The impact of consanguinity on the frequency of inborn errors of metabolism

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ABSTRACT

INTRODUCTION: We investigated the frequency of consanguinity among the parents to newborns with inborn errors of metabolism (IEM) diagnosed by neonatal screening.

METHODS: Data were obtained from 15 years of national newborn screening for selected IEM with autosomal recessive mode of inheritance. Among the 838,675 newborns from Denmark, The Faroe Islands and Greenland, a total of 196 newborns had an IEM of whom 155 from Denmark were included in this study. These results were crosschecked against medical records. Information on consanguinity was extracted from medical records and obtained through telephone contact with the families.

RESULTS: Among ethnic Danes, two cases of consanguinity were identified among 93 families (2.15%). Among ethnic minorities, there were 20 cases of consanguinity among a total of 33 families (60.6%). Consequently, consanguinity was 28.2 times more frequent among descendants of other geographic places of origin than Denmark. The frequency of consanguinity was high among children of Pakistani, Afghan, Turkish and Arab origin (71.4%). The overall frequency of IEM was 25.5 times higher among children of these ethnic groups than among ethnic Danish children (5.35:10,000 versus 0.21:10,000). The frequency of IEM was 30-fold and 50-fold higher among Pakistanis (6.5:10,000) and Afghans (10.6:10,000), respectively, compared with ethnic Danish children.

CONCLUSIONS: The data indicate a strong association between consanguinity and IEM. These figures may be useful to health professionals providing antenatal, paediatric and clinical genetic services.

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Inborn errors of metabolism (IEM) are a heterogeneous group of rare genetic disorders that constitute an important cause of morbidity and mortality in children and adults. The outcome of many IEM is directly related to how early correct diagnoses are made and appropriate treatment instituted. Most of the IEM are inherited in an autosomal recessive manner, and the majority of cases are due to enzymatic defects arising from aberrations in single genes. According to one study, about 80% of enzyme defects are inherited in an autosomal recessive manner [1]. Autosomal recessive IEM are characterised by their varying frequencies in different ethnic groups as a result of natural selection, genetic drift, founder effect and large-scale migration from countries where consanguinity is favoured [2]. This is apparent in a somewhat ethnically diverse country like Denmark and other Western societies, where migration from countries with a tradition for consanguineous unions has been a significant demographic feature [3], thus, having an impact on the patient profile of medical genetics clinics in recipient countries [4, 5].

To determine the genetic basis of IEM in Denmark, we conducted a national study and investigated the frequency of IEM among ethnic minorities and the ethnic Danish population to establish whether an association exists between the frequency of consanguinity and the prevalence of IEM with an autosomal recessive mode of inheritance.

METHODS

This study was retrospectively designed in the Department of Clinical Genetics, Rigshospitalet, Denmark. Based on results from the National Danish expanded neonatal screening for selected IEM that was initiated in 2002 [6], the medical records of all neonates from 2002 to April 2017 with a true positive result for an IEM were reviewed for consanguinity. In cases where the information stated in the medical records was not adequate, additional information was gathered through telephone contact with the affected children's parents.

The selection of IEM was based on criteria such as national disease frequencies; availability of effective treatment, severity of disorder; benefit of early treatment; prevention of early death; no clinical signs at birth; detectability by an easy and precise screening method – for further details see Lund et al [6].

In our study, parental consanguinity was defined according to the definition applied in clinical genetics as a union between two individuals related as second cousins or closer [7].

Figure 1 presents a flow diagram of the inclusion of cases. A total of 196 neonates were reported with an IEM. Among these, 41 referred to the department from Greenland and The Faroe Islands were excluded. These

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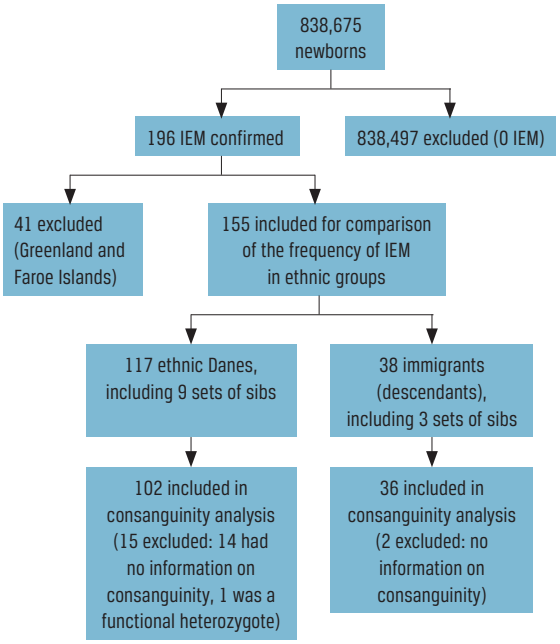
FIGURE 1

Flow diagram of steps in the analysis, 2002-2017.



IEM = inborn errors of metabolism.

are relatively small and homogenous populations, and we wanted to establish if there was any significant difference in the frequency of consanguinity between ethnic Danes and ethnic minorities with an IEM with a recessive mode of inheritance in a population of significant size and ethnic diversity. The remaining 155 patients comprised 117 ethnic Danes, including nine sets of sibs, and 38 (Turks n = 10, Pakistanis n = 7, Afghans n = 8, Arab n = 8, other n = 5), including three sets of sibs, primarily originating from Turkey, Pakistan, Afghanistan and the Middle East. Among the 155 patients, information about consanguinity could not be obtained in 16 patients, and one was a functional heterozygote (both mutations were on the same chromosome, inherited from his father). Nonetheless, the 16 patients were included in the calculation of the prevalence of disease since the diagnosis and ethnicity were known. However, among these same 16 patients, 14 in the ethnic Danish patient group and two in the ethnic minority groups were not included in the calculation of consanguinity. Knowing their IEM diagnosis, omitting these patients would have given a false impression of disease frequencies of IEM in the different ethnic groups.

When calculating the prevalence of disease and consanguinity in the ethnic groups, more than one case of the same disease in a sibship was counted as a single case.

We gathered information related to the patient's name and personal identification number, nationality/ethnicity (by maternal country of birth), diagnosis, mutation and family history – whether the neonate was born to consanguineous parents or not, and previous history of genetically affected sibs.

Demographic and statistical data on ethnic groups were gathered from the Danish Statistics Bureau, Statistics Denmark Since all the neonates in the ethnic minority groups were born in Denmark they are, according to the classification in Statistics Denmark, defined as descendants [8]. We defined ethnicity of the child by the mother's country of birth, similar to the definition used by Statistics Denmark. The statistics are based on data obtained from the Danish Central Population Register [8, 9].

We collected data on the number of inhabitants in Denmark (Danish citizenship) on 1 April 2017, number of inhabitants in Denmark defined as ethnic Danes, i.e. inhabitants with Denmark as their country of origin on 1 April 2017, and number of Pakistani, Turkish, Afghan and Arab (Arab = Jordanians, Somalis, Palestinians) descendants in Denmark with Danish and foreign citizenship on 1 April 2017.

The inclusion criteria were a confirmed diagnosis of an autosomal recessive metabolic disorder, address in Denmark and knowledge of family history (± consanguinity).

Trial registration: not relevant.

RESULTS

During the 15 years succeeding the introduction of the National Danish expanded neonatal screening for selected IEM, 838,675 children were born in Denmark, Greenland and The Faroe Islands. By April 2017, IEM with autosomal recessive mode of inheritance affecting the major biochemical areas of amino acid, organic acid and carbohydrate metabolism had been diagnosed in 196 children born during this period. **Table 1** shows the cases of IEM detected in ethnic Danes and ethnic minorities. All the patients are included, including cases among sibs.

In the ethnic Danish population (Table 1), nine cases of disease were found among sibs. Additionally, one patient was a true screen positive for an autosomal recessive metabolic disorder (holocarboxylase synthetase deficiency), but further examination by use of molecular genetic analysis showed that the patient was functionally a heterozygote, i.e. both mutations were on the same chromosome inherited from his father. These ten cases were excluded. The remaining 107 patients represented 107 families with autosomal recessive disease.

Among ethnic minorities (Table 1), there were three cases of disease among sibs, which were ex-

cluded. The remaining 35 patients represented 35 families with autosomal recessive disease.

Table 1 shows that medium-chain acyl-CoA dehydrogenase deficiency (MCADD) was the most frequently found IEM among ethnic Danes and ethnic minorities alike. Among Danes, 58% had MCADD; among ethnic minorities, the frequency was 36.8%.

Table 2 shows the frequency of consanguinity in the different ethnic groups. Of the 33 sets of parents from ethnic minorities, about whom information about consanguinity was available, 20 were consanguineous, i.e. 60.6%. Among Danes, two cases of consanguinity were found among 93 families, i.e. 2.15%. Thus, the frequency of consanguinity was 28.2 times more frequent among ethnic minorities than among ethnic Danes. The frequency of consanguinity was conspicuously high among children of Pakistani, Afghan, Turkish and Arab origin (71.4%).

Table 3 shows the prevalence of IEM in the different ethnic groups. More than one case of disease among sibs was counted as a single case. In addition to a high frequency of consanguinity, the prevalence of disease was also significantly higher in ethnic minorities than in ethnic Danes. The frequency of IEM among Danes and ethnic minorities compared with the overall number of Danes and descendants of the above-mentioned ethnic groups was 0.21/10,000 and 5.35/10,000, respectively. As a result, the frequency of autosomal recessive metabolic disorders was 25.5 times higher among children of Pakistani, Turkish, Afghan and Arab origin than among ethnic Danes.

DISCUSSION

This is the largest report of IEM in the offspring of consanguineous unions in Denmark. Although the nationwide neonatal screening for IEM is limited to selected disorders, it is important to remember that IEM are a heterogeneous group of rare genetic disorders and that the total number of patients in the study diagnosed with an IEM is relatively high.

The high frequency of MCADD is, especially for the Danish group (58.0%), not a striking observation given that MCADD is the most prevalent non-phenylketonuria congenital metabolic disorder in Western countries [11]. Moreover, increased frequencies of mutations have been found following the implementation of neonatal screening [6].

Compared to the ethnic Danish population, the prevalence of autosomal recessive IEM is conspicuously high among ethnic minorities in the study (Table 3). The findings show a highly significant association between consanguinity and IEM. This association with consanguinity is predictable since all cases of IEM in the study have an autosomal recessive mode of inheritance, and migrants from countries where consanguinity is common tend to preserve traditional patterns of marriage [12, 13]. In the present study, consanguineous unions were found to be more frequent among

TABLE 1

Diseases among ethnic Danes (n = 117) and ethnic minorities (n = 38) born between January 2002 and April 2017.

	Groups, n (%)		
Diagnosis	Danish[a]	ethnic minority[b]	OMIM
Argininosuccinic acidaemia	4 (3.4)	0	#207900
Biotinidase deficiency	13 (11)	7 (18.4)	#253260
Carnitine palmitoyltransferase IA deficiency	0	1 (2.6)	#600528
Carnitine transporter deficiency	3 (2.6)	1 (2.6)	#212140
Citrullinaemia	0	1 (2.6)	#215700
Galactosaemia	1 (0.85)	0	#230400
Glutaric acidaemia type 1	7 (5.9)	3 (7.9)	#231670
3-hydroxy-3-methylglutaryl-CoA synthase deficiency	0	1 (2.6)	#605911
Holocarboxylase synthetase deficiency[c]	2 (1.7)	0	#253270
Isobutyryl-CoA dehydrogenase deficiency	1 (0.85)	0	#611283
Isovaleric acidaemia	1 (0.85)	0	#243500
Long-chain hydroxyacyl-CoA dehydrogenase deficiency	3 (2.6)	2 (5.3)	#609016
Medium-chain acyl-CoA dehydrogenase deficiency	68 (58)	14 (36.8)	#201450
3-methylcrotonyl-CoA carboxylase deficiency	6 (5.1)	1 (2.6)	#210200
3-methylglutaconyl-CoA hydratase deficiency	0	1 (2.6)	#250950
Methylmalonic acidaemia	2 (1.7)	3 (7.9)	#251000
Propionic acidaemia	2 (1.7)	0	#606054
Tyrosinaemia type 1	1 (0.85)	1 (2.6)	#276700
Very long-chain acyl-CoA dehydrogenase deficiency	3 (2.6)	2 (5.3)	#201475
Total	117 (99.7)	38 (99.8)	

3-MCC = 3-methylcrotonyl-CoA carboxylase; MCADD = medium-chain acyl-CoA dehydrogenase deficiency; OMIM = Online Mendelian Inheritance in Man.
a) 9 cases of IEM among sibs in the Danish group: 8 MCADD + 1 3-MCC deficiency.
b) 3 cases of IEM among sibs in the ethnic minority group: 2 MCADD + 1 glutaric acidaemia, type 1.
c) 1 case in the Danish group was functionally a heterozygote.

TABLE 2

Consanguinity among ethnic minorities.

Ethnic group[a]	N	Excluded, n[b]	Couple, n[c]	Consanguineous married, n (%)[d]
Pakistani	7	1	6	6 (100.0)
Arab	8	1	7	2 (28.6)
Turkish	10	0	10	9 (90.0)
Afghan[e]	8	0	5	3 (60.0)
Subtotal	33	2	28	20 (71.4)
Other[f]	5	0	5	0
Total	38	2	33	20 (60.6)

a) By maternal country of birth.
b) Patients with no available information about consanguinity.
c) Sets of parents/marriages.
d) % of couples.
e) 3 sets of sibs.
f) Iceland, Great Britain, Bosnia-Herzegovina, Lithuania, Switzerland.

TABLE 3

Prevalence of inborn errors of metabolism by ethnic group. Only patients with an autosomal recessive disease are included, regardless of whether the degree of relationship between the parents is unknown. More than one case of disease in a sibship is counted as a single case. Patients with no autosomal recessive disease and sibs are excluded.

Ethnic group[a]	n	People in Denmark, n[b]	Illness per 10,000, n
Pakistani	7	10,775	6.5
Arab	8	10,446	7.65
Turkish	10	30,101	3.32
Afghan	5	4,695	10.64
Subtotal	30	56,017	5.35
Other[c]	5	10,241	4.88
Danish	107	5,007,197	0.21
Total	142	5,073,455	0.28

a) Based on information from the medical records about country of origin (mothers country of birth) and, if necessary, telephone conversations with the parents of the affected children. The patients' citizenship is unknown, so there can be a discrepancy in the information in this paper and the figures provided by Statistics Denmark.
b) Source: [10].
c) Iceland, Great Britain, Bosnia-Herzegovina, Lithuania and Switzerland.

people from Pakistan, Turkey and Afghanistan. These are countries where consanguineous unions are common [3]. The high proportion of Pakistani, Turkish, Afghan and Arab patients might be the result of the high rate of parental consanguinity. Although control for medical and sociodemographic variables, e.g. maternal age, Body Mass Index, occupation, education, smoking, alcohol consumption, nutrition, parity and medical problems during pregnancy could have been instructive, it is highly unlikely that most of these variables would increase the frequency of a disease with an autosomal recessive mode of inheritance [7, 14].

Some well-investigated studies on risk factors for congenital anomalies that also controlled for non-genetic variables have demonstrated a highly significant association between consanguinity and congenital anomalies. These studies had contemporary control groups and were of sufficient size to achieve significance in comparisons between the offspring of consanguineous and those of non-consanguineous unions. In a Norwegian study [15], the proportion of congenital anomalies in children of Pakistani origin born to first cousins that could be attributed to consanguinity was 28%, which is similar to what was reported from a UK study (31%) [16]. The Norwegian and the UK study reported an adjusted relative risk for congenital anomaly of 2.15 and 2.19, respectively, for children of Pakistani origin who were the product of a first-cousin union. The Danish Pakistani community merits particular attention. Many studies have identified consanguinity as a causal factor for the elevated rates of congenital anomalies among some ethnic minorities, particularly the Pakistani community. Specifically for IEM, another prospective study on births in Birmingham during the 1980s concluded that if the tradition of consanguineous marriage was abandoned by the Pakistani community, a 60% reduction in deaths and severe morbidity would be achieved [17]. An associated study reported that the overall prevalence of IEM in UK Pakistani children was ten-fold higher than in children of European heritage, among whom parental consanguinity was estimated to be 0.2% [2]. Comparing countries separately, our findings show that children of Pakistani origin had the second highest prevalence of IEM, and the highest proportion of consanguinity. Consequently, consanguinity was 46.5 times more frequent among Pakistani descendants than among ethnic Danes (2.15%). The prevalence of IEM among Pakistani descendants was 6.5/10,000 (Table 3). As a result, the frequency of autosomal recessive metabolic disorders was 31 times higher among children of Pakistani origin than among ethnic Danes (0.21/10,000). The relatively high number of diagnosed cases (n = 41) referred from Greenland and The Faroe Islands is most likely explained by a founder effect and genetic drift [18]. In a previous study by the authors (AL, FS), it was observed that carnitine transporter deficiency and holocarboxylase synthetase deficiency were relatively frequent among patients referred from The Faroe Islands to our department for diagnosis and treatment [19].

CONCLUSIONS

The study is the largest report relating to data for IEM in the offspring of consanguineous unions in Denmark. Our findings confirm that the offspring of consanguineous unions have an increased risk of IEM. Couples contemplating such unions should be advised of these risks; however, advice should be given with sociological awareness. Ethnic groups may have different perceptions of genetic disease and risk factors. This can have an impact on their preferences toward genetic counselling and treatment [20]. Linguistic barriers may also limit comprehension of genetic issues. A study found increased attendance of Pakistanis at a medical genetic clinic if a Pakistani doctor was also present, possibly due to an enhanced understanding of language and culture [21].

Demographic changes have significantly impacted the patient profile of clinical genetic services in many countries [4, 5]. As a result, knowledge about the health outcomes of consanguinity is pertinent for healthcare professionals providing clinical genetic services and for primary care takers who assist consanguineous couples in making informed decisions about family planning. Perhaps even education programmes

at the secondary school level and leaflets in relevant languages on recessive diseases and consanguinity might prove beneficial. The results of this study will hopefully increase the knowledge of and inform health personnel who work with communities at increased risk.

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