15 patients | 6 gene markers forming haplotypes | | | | | |
|---|---|---|---|---|---|---|
| | D8S257 | D8S559 | D8S1808 | D8S1762 | D8S546 | D8S1714 |
| 1 | 1 | 4 | 2 | 5 | 7 | 5 |
| 2 | 1 | 4 | 2 | 5 | 7 | 5 |
| 3 | 1 | 4 | 2 | 5 | 7 | 5 |
| 4 | 1 | 4 | 2 | 5 | 7 | 5 |
| 5 | 1 | 4 | 2 | 5 | 7 | 5 |
| 6 | 1 | 4 | 2 | 5 | 7 | 1 |
| 7 | 1 | 4 | 2 | 5 | 7 | 1 |
| 8 | 1 | 4 | 2 | 5 | 7 | 1 |
| 9 | 1 | 4 | 2 | 5 | 7 | ? |
| 10 | 1 | 4 | 2 | 5 | 7 | ? |
| 11 | 1 | 4 | 2 | 5 | 7 | ? |
| 12 | 1 | 4 | 2 | 5 | 7 | 7 |
| 13 | 1 | 4 | 2 | 5 | 7 | 6 |
| 14 | 2 | 4 | 2 | 5 | 7 | 5 |
| 15 | 2 | 4 | 2 | 5 | 7 | 5 |
| 16 | ? | 4 | 2 | 5 | 7 | 5 |
| 17 | ? | 4 | 2 | 5 | 7 | 5 |
| 18 | 2 | 4 | 2 | 5 | 7 | 1 |
| 19 | 2 | 4 | 2 | 5 | 7 | 1 |
| 20 | ? | 4 | 2 | 5 | 7 | 2 |
| 21 | 2 | 4 | 2 | 5 | 7 | 6 |
| 22 | 2 | 4 | 2 | 5 | 7 | 6 |
| 23 | 2 | 4 | 2 | 5 | 7 | ? |
| 24 | 3 | 6 | 2 | 5 | 7 | ? |
| 25 | 4 | 6 | 2 | 5 | 7 | ? |
| 26 | 4 | 6 | 3 | 5 | 1 | 7 |
| 27 | 2 | 6 | 3 | 1 | 2 | 7 |
| 28 | 2 | 6 | 3 | 1 | 2 | 3 |
| 29 | 2 | 6 | 3 | 1 | 7 | 7 |
| 30 | 3 | 7 | 3 | 3 | 1 | 6 |

**Fig. 13** The haplotype distribution of 30 parents of 15 Cohen families. *Parents 1–5* share a similar haplotype of six markers. In *parents 6-13*, the marker farthest *right* has changed because of recombinations. In *parents 14–23*, also the marker farthest *left* has changed because of recombinations. In *parent 26*, only marker 5 remains from the original haplotype and probably is close to the mutated gene common for *parents 1–26*. *Parents 27–29* have another haplotype in common and probably represent another mutation at the same locus. These three parents have ancestors from the same commune

## Age of gene mutations

How can the age of disease gene mutations be estimated? Indeed, instead of the actual moment of the molecular mutation, it is more sensible to try to determine the time period or number of generations that have elapsed from the appearance of the mutation in one or a few individuals living in the Finnish area.

Genealogical and geographic data allow some approximations. If, exceptionally, almost all parents can be shown by the aid of church records to be consanguineous, as in Northern epilepsy (Hirvasniemi et al. 1994), then the minimum time period from the founder mutation to the present is less than 400 years or sixteen generations. In a disease restricted to one county but not to one pedigree, such as Jansky-Bielschowsky disease (Varilo et al. 1996), the common ancestor is probably farther back than 400 years but not much more than 500 years or 20 generations.

About one half of the disorders are distributed through many counties but are still restricted to the area of late settlement begun in the 1500s. The common ancestor must then be beyond 500 years or 20 generations. Probably in southern Savo, in the area of origin of this settlement, there must have been more than one carrier of the gene. Thus, the age of the disease gene is probably considerably older than 500 years.

If the disease gene is found distributed through most parts of the country, the gene must be much older, perhaps thousands rather than hundreds of years. Carried by hunters and fishermen, the genes may have been shuffled widely throughout the country. Nevertheless, some of these genes might also have participated in the distribution of the Savo people. This circumstance explains the local clusters in the area of late settlement, e.g., in the widely spread CNF, viz., the clusters and group consanguinities that actually led to the discovery of the FDH.

An interesting exception is shown by diastrophic dysplasia and Meckel syndrome. Their gene distribution is the densest in early settled, western Finland and follows the population density of the country. These genes may be very old and may have been brought to Finland by western, so-called Indo-European settlers thousands of years ago, perhaps with the Battle-Axe culture (Part II, Norio 2002a).

Concerning the original age of Finnish mutations, Unverricht-Lundborg's progressive myoclonus epilepsy offers exceptional insights. It is caused by the same mutation in Finland and in Mediterranean countries where the disease was previously called Ramsay-Hunt disease (Virtaneva et al. 1997). It is possible (and even probable) that only one carrier transported the disease gene to Finland, e.g., with the ancient trading expeditions from the Mediterranean countries to the faraway northern fur markets in the *Ultima Thule*. The Finns then multiplied the gene and spread it within Finland by their own methods.

Attempts have also been made to determine the age of the mutations mathematically, starting from molecular genetic findings. The method of Luria and Delbrück (1943) was originally developed to estimate mutational phenomena in bacteria reproducing exponentially. Its application to the Finnish disease mutations has given plausible results (Hästbacka et al. 1992; Lehesjoki et al. 1993; de la Chapelle and Wright 1998), although the reproduction of the Finnish population is far from exponential and estimates of other required parameters are arbitrary. It would be worthwhile to test the Luria-Delbrück and other mathematical methods systematically by using various values of assumptions for different parameters. This does not, however, belong to the scope of the present review.

## Frequencies of disease genes and carriers

A glance at the disease maps is enough to convince that the frequencies of the Finnish disease genes and their carriers vary greatly according to geographic area. This regional variation explains why attempts to calculate national gene frequencies by the Hardy-Weinberg method starting from national incidence figures give unreliable and even misleading estimates. Regional carrier frequen-

cies have been calculated by the Hardy-Weinberg method for CNF (Norio 1966). In the peak area of Lappajärvi, in the large area of CNF prevalence in Savo, and a sparse CNF area of southern Finland, carrier frequency estimates were 1:10, 1:25, and 1:100, respectively.

Starting from the ten most frequent Finnish disorders, an approximation of 1:7 was obtained by the Hardy-Weinberg method to estimate how many Finns carry at least one of the Finnish disease genes (this figure must not be counted by adding carrier frequencies of individual diseases but by multiplying the individual probabilities of not being a carrier and subtracting this figure from unity). This estimate, however, is very rough, being too high for southern Finland and the cities and far too low for several isolate regions.

Pastinen et al. (2001) analyzed the carrier frequencies of 16 Finnish diseases on DNA-array microchips with 2151 samples collected from four regions, viz., the cities Helsinki (south) and Oulu (north), an eastern rural area representing late settlement, and a western rural area intended to represent early settlement. Carrier frequencies denser than 1:50 ($q^2$=1:10,000) were found in three diseases in the east, three in the west, one in Oulu, and none in Helsinki. Carrier frequencies lower than 1:50 but higher than 1:100 ($q^2$=1:40,000) were found in five diseases in every population. Considerable regional differences were found even in the most common Finnish diseases. In general, the carrier frequencies were in good accordance with my disease maps depicting the birth places of grandparents (Part III, Norio 2002b). Peculiar exceptions to this accordance were seen in diastrophic dysplasia and, with respect to Oulu, in congenital chloride diarrhea. Unfortunately, the western area of the study does not properly represent the zone of early settlement, because the immigration of the Savo people in the 1500s extended to this area.

## The future of FDH

The status of FHD in Finland is well-established. The number of new diseases presently being discovered seems to be decreasing and the speed of such discoveries is becoming slower. The course of research procedures has stabilized. Thus, the initial observations of alert clinicians lead to the collection of the patient series, then to the unraveling of the clinical picture, the elucidation of the pathogenesis, and the development of procedures for treatment and support at various levels. Basic analysis of the mode of transmission and tracing of the geography of the disease has continued by mapping and characterizing the gene. The solving of the main mutation has yielded a highly reliable diagnostic test for patients, their near relatives, and fetuses at high risk.

What will happen next? The mapping and characterization of genes still awaiting these procedures and the determination of major and minor mutations are mainly questions of time and workload. The microchip method offers technical possibilities for heterozygote screening in several Finnish disease genes either to a nationwide or regional extent (Pastinen et al. 2001). Testing procedures, however, involve striking ethical, informational, and other practical problems, and their benefits in general and in relation to the costs are not easy to judge.

The most important challenge for the future of FHD is moving from genes to proteins, to elucidate what happens in the organism because of wrong genetic information. This progress is also the key to curative treatment, of which little is as yet to hand. Mouse models are an important stage in reaching this goal. Gene studies of specific diseases are often exaggerated in the media as being steps to understanding more universal pathogenetic mechanisms, such as the causes of epilepsy or retinal degeneration. The results obtained so far have not been abundant. Perhaps the discovery of nephrin and its significance for protein leakage through the slit diaphragm of the renal glomerular wall in CNF offers real progress for solving problems of proteinuria in general (Ruotsalainen et al. 2000).

Some sceptics take pleasure in asking whether FDH is a vanishing natural resource. Indeed, the incidence of Finnish recessive diseases should diminish together with the gradual loosening of isolation and with the migration from rural areas to cities. Is this diminution already in operation? This is difficult to judge, because the follow-up time is too short. An attempt to investigate this has been made with CNF, the "oldest" known Finnish disorder (Laakso et al. 1992). Surprisingly, its incidence was increasing rather than diminishing, which may at least partly be because some fetuses that are heterozygous for the CNF gene may temporarily simulate affected fetuses by showing elevated alpha-fetoprotein values in the amniotic fluid (Patrakka et al. 2002; Norio 2002b).

On the other hand, the diminishing incidence of diseases is perhaps not so apparent as is believed. The genes of half a dozen of the Finnish diseases are distributed all over the country. In some others, the regional frequencies of the gene are so high that two similar genes have considerable possibilities of coming together from different communes and even in the regional cities.

Be that as it may, Finnish researchers cannot wait for FDH to vanish but must do their best to help the patients of today and the future. They must also investigate the disease mechanisms as long as their research facilities are not reduced unreasonably. However, when the need for investigating rare recessive disorders diminishes, the excellent Finnish possibilities for studying hereditary components of common multifactorial disorders may step to the forefront (Laitinen et al. 1997, 2001; Varilo et al. 2000). Perhaps, then, the definition of the FDH must be changed.

"Where large isolates are long maintained, or small groups migrate and subsequently populate broad territories, does it seem probable that drift is operative in major variety formation." This sentence of William H. Womble (1951) sounds as if it were written to describe FDH as a result of the immigration movement of the Savo people.

FDH and the well-advanced knowledge accumulated about it are attributable to the constellation of three factors: the peculiar, perhaps primitive, population structure,

the unique church records, and a sufficient continental niveau of medicine run with the full collaboration of vigorous clinicians and researchers. Moreover, the abundant research of rare hereditary diseases has experienced a type of "institutionalization" in Finland. Has anyone heard about a Swedish or Norwegian disease heritage?

The knowledge gained about the Finnish diseases does not benefit only the Finns, but also helps those patients who happen to suffer from these diseases in other countries. If the elucidation of various pathogenetic disease mechanisms proceeds aided by these Finnish experiments of Nature, then the benefit will not be isolated but global.

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