Consanguinity and Endogamy in the Netherlands: Demographic and Medical Genetic Aspects

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Key Words

Consanguinity · Endogamy · The Netherlands ·
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Abstract

This paper reviews what is currently known about the presence of consanguinity and endogamy in the Netherlands, in the past and today, and concludes with a discussion of medical genetic aspects. First geographic characteristics, the demographic history, the genetic make-up of the native population, legal aspects and the public opinion are reviewed. Then data on the prevalence of consanguinity in the native population are presented for marriages since 1840, followed by data on consanguineous marriages among immigrants from countries with a tradition of close-kin marriages. It is estimated that approximately 1% of at-risk consanguineous couples are referred to clinical genetic centres for prospective genetic counselling in the Netherlands. This picture will change dramatically if and when next-generation sequencing is introduced to identify couples at $\geq 25\%$ risk prospectively.

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Introduction

This paper reviews what is currently known about the presence of consanguinity and endogamy in the Netherlands, in the past and today, and concludes with a discussion of medical genetic aspects. To set the scene for these themes, the following background determinants of both the prevalence of consanguinity or endogamy and of the nature of the disorders that may become manifest as a result of them are described first: geographic characteristics, the demographic history, the genetic make-up of the native population, legal aspects and the public opinion. Data on the prevalence of consanguinity in the native population are presented for marriages since 1840 and show a continuous decline of consanguineous marriages, followed by data on consanguineous marriages among immigrants from countries with a tradition of close-kin marriages starting in the second half of the 20th century. It is estimated that approximately 1% of at-risk consanguineous couples are referred for prospective genetic counselling to clinical genetic centres in the Netherlands. This picture will change dramatically if and when next-generation sequencing is introduced to identify couples at $\geq 25\%$ risk for autosomal recessive disorders in their offspring.

Fig. 1. Map of the Netherlands, showing its neighbouring countries and the North Sea, its main rivers and their branches, the Zuiderzee (Z), its 12 provinces (1–12), the major cities (A, H, R, U), and the position of the Bible Belt (shaded area). Dams between islands in Zeeland and in the Zuiderzee are not shown, apart from the 32-km-long dam which transformed the Zuiderzee into a freshwater lake. 1 = North Holland; 2 = South Holland; 3 = Zeeland; 4 = Groningen; 5 = Friesland; 6 = Drenthe; 7 = Overijssel; 8 = Gelderland; 9 = Utrecht; 10 = North Brabant; 11 = Limburg; 12 = Flevoland. A = Amsterdam; H = The Hague; R = Rotterdam; U = Utrecht.

Geographic Characteristics

The Netherlands is a small but rather densely populated European country bordered by Germany in the East, Belgium in the South and the North Sea in the West and North. It covers an area of about 40,000 km² and has almost 17 million inhabitants. On their way to the North Sea, two major rivers, the Rhine and the Meuse, cross the country, forming an extensive delta separating the Southern part from the rest of the country (fig. 1). Another natural border, separating the Western part from the Eastern and Northern part, used

to be the Zuiderzee, an extension of the North Sea in a North-South direction. The Zuiderzee was closed off from the North Sea by a 32-km-long dam built in the 1930s, creating a huge freshwater basin, large parts of which have since been reclaimed as polders. The main rivers, the Zuiderzee, and the estuaries, in the North and especially in the South-Western province of Zeeland, formed partial barriers to random mating in the past and explain in part both the genetic substructure of the native Dutch population (see below) and, to a lesser extent, the presence of endogamy and consanguinity in this population.

Demographic History

The demographic history of the country is characterized by immigration. While there are many traces of prehistoric life and living, the earliest written account of the country dates from the advent of the Romans in the 1st century BC. According to their description, large numbers of Batavians floated down the river Rhine from Germany into the Netherlands. They were followed in later centuries by large groups of economic immigrants and religious refugees from many parts of Europe, especially in the 16th and 17th centuries, and after the end of World War II by immigration from many other countries like Indonesia, Surinam, the Antilles, Morocco, and Turkey. It is estimated that some 75% of the ancestors of what is currently called the ‘native’ Dutch population immigrated into the Netherlands during the last 20 centuries [1, 2]. Taken together, these native citizens make up 79% of the present Dutch population, while Western and non-Western immigrants account for 9 and 12%, respectively [3]. The two largest subpopulations of non-Western citizens are Moroccans and Turks, numbering over 360,000 and 390,000 individuals, respectively. They are overrepresented in the larger cities (Amsterdam, Rotterdam, The Hague and Utrecht).

An important historical determinant of population stratification and the presence of consanguinity and endogamy in the native population is the segregation between Catholics and Protestants, and also between several denominations within the Protestant faith, each having their own churches, schools and political parties. A study of 3,042 spouse pairs from two current databases in the Netherlands showed a significant correlation between husband and wife’s religious affiliation, defined as Catholic, Protestant or not religious [4].

Genetic Make-Up of the Native Dutch Population

Abdellaoui et al. [1] performed a principal component analysis on genome-wide SNP data in over 4,000 unrelated subjects, after removing individuals with non-Dutch and non-European ancestry. Three principal components showed a significant correlation with geography, distinguishing between: (1) North and South; (2) East and West, and (3) the middle band and the rest of the country. Boomsma et al. [5] confirmed this finding in 250 trio-families from all (presently 12) provinces of the Netherlands.

At the individual mutation level, regional trends and differences in frequencies, reflecting the genetic heterogeneity of the population, are clearly visible [6, 7]. Zeegers et al. [8] reported founder mutations for 5 disorders in 5 different genetic isolates, and for another 8 diseases not restricted to isolates but frequently showing a regional distribution. More disorders in more isolates have been described since then.

Legal Aspects and Public Opinion

According to the Dutch Civil Law, marriages between first cousins are allowed; Catholics, however, need dispensation from their church for such unions. Under Dutch Civil Law, uncle-niece and aunt-nephew marriages are not allowed, but dispensation by a Royal Decree can be given. The public opinion at present is opposed to consanguineous marriages, since it has long been generally felt that consanguinity of the parents is a threat to the health of the children. A ban on consanguineous marriages is being prepared by the present government in an attempt to fight forced marriages [9]. According to the Explanatory Memorandum, the impediment to marriage does not apply if both prospective spouses declare under oath that they freely give consent to enter into this marriage [10].

Prevalence of Consanguinity in the Native Population

1840–1922

Bras et al. [11] studied kin marriage using a unique database, named GENLIAS, which contains information on over 1 million marriage certificates from 5 of the (then) 11 Dutch provinces during the period 1812–1922. Almost 2% of all marriages in these provinces were between first cousins. There has been a clear downward trend in the prevalence of first-cousin marriages during the observa-

tion period. They were more frequent in 3 out of 6 social classes, and more prevalent among orthodox Protestants in the so-called Bible Belt area, stretching from the South-Western province of Zeeland to the North-Western part of the province of Overijssel. The 6 distinguished social classes were: (1) higher managers and professionals; (2) lower managers and professionals; (3) farmers and fishermen; (4) lower skilled workers; (5) unskilled workers, and (6) farm workers. Classes 1, 2 and 3 were overrepresented among the consanguineous couples. Bras et al. [11] argued that for these social classes cousin marriages served both an economic and a political purpose. A limitation of the study is that important provinces (i.e. North Holland, South Holland and Utrecht), in which the major cities (i.e. Amsterdam, Rotterdam, The Hague and Utrecht) are located, were not included.

1906–1918 and 1937–1948 (Excluding 1945)

Polman [12] studied Central Statistical Office data on 572,932 (1906–1918) and 843,005 (1937–1948) marriages, respectively, from the 11 provinces (at that time) in the country and found a considerable decline in the frequency of first-cousin, uncle-niece and aunt-nephew marriages from 0.70 to 0.17% (and from 0.67 to 0.15% for first-cousin marriages alone). Of all provinces, the province of Gelderland had the highest percentage of consanguineous marriages in both periods.

1951–1965

Van de Kamp [13] determined the frequency of third- and fourth-degree consanguineous marriages in Central Statistical Office data during the years 1951–1965. Third-degree marriages were found in 0.015% of all marriages and fourth-degree marriages in 0.11% of all marriages. He also compared the population coefficient of inbreeding during this period with the two periods studied by Polman [12]. This revealed a further decrease from 46.1×10^{-5} in the period 1806–1918 and 12.3×10^{-5} in the period 1937–1948 to 8.7×10^{-5} in the years 1951–1965.

1906–1982

Van Straaten [14] reviewed Central Statistical Office data again in 1980/1982 and found a further reduction of the close-kin consanguineous marriages analyzed by Polman [12] to 0.06% (0.05% for first-cousin marriages alone). He also reports that the percentage of first-cousin marriages among the Jewish population in the pre-World War II period in Amsterdam (at that time representing about 10% of the population) was 2%.

Genetic Isolates

There are a number of communities in the Netherlands, in which certain autosomal recessive disorders and parental consanguinity or at least endogamy are more prevalent. One-time islands in the former Zuiderzee and fishing towns, such as the ones around it, are familiar examples. Other examples are Catholic communities in mainly Protestant provinces, or places elsewhere that were genetically isolated for social reasons. These places are well-known to regional clinical geneticists and other professionals, but a national overview does not exist.

Prevalence of Consanguinity among Recent Immigrants

According to Troe (cited by Waelput and Achterberg [15]), the percentage of women with a consanguineous partner among 7,683 participants in the Generation R Study in Rotterdam was 24% in Turks, 22% in Moroccans and 0.1% in native Dutch participants. Just over 50% of these consanguineous marriages concerned first cousins, and about 40% second cousins. Participants in the Generation R Study were mothers living in the city of Rotterdam who had given birth between April 2002 and January 2006 [16].

Other Measurements and Observations of Consanguinity or Endogamy

Ekamper et al. [17] studied the distances between birthplaces of marriage partners in the GENLIAS database mentioned above (over 1 million marriage certificates; 5 provinces; 1812–1922). They observed an increase of 10 km in the average distance over time (from 15–20 to 25–30 km) in parallel with the increase in transportation and means of communication in that period. There were, however, large differences between the 5 provinces, and social status had a strong effect on distance. The higher social classes had a much wider radius than any other social class, with farmers and rural labourers having the smallest.

Isonymy structure in the Netherlands was studied by Barrai et al. [18] using the surname distribution of 2.4 million private telephone users selected from a 1996 commercial CD-ROM. From their analysis, a clear isolation by distance emerged, although much weaker than in

Fig. 2. Mean number of publications per year, ordered by decade, found on PubMed, searching for the combination [(consanguin* OR endogam*) AND (Dutch OR Netherland*)]. A total of 292 publications were found. For the most recent decade, starting in 2010, only the first three years (2010–2012) were included.

Switzerland, Austria, Italy and Germany. The Northern part of the country, and especially the province of Friesland, appeared to be more inbred than the rest of the country.

Abdellaoui et al. [4] measured autozygosity in 4,022 unrelated subjects. They used the proportion of runs of homozygosity in relation to the whole genome (F_{roh}) and found a significantly higher figure for both Protestants and Catholics compared to non-religious persons. This effect remained after excluding outliers, since these are expected in the case of consanguinity.

Family distances, defined as summary measures of geographic distances between the birthplaces of paternal and maternal ancestors, have also been used to detect signs of endogamy to be used in clinical genetics [19, 20], but they did not meet the expectations for this purpose due to a lack of sensitivity [21].

Case Reports on Consanguinity or Endogamy

As far as consanguinity is concerned, some of the measures mentioned above are more remote from the event than others. Isonymy of marriage partners, for instance, will recognize only part of the existing consanguineous unions and, if found, is still no proof of consanguinity. Given the scarcity of data on consanguinity in the Netherlands, we investigated the result of an even more remote measure: the number of published case reports of genetic disorders in patients with related parents. This was done by searching PubMed for publica-

tions mentioning endogamy or consanguinity, on the one hand, and Dutch or the Netherlands, on the other. 292 papers were found covering the period 1964–2012. There was an impressive continuous increase in their number with 1 paper every 2–3 years in the 1960s and 1970s up to almost 15 papers a year in the first years of the second decade of this century (2010–2012; fig. 2). Most of these papers are on observations of single cases or families with an autosomal recessive disorder and parental consanguinity. The increase in the number of papers is probably primarily a reflection of the progress that has been made in genetic science and methodology, and the growth of clinical and molecular genetics specialties in the Netherlands. However, while all papers in the first decades were devoted to natives, the vast majority of recent papers reported only on immigrant cases and families.

Scientific Progress as a Spin-Off of Studying Consanguineous Couples

Most of the above-mentioned papers, published since the 1980s in the Netherlands, deal with observing new mutations in new genes in patients with autosomal recessive disorders who have consanguineous parents. Homozygosity mapping and exome sequencing are among the new methods currently being used. However, classical approaches pre-dating the era of molecular diagnostics, if applied now, could reveal new insights. As far as we know, the first study to report on a compound heterozygous patient whose parents were related and lived in a genetic isolate originated from the Netherlands [22]; this same paper showed how the frequency of patients whose mutations were not identical by descent depends on the inbreeding coefficient and the total pathogenic allele frequency of the relevant gene. Subsequently, it was shown that knowledge of those parameters and knowledge of the relative frequency of the pathogenic alleles would be sufficient to calculate the proportions of homozygotes identical by descent, identical by state (but not by descent) and compound heterozygotes; and from this, the conclusion was drawn that the total pathogenic allele frequency could be inferred from the knowledge of the other parameters that may be available from molecular diagnostic centres [23]. Gialluisi et al. [24, 25] demonstrated the feasibility of this approach for familial Mediterranean fever, phenylketonuria and Wilson disease. Their homozygosity index was the same as 1 minus the frequency of compound heterozygotes.

Medical Intervention and Responsibility

It is not known precisely how many children with autosomal recessive diseases are born each year to consanguineous parents in the Netherlands, but an educated guess can be made taking the annual number of children born to Turkish or Moroccan mothers (15,000 according to the Dutch Statistical Office [3]), assuming a frequency of 25% consanguineous marriages and a risk of 1% autosomal recessive diseases in this group. This results in about 40 patients per year. We assume that these children will be presented to the appropriate medical professionals and hope that their parents will be counselled appropriately about the recurrence risk and reproductive options. There are 8 clinical genetics centres in the Netherlands with expertise in molecular genetics and counselling, which can easily accommodate this small number of cases.

However, in so far as the 1% quoted above is an accurate estimate, the number of at-risk consanguineous parents is 100 times greater, i.e. 4,000 couples annually. Ideally these couples should receive appropriate counselling in the preconception phase. We know that in recent years about 40 consanguineous couples per year have been referred for prospective counselling, mainly by primary care physicians, to clinical genetics centres (data from the annual reports of the Dutch Society of Clinical Genetics). So, the question is: who counsels the remaining 4,000 or so couples at increased risk of having an affected child? And are they ever counselled? Although primary care professionals consider it their role to inform couples about the risk of consanguinity, their beliefs about their clients' religious and social values, their attitudes toward the risk and perceived limited options for referral are hindering them in addressing the topic of consanguinity [26]. Part of the above-mentioned beliefs of primary care professionals do not match with the actual attitudes of the non-Western immigrants [27], nor with the views of Muslim theologians, spiritual counsellors, Imams and physicians [28]. One must agree with the primary care professionals, however, that the possibilities of clinical genetics to reliably predict which couple is at high risk ($\geq 25\%$) and for what diseases are still limited in these early decades of the genomic era. Translating the possibilities of genome-wide or targeted screening should be explored to improve preconception risk assessment and enable informed decision making for consanguineous couples [29–31].

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Note Added in Proof

Since submission of our manuscript the proposed ban on consanguinity was approved by the Dutch House of Representatives, and now awaits approval by the Dutch Senate.