Addressing reproductive risk in consanguineous couples

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CHAPTER 1

General introduction

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A consanguineous marriage is usually defined as a marriage between people who are second cousins (fifth-degree relatives) or closer related family members (Bittles, 1994). Worldwide, it is a frequent phenomenon: consanguineous couples and their offspring account for more than 10% of the world's population (Bittles and Black, 2010a). In Western society it has been an uncommon tradition and sometimes subject to taboo, and, if present, mostly found in small communities. In the last decades, however, the prevalence of consanguinity in Western countries has increased with the migration of ethnic groups practicing consanguinity (Bittles and Black, 2010a; Modell and Darr, 2002). Cousin couples are at increased risk of having a child with a hereditary/ congenital disorder. This extra risk is caused by the fact that the child can inherit the same mutated allele from both parents that originates from a common ancestor. First cousin couples are said to have 1.7-2.8% extra risk on top of the background risk that every couple has of having a child with a hereditary/congenital disorder (Hamamy et al., 2011; Bennett et al., 2002). This extra risk entails mostly autosomal recessive (AR) disorders: disorders that only come to light when a child has inherited two mutated copies of the same gene from its parents. When both parents are carriers (i.e. only have one mutated copy) their chance for each of their children to inherit both mutated copies is 25%. It is, however, an average risk figure. In fact, only a minority of consanguineous couples has an increased risk of 25% of having an affected child, while the great majority of couples has a risk that is similar to that of the general population. Moreover, if a consanguineous couple has an affected child, this is not always caused by the consanguinity of the parents.

Most consanguineous couples are unaware of their carrier status and the birth of a child with an AR disorder is therefore usually unexpected. Moreover, many consanguineous parents are not familiar with the fact that their relatedness increases their chance of having an affected child. On the one hand, awareness is low among the couples themselves, and, at the same time, health care falls short of providing adequate information and care. In Western countries, like the Netherlands, a complicating factor is the fact that often consanguineous couples belong to ethnic groups that are known to have less access to health care (Stronks et al., 2001). Moreover, consanguinity has been a topic of political debate (Asscher, 2010), contributing to the sensitivity of the matter. It has been argued that every consanguineous couple should be informed about their increased risk, preferably before pregnancy (Bennett et al., 2002; Waelput and Achterberg, 2007). This period is also referred to as the preconception phase. When aiming to improve risk assessment and thereby increasing reproductive choice for individual consanguineous couples, three perspectives have to be considered. From the clinical genetic and population genetic perspective the risk associated with consanguinity can be approached by improving the risk calculation by means of genomic tools and looking at the feasibility of such a new approach. Equally important is the acceptance *and* perceived need of an offer of a (preconception) risk assessment and information by the target population. Finally, the perspective of primary health care

providers who see consanguineous couples in their practices is of importance as they play an important role in conveying information and discussing the possibility of referral for genetic counseling

CONSANGUINITY: PREVALENCE, PREJUDICES AND POLITICS

Consanguineous marriage is an integral part of social and cultural life in many societies in which the choice of a spouse from outside the family is perceived as a risky and disruptive option (Bittles, 2001; Modell and Darr, 2002). By far the highest concentration of consanguineous couples is found in North Africa, the Middle East and certain other parts of Asia, where up to 50% of all marriages or more may be consanguineous (see Figure 1). In contrast, most of the marriages in North-America, Europe and Australia (>99%) are not consanguineous. In these Western countries, however, there are certain groups that show higher rates of consanguineous marriage. Frequently, this can be explained by migration from regions where consanguineous marriage is common. The Netherlands, like many other Western countries, originally has had a relatively low percentage of consanguineous marriage, although several small communities can be identified where endogamy is a common tradition (Ten Kate et al., 2014). Endogamy is the tradition of marriage within the community or (social) group. This can lead to couples having a higher proportion of DNA identical-by-descent (IBD) than would be expected because of their family relationship, with similar consequences as consanguineous marriages.

From the 1950s onwards, immigrants from countries with a higher rate of consanguineous marriages, like Morocco and Turkey, have settled in the Netherlands. The number of consanguineous couples in the Netherlands is based on estimations. A cohort study of 10,000 newborns in one of the major Dutch cities in which a large percentage of the newborns were included between 2002 and 2006, has shown that 22.2% of Moroccan, 23.9% of Turkish and 0.1% of the Dutch mothers reported that they were married to a second cousin or closer related spouse (Waelput and Achterberg, 2007). A comparable survey was done in Belgium, which showed that 28% of Moroccan marriages and 22% of Turkish marriages were consanguineous (Reniers, 2010).

In Western society this type of marriage is often considered undesirable, in particular since the 19th century when concerns were raised about the harmful effects on the offspring of such marriages (Bittles, 2009). Despite the relatively low increase in risk, prejudices and misunderstandings remain common (Bittles and Black, 2010b) and a consanguineous marriage is often viewed as causing physical and mental incapacity (Modell and Darr, 2002). It has been reported that the general public and many healthcare professionals have an exaggerated view of the genetic disadvantages of consanguineous marriage (Qureshi, 1997).

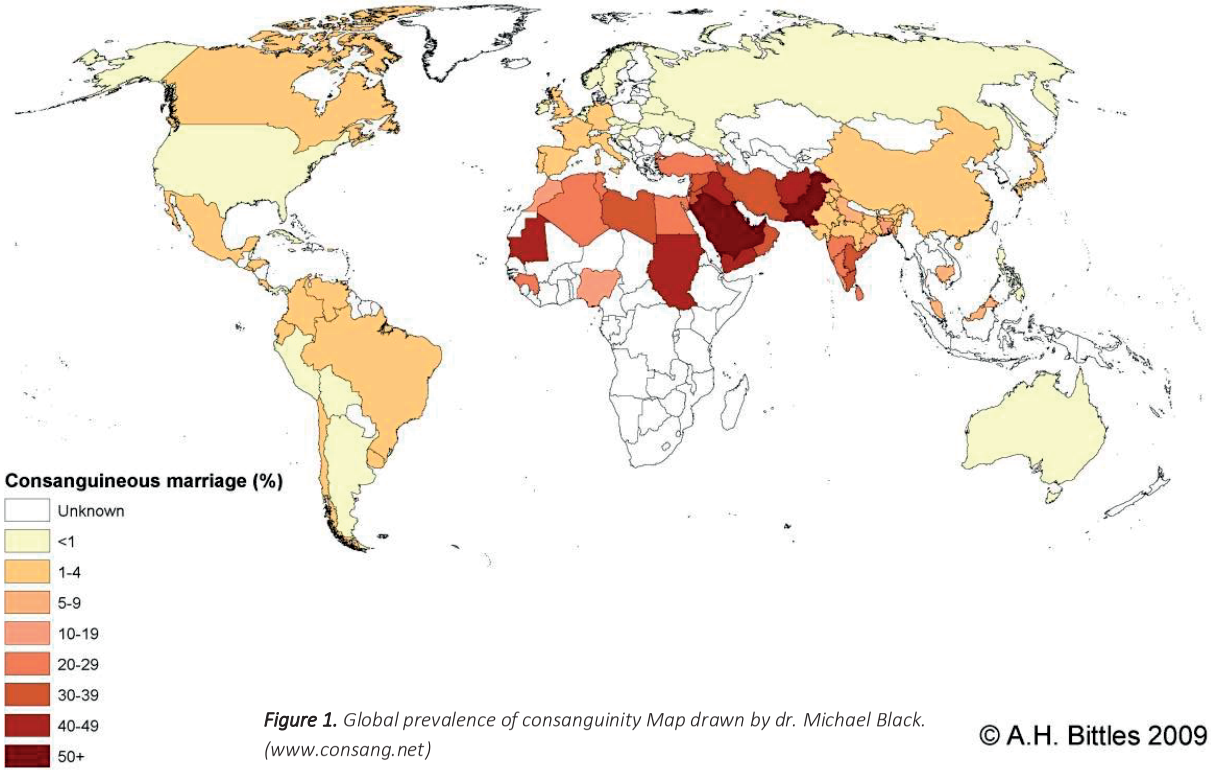

Figure 1. *Global prevalence of consanguinity Map drawn by dr. Michael Black. (www.consang.net)*

A common misunderstanding among the Dutch population is that first cousin marriages (3rd degree relatives) were forbidden in the past in the Netherlands (Asscher, 2010). However, the law that was enacted in 1838, and withdrawn in 1970, applied to uncle-niece marriages (2nd degree relatives) and to marriages between a brother and sister in law without genetic relation (Article 88 of the Old Netherlands Civil Code).

When looking at the last decade alone, cousin marriage has been discussed in public debates on several occasions. In 2001 and 2002, for example, the debate flared up, as research showed that the perinatal mortality rate in the Netherlands was high in comparison with surrounding countries (Schulpen, 2002). One of the risk factors that was held accountable was the high consanguinity rate among migrant couples in the Netherlands (Schulpen et al., 2001). The emphasized relationship between parental consanguinity, congenital disorders and the Moroccan and Turkish migrant population led to public discussions and to questions from politicians about the desirability of a ban on cousin marriage.

Until 2010 the government took a position in which it let values like autonomy and non-directiveness prevail. However, the former and current Dutch government coalition both expressed plans to prohibit cousin marriage. The ban on cousin marriages was ranked among measures intended to limit immigration, which included a prohibition of forced marriage. No mention was made of the increased medical risks at this point. The new element in the discussion on banning cousin marriages, namely the alleged connection with forced marriages, has caused a blurring of the debate. Now, there seem to be two arguments that are used interchangeably: the increase in risk for the offspring and the alleged high proportion of forced marriages among cousin marriages. The two arguments are not supported by evidence that a ban on cousin marriage would be proportional and effective in resolving the raised issues, but nevertheless they contribute to increasing the sensitivity of the subject. The political and societal climate, however, will undoubtedly be of influence in the setting in which the care for consanguineous couples is/ought to be organized.

A CLINICAL AND POPULATION GENETIC PERSPECTIVE: RISK ASSESSMENT IN CASE OF CONSANGUINITY

Over 1000 different AR diseases are known at present, but new ones are being identified continuously (Bell et al., 2011). Most of these are rare, if not very rare, but their total is still substantial, causing serious morbidity and mortality in at least 25/10,000 children (UNSCEAR, 2001). Most genes show variation in the population, these different variations are called alleles: in addition to the most frequent normal allele in the gene, one or more pathogenic alleles are found. In clinical genetics the frequency of the pathogenic allele(s) is often referred to as ‘allele frequency’ or even

'gene frequency'. An important parameter in the context of risk calculation is the so-called total pathogenic allele frequency: the sum of all pathogenic alleles in a gene.

If one knows the frequency of different mutations in a population, it is possible to infer total pathogenic allele frequency of that population (also referred to as *q)* or how many people are carriers for the disorder (2*pq*). The frequency of affected individuals is referred to as q^2. These frequencies are population-specific and can be used for calculating risk for individuals in a population.

When a child with an AR disorder is born, it is clear that there must be several carriers in the family: both parents[1], at least two grandparents, and perhaps some aunts and uncles, siblings, etc. To be able to calculate the risk for the offspring of a consanguineous couples of having an AR disorder it is important to know if the disorder has occurred in the family before. The grey boxes contain a further disquisition of the risk involved in couples with both a positive (A) and negative family history (B).

Box A. Disorders already present in the family

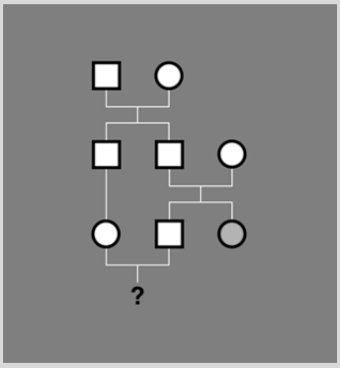

Figure 2. *First cousins with a positive family history*

Suppose a healthy man who has a sister with cystic fibrosis (CF), a severe autosomal recessive disorder causing recurrent lung infections and gastrointestinal problems, marries the daughter of his father's brother (Figure 2) (a first cousin marriage with a positive family history). What are the chances for a child of this couple to be affected with CF? To answer this question the chances have to be calculated that the future father and his cousin, the future mother, are carriers. Two thirds of the healthy siblings of a patient with an autosomal recessive disease are carriers. So the chance that the future father is a carrier is 2/3. For his cousin the possible track of the mutated allele has to be followed through the pedigree. It can be assumed that the father of the future father is a carrier: he has a daughter with CF. It can also be assumed that one of the parents of this father is a carrier. The chance that the brother of his father (the uncle of the future father) has the same mutated gene is therefore 1/2. When this brother of his father is a carrier indeed, there is a 1 in 2 chance that he passes the mutated gene on to his daughter, the future mother. So her chance of being a carrier is 1/2 (her father is a carrier) x 1/2 (she inherits the mutated gene if present in her father), or 1/4. So the chances that the future father and his cousin are both carriers is 2/3 x 1/4, or 1/6, and the chance that a child of them will be affected by CF is 1/4 x 1/6, i.e. 1/24.

How does this compare to a marriage with an unrelated partner? If the future father of the previous example would have married an unrelated partner, the best estimate of the future mother to be a carrier is the carrier frequency in the population. For the population in this example this is 1/30, i.e. 7.5 times less than in a first cousin. So chances of CF in a child of the brother of the CF patient are 7.5 times higher if he marries a first cousin, than when he chooses an unrelated bride: 1/24 compared to 1/180.

[1] There are exceptions to this rule: if the disorder is less severe and does not interfere with reproduction one or even both parents may have two mutated copies of the relevant gene, and are thus affected too. Families with autosomal recessive deafness provide many examples of this situation. Another, but very rare exception to the rule is when only one of the parents of a child with an autosomal recessive disease is a carrier, while the other is not a carrier. Apart from non-paternity and new mutations, this situation may occur when both copies of the relevant gene in the patient derive from the carrier parent with no contribution from the other parent. This phenomenon is known as uniparental disomy.

Fortunately, carrier testing is now available for a large number of recessive diseases, and if both partners turn out to be carriers, reproductive options can be discussed.

In the first situation described above (brother of CF patient marrying his first cousin) the possibility was ignored that the mother of the first cousin could be a carrier of CF. This simplification is justified because the risk resulting from taking this possibility into account is very small compared to the risk based on the consanguineous relationship between the man and his first cousin. Therefore the risks that were calculated (1/24) apply to every other rare autosomal recessive disorder as well.

In the other situation described above (brother of patient marrying an unrelated partner) the carrier frequency cannot be ignored. If the carrier frequency would be, say 1/300, the risk that the child will have the same recessive disease as the sister of the man, becomes 1/1800. So here the risk from a consanguineous marriage is 75 times higher than when a sibling of a patient has an unrelated spouse.

Box B. Disorders not (already) present in the family

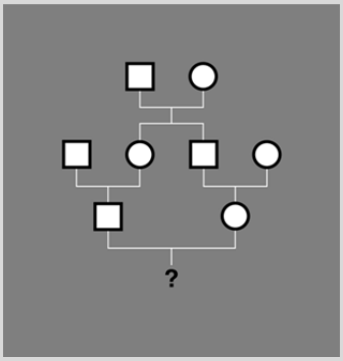

Figure 3. *First cousins with a negative family history*

The risk of CF in a child if the condition is not known to have occurred in the family is 1 in 3600 in case of unrelated parents. When partners are related the risk is higher; the more so if they are closer related.

Figure 3 shows a related couple with their parents, grandparents and expected child. The main difference with an unrelated couple is the probability that a particular copy of the CFTR gene of one of the grandparents is transmitted to the expected child through both its father and its mother. So then this grandparental copy of the gene 'meets itself' in the child. It is said to be identical-by-descent (IBD). The probability that a gene is identical-by-descent in a child of consanguineous parents can be calculated by multiplying the probability of transmission of a particular copy of a gene from one generation to the other through both parents with the total number of copies of this gene in each of the closest common ancestors. This probability is called the inbreeding coefficient, and is dependent on the type of relatedness of the parents of the expected child. Figure 4 shows the pedigrees and the associated inbreeding coefficients for a number of situations.

Being IBD in itself does not make a gene variant harmful, but when the gene contains a pathogenic mutation the child having two mutated copies will be affected. If, following common practice, the population frequency of the total pathogenic allele frequency of a gene is called *q,* and the inbreeding coefficient is called *F,* then the probability of a recessive disease on the basis of identity-by-descent of the gene will be *F* x *q*, or *Fq* for short.

However, this is not the only way in which this child can have two mutated copies. This is also possible when there is no identity-by-descent, but when mutated copies are coming from two different ancestors of which at least one has obtained the mutation from a parent outside the family. The probability of this event (in which two alleles are not identical-by-descent) is the complement of the probability of identity-by-descent, and therefore can be written as *1-F*. In this case a recessive disorder can occur only if by chance both copies of the gene are mutated, the frequency of which is *q x q*. The total chance can now be calculated that the expected child will have a specific autosomal recessive disorder if the disorder is not known to occur in the family. This chance is the sum of both probabilities of having two mutated copies of the gene, one based on identity-by-descent and the other in the absence of identity-by-descent: $Fq+ (1-F) q^2$. In fact, this equation also holds when there is no consanguinity: In that case, *F* equals zero and the equation reduces to q^2.

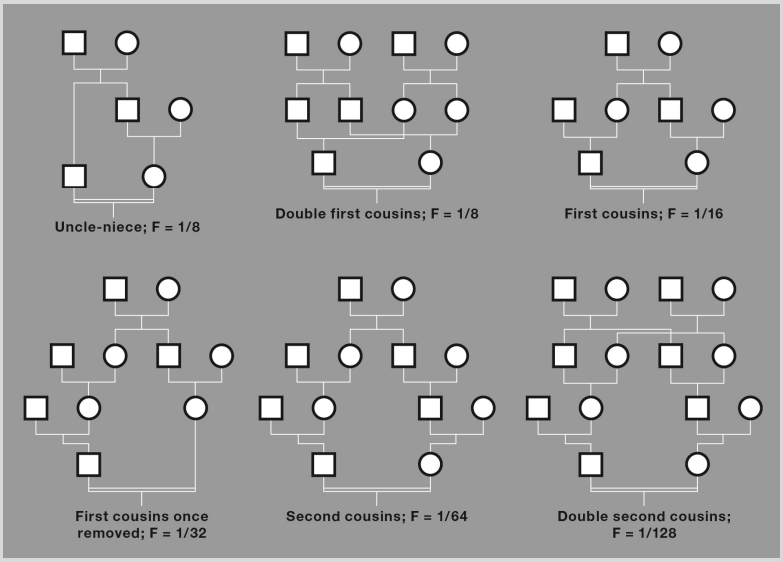

Figure 4. *Different types of consanguineous marriages and the associated inbreeding coefficients*

Table 1 lists probabilities for first- and second cousins by a number of different gene frequencies. The increase in risk and the fraction attributable to consanguinity are higher as the disorder is rarer and as the degree of consanguinity increases. As shown in this table, the fraction not attributable to the existing consanguinity is larger than the fraction due to consanguinity for offspring of second cousins when the gene frequency is 1/60 or higher. Consequently, when observing an AR disorder in a child of consanguineous parents, one should not jump to the conclusion that this is the result of the consanguinity (Ten Kate et al, 1991). It is possible to refine this more if it is known which mutations are involved. When two different mutations are found, it is clear that the parental consanguinity cannot be blamed for the disease in the child. Two different mutations in the same gene is called compound heterozygosity. If the patient has two similar mutations (homozygosity) the two may be IBD, or just identical-by-state, but not by descent.

When discussing the total risk of AR disease in children of consanguineous parents, one should realize that the presence of mutations in different genes can be regarded as independent events. As there is no knowledge of all gene frequencies for all AR disorders, empirical data are needed that are available on both the total risk of congenital and/or genetic diseases in children of unrelated parents, and the additional risk in children of consanguineous parents.

Table 1. Comparison of expected frequencies of some selected autosomal recessive diseases in the general population and in offspring of first- and second cousins, with fractions attributable to the consanguinity of the parents

Disorder	General population		Offspring of first cousins				Offspring of second cousins			
	Gene frequency	Disease frequency	Disease frequency	Increase in risk	Fraction due to consanguinity	Fraction not due to consanguinity	Disease frequency	Increase in risk	Fraction due to consanguinity	Fraction not due to consanguinity
Cystic fibrosis	1/60	1/3600	1/768	5x	80%	20%	1/1873	2x	49%	51%
PKU	1/126	1/16000	1/1796	9x	89%	11%	1/5404	3x	66%	34%
Pompe disease	1/187	1/35000	1/2770	13x	93%	7%	1/8957	4x	75%	25%

The table is meant to illustrate the importance of gene frequency and degree of consanguinity for disease frequency, increase in risk, and fractions due or not due to consanguinity. As gene frequencies differ by population, the precise figures of disease frequency, risk increase, and fractions due or not due to consanguinity will also differ by population.

In this thesis it is assumed that the background population risk is approximately 2-3% for medically relevant congenital anomalies and 0.25% for serious AR diseases, excluding hemochromatosis, a rather frequent late onset and relatively easily treatable condition (UNSCEAR, 2001). The prevalence of congenital anomalies in offspring of first cousins is estimated to be about 1.7-2.8 percentage points higher than the background population risk and is mostly attributable to AR diseases (Hamamy et al, 2011). Recently a study in the UK has shown that among British Pakistani mothers that were in a first cousin relationship the risk of having an affected child by a congenital disorder was doubled (multivariate risk ratio [RR] 2.19, 95% CI 1.67-2.85), which is more or less similar to the above quoted known risk figures. The study found an increased prevalence of especially cardiac and neurological anomalies in the offspring of first cousins, like microcephaly, atrial septal defects, ventricular septal defects, and patent ductus arteriosus (Sheridan et al., 2013). This study did not account for the subdivision of the Pakistani community resulting from marriage patterns along male lineages (biraderi patterns) that will lead to a higher amount of DNA identical-by-descent compared to the reported relationship and therefore will increase the prevalence of AR disorder in offspring (Makrythanasis et al., 2014).

The extra risk for first cousins is about two times the background risk for congenital anomalies, and about ten times the background risk for AR diseases. Adding the extra risk of 1.7-2.8% to the population background risk of 0.25% for AR disorders results in an overall risk of, say, 2-3% AR disorders in children of first cousins. For second cousins this risk can be translated into an extra risk of 0.4-0.7% in offspring (four times less than first cousins, as F=1/64 is also 4 times less) and of 3.4-5.6% in offspring of an uncle-niece relation two times higher since F is here 1/8). When a pedigree has several consanguineous loops the inbreeding coefficient will be much higher than in the case of a simple pedigree with only one loop. Additional loops may not always be evident or

known to the consanguineous couple, for instance when they have occurred in earlier generations making the couple more related than assumed at first view.

The fact that 1.7-2.8% of first-cousin couples will have a child with an AR disorder because of their consanguinity, combined with the mode of inheritance of this disorder (carrier couple will have an affected child in 25% of cases), leads to the conclusion that not all couples are carriers. It is currently not possible though to differentiate between these high- and low risk couples.

As already explained, the risk of being a carrier couple depends on the degree of relatedness of the parents. At the same time, the quantity of DNA identical-by-descent between couples with the same degree of relatedness shows a remarkable variation. This is due to hidden ancestral loops and stochastic variation during meiosis (Teeuw et al., 2010).

In summary, the risk for consanguineous couples to have affected offspring is the sum of three different risks:

a. The baseline risk for all parents-to-be getting affected offspring
b. The risk caused by disorders already present in the family
c. The extra risk due to their consanguineous relationship for disorders not already present in the family

The above shows that risk assessment is complex, and the additional average risk, for example, of 1.7-2.8% for first cousins, does not represent an individual couple's risk. Since it is not possible to distinguish between low (population background risk) and high risk (25%, or more in case of positive carrier status for more than one AR disorder), a first-cousin couple without family history will be given an additional risk of 1.7-2.8% because of their consanguinity.

The field of genetics is developing rapidly and new discoveries are reported almost every other day. Especially in the case of consanguinity, by focusing on the common strands of DNA, it is increasingly possible to identify the causative gene for a disorder in a child, by making use of next generation sequencing techniques. These new techniques should allow a better preconception risk assessment for consanguineous couples (Bell et al., 2011; Makrythanasis et al., 2014; Sheridan et al., 2013).

THE PERSPECTIVE OF THE TARGET POPULATION

To what extent the public is aware of the risk associated with consanguinity was investigated by several studies among populations with a high prevalence of consanguinity (Jaber et al., 2005; Kisioglu et al., 2010; Sandridge et al., 2010; Sedehi et al., 2012). These studies showed that the social advantages of marrying kin were found to be widely acknowledged and awareness about the link between consanguinity and

risk of affected offspring was not always present or was disregarded. Moreover, if people have heard about the medical risk, they are not always convinced that this information is accurate (Shaw and Hurst, 2008). Issues surrounding consanguinity and reproductive options are also the focus of debates by Islamic scholars. Sunni and Shiite scholars have different opinions; nevertheless some Islamic scholars accept and promote new reproductive technology (Serour, 2008; Inhorn, 2006).

There is little research available on the attitudes and understanding among consanguineous couples from ethnic groups in Western society. Studies in the UK among British Pakistanis showed that misconceptions regarding genetics are present. Moreover, the British Pakistani participants also showed skepticism about the claimed link between consanguinity and risk (Shaw and Hurst, 2008; Darr et al., 2013). It has also been shown that, after receiving genetic counselling because of an increased chance of being a carrier for an AR disorder, many people felt that genetic information was private and potentially stigmatizing. This made them reluctant to share this information with relatives or sometimes even their own partner (Shaw and Hurst, 2009).

At the same time, in some countries with a high frequency of cousin marriage, such as Jordan, Iran, Iraq, Saudi Arabia and Turkey, premarital counseling - including carrier testing for frequent AR disorders - is available, and in a few countries this is even mandatory (Hamamy, 2012). It is said that, as a result of these counseling programs, awareness about genetics and the risk associated with consanguinity in particular is increasing in these countries, resulting in an growing number of couples seeking preconception advice (Hamamy, 2012). In Western countries, the general public, including ethnic minorities, seems receptive to the idea of (preconception) carrier testing (Lakeman et al., 2009; Darr et al., 2013). In a Dutch study among Turkish women it was found that they were rather positive towards the possibility of preconception carrier testing for hemoglobinopathies (Van Elderen et al., 2010).

How the target population in the Netherlands where consanguinity is a frequent phenomenon perceive consanguinity and the associated risk for offspring, and whether they would welcome information concerning this risk is not well known.

THE PERSPECTIVE OF PRIMARY HEALTH CARE PROVIDERS

Current preconception counselling practices for consanguineous couples focus on taking a thorough medical and family history and informing couples about their increased risk. Carrier screening is not advised based on consanguinity alone (Bennett et al., 2002; Modell and Darr, 2002). If the couple has a positive family history for a genetic disorder with a known mode of heritance the percentage of additional risk for offspring can be predicted for this specific disorder and, if available, genetic testing and reproductive options can be offered to the couple. The absence of a family history of a genetic condition, however, still leaves the couple with an average increased risk of 1.7-

2.8% of having affected offspring. In these cases genetic screening of parents-to-be for carrier status of frequent disorders in a population might be considered.

Because of the rapid developments in genetic technology it is conceivable that in the near future new diagnostic facilities will be available which will improve preconception risk assessment (Bell et al., 2011; Teeuw et al., 2010). Consanguineous couples are likely to benefit from these new technologies.

Although there seems to be consensus about the need for providing risk information to consanguineous couples, a comprehensive national infrastructure for this special target group is lacking in the Netherlands. The number of referrals to clinical genetic centres for consanguinity counselling at this moment is relatively low, and there is ambiguity regarding the criteria for referral. In 2006, 50 couples nationwide were referred on the basis of their consanguinity alone. In that year there were over 22,000 referrals to a clinical genetic centre in total (Personal communication, Vereniging Klinische Genetica Nederland). Although consanguinity is indicated as a legitimate reason for referral and therefore genetic health care is also reimbursed (less the policy deductible) by the health care insurance, no consensus exists between the individual genetics centres in the Netherlands as to what is best practice in preconception counselling for consanguineous couples. Some of the eight clinical genetics centres in the cities with a high prevalence of migrant populations in the Netherlands offer extensive genetic counselling with a focus on medical family history, pedigree analysis and estimation of the inbreeding coefficient. In addition, ancestry-based carrier testing is sometimes offered. Others only briefly address a possible positive family history by telephone consultation and, in the absence of any genetic family history, quote the average risk figure (Personal information F. Petrij, clinical geneticist). The lack of consensus among clinical genetic centers may be of influence on the number of referrals.

Primary care is commonly perceived as a place for accessible continuous care, with a focus on informing the patient, preventive medicine, and if necessary, referring for secondary or tertiary care (Rawaf et al., 2008). This setting seems the most appropriate place for the offer of preconception care. In the Netherlands, primary care for pregnant women or women who wish to become pregnant is offered by two types of professionals in primary care: the midwife and the general practitioner. Earlier advice by the Health Council of the Netherlands and the Steering Committee Pregnancy and Birth (Anon 2007; Stuurgroep Zwangerschap en Geboorte 2009) to organize and fund a national program for preconception care has not been taken over by the government. Therefore, some health professionals consider it their responsibility to take up this task themselves. Both the general practitioner and the midwife can address the risks associated with consanguinity during a consultation and map the medical (genetic) family history.

Existing recommendations for professionals in Dutch primary care are not uniform in the way they approach parental consanguinity. In an opinion paper of the Royal Dutch

Organization of Midwives the professionals are advised to note any consanguinity and genetic family history of a couple in the preconception or prenatal phase (De Jong, 2005). The paper informs midwives about the possibility of carrier screening and referral to a clinical geneticist. In 2011 a guideline was published by the Dutch College of General Practitioners about preconception care, where the focus is on referral for genetic testing in case of a positive family history (De Jong-Potjer et al., 2011). Special attention is given to carrier testing of hemoglobinopathies. However, no special policy on how general practitioners can address consanguinity in their practice is formulated.

The lack of guidelines and information about how to address (the risks of) parental consanguinity leads to a situation where it greatly depends on the skills and knowledge of the individual health professional if and how the subject is addressed and if the couple is referred to a clinical genetic centre when needed. Taking a thorough genetic family history and drawing a pedigree requires special skills (Bennett et al., 2002). The level of knowledge and skills of non-genetic health care professionals to deal with the rapid developments in genetics has been questioned (Greendale and Pyeritz, 2001). Knowledge levels show deficiencies and professionals indicate that education is needed to prepare them for the impact of ongoing rapid advances in genetic technology (Baars et al. 2005; Houwink et al. 2011). Not much is known about how primary care professionals in the Netherlands deal presently with consanguinity in their practices and what barriers they experience in providing couples with information or referring them for genetic counselling.

It is clear that preconception care for consanguineous couples in the Netherlands is not uniformly organised and is not systematically reaching those couples who might benefit most.

THE STUDY

The VERWANT – the Dutch word for 'related' – study was set up to improve the risk assessment of individual consanguineous couples. The aim was to develop a new tool, by using genomic tools that are widely available, to identify couples at high risk of having an affected child and to increase their reproductive options.

In this thesis the risk in consanguineous couples was studied from three different perspectives:

(1) on a genomic level
   (a) from a clinical genetic perspective to improve risk assessment and counseling for consanguineous couples and to investigate if a genome wide testing approach can better predict the risk;
   (b) from a population genetic perspective to estimate (quantitative) variables needed for risk assessment;

(2) from the perspective of the target population in order to gain insight into attitudes and beliefs of the target population and possibilities for improving care in a culturally sensitive manner;
(3) from the perspective of primary health care professionals to explore barriers and possibilities for organizing care for consanguineous couples.

The following research questions were addressed:

I. a. Can the risk for consanguineous couples of having affected offspring be better predicted by focusing on the percentage of DNA IBD through genome wide SNP-arrays? (Chapter 2 and 3)
   b. When performing exome sequencing in consanguineous couples with a child affected by an AR disorder, is the carrier status for this disorder indeed identified in the parents? (Chapter 4)
II. What can be inferred from mutational data of affected children of consanguineous parents?
   a. How can information on homozygosity and compound heterozygosity among patients of consanguineous parents be used to infer the total pathogenic allele frequency in the population? (Chapter 5 and 6)
   b. Is it possible to calculate the total pathogenic allele frequency in the case of partly uninformative data? (Chapter 7)
III. What are the attitudes of the Dutch population who would be targeted with the offer of preconception risk assessment in case of consanguinity - consisting for the greater part of Dutch Turks and Moroccans - regarding consanguinity and its associated reproductive risks? (Chapter 8)
IV. What are primary care professionals' attitudes and beliefs towards consanguinity and their care for consanguineous couples? (Chapter 9)

OUTLINE OF THIS THESIS

Chapter 2 describes the methodology of the case-control study focused on comparing consanguineous parents with (a) child(ren) affected by an AR disorder, with consanguineous parents who only have had healthy children with respect to the percentage of DNA IBD. In Chapter 3 the results of this case-control study are presented.

In Chapter 4 a proof-of-principle study is reported that investigated whether by means of exome sequencing the carrier status in consanguineous parents can be confirmed if they are known to be carriers of an AR disorder.

Chapters 5, 6 and 7 are focused on the inferences that can be made from the mutational data of children of consanguineous parents. Chapters 5 and 6 describe different methodologies to infer the allele frequency of a specific disorder in a

population. Chapter 7 presents an example in which the methodology is used, and investigates whether in the case of partly uninformative data it can still be used to calculate the allele frequency.

Chapter 8 presents the results of on online questionnaire survey that was conducted among Dutch Moroccans and Turks about their attitudes towards consanguinity and reproduction, as well as their awareness of the reproductive risk and their views of preconception information regarding this risk.

Chapter 9 describes an exploratory qualitative study that was performed among general practitioners and midwives about the views of their care for consanguineous couples and identifies factors that are of influence on how primary care professionals deal with consanguineous couples.

In Chapter 10 the findings of the conducted studies within the scope of this thesis are discussed and suggestions are made for practical implications and future activities.