Addressing reproductive risk in consanguineous couples

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Summary

Consanguineous 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 congenital/hereditary disorder. This extra risk entails mostly autosomal recessive 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) for each of their children their chance to inherit both mutated copies is 25%. The extra risk 1.7-2.8% is, however, an average percentage. In fact, only a minority of consanguineous couples has an increased risk of 25%, while the great majority of couples has a risk that is similar to that of the general population. The Netherlands, like many other Western countries, is a country where prejudices and misunderstandings about parental consanguinity in public debates are coinciding with a strong tradition of consanguineous marriage among its migrant populations. Politicians approved legislation to ban cousin marriage (De Koning et al. 2014). In the meantime, in health care, a general consensus exists that consanguineous couples should be aware of their elevated reproductive risk. There is no consensus, though, on how this can be achieved. The main objective of this thesis is to give guidance as to how the reproductive risk in consanguineous couples can be addressed in the future. Three different approaches were taken: to study the clinical genetic and population genetic perspective, the perspective of the target population and the perspective of the (primary) health care provider. The latter two focused on the situation in the Netherlands.

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

Chapter 2 describes the methodology of a case-control study focused on comparing consanguineous parents with (a) child(ren) affected by an autosomal recessive disorder (case), with consanguineous parents who only have had healthy children (control) with respect to the amount of DNA identical-by-descent (IBD) they were sharing. This study was focused on developing a new approach to improve risk assessment in consanguineous couples. In Chapter 3 the results of the study are presented: for 151 consanguineous couples (73 cases and 78 controls) from 10 different ethnic backgrounds a genome wide SNP array was done. Kinship coefficients were calculated using three different toolsets: PLINK, King and IBDelphi, yielding five different estimates

(IBDelphi, PLINK (all), PLINK (by population), King robust (all) and King homo (by population)). We performed a one-sided Mann Whitney test to investigate whether the median relative difference regarding observed and expected kinship coefficients is bigger for cases than for controls. Furthermore, we fitted a mixed effects linear model to correct for a possible population effect.

Although the estimated degrees of genomic relatedness with the different toolsets show substantial variability, correlation measures between the different estimators demonstrated moderate to strong correlations. Controls had higher point estimates for genomic kinship coefficients. The one-sided Mann Whitney test did not show any evidence for a higher median relative difference for cases compared to controls. Neither did the regression analysis exhibit a positive association between case-control status and genomic kinship coefficient. In this case-control setting a higher degree of genomic relatedness was not significantly associated with a higher likelihood of having an affected child. Further studies on DNA IBD sharing with regard to this purpose seem redundant as next-generation sequencing techniques are more promising.

Chapter 4 reports a proof-of-principle study that investigated whether by means of exome sequencing the carrier status in consanguineous couples can be identified if they are known to be both carriers of the same AR disorder. The analysis of the couples' DNA samples was restricted to find identical, previously described, or evidently pathogenic mutations in both parents of each couple, in over 400 genes known to result in severe autosomal recessive disorders. Out of the six autosomal recessive disorders known to the four couples studied, two were correctly identified. Additionally, the carrier status of one not previously known autosomal recessive disorder was discovered. The restriction to detecting only couples with identical mutations diminishes the risk of revealing unsolicited findings and shortens the time needed for analysis, but also results in missing couples with different mutations in the same gene. In addition to the proposed pipeline, couples should be offered testing for carrier status of frequent disorders that can present themselves by large deletions, non-exonic mutations or compound heterozygous mutations (e.g. thalassemia, spinal muscular atrophy, cystic fibrosis). Even though sensitivity is reduced, offering exome sequencing prospectively will increase reproductive options for consanguineous couples.

Chapter 5, 6 and 7 focus on the inferences that can be made from the mutational data of children of consanguineous parents. The short communication in Chapter 5 deals with the questions how to calculate the expected proportion of compound heterozygous patients among affected offspring of consanguineous parents, and how to calculate from the observed proportion of compound heterozygotes both the proportion of homozygotes not IBD and the frequency of pathogenic alleles in the population. This estimate of allele frequency may be particularly useful in populations with a high frequency of consanguineous matings.

A further development and improvement of the use of mutation data and the inbreeding coefficient to estimate the total pathogenic allele frequency of AR disorders is presented in Chapter 6. A maximum likelihood method is applied for estimating total pathogenic allele frequencies and it is explained how confidence intervals can be constructed for this frequency. The results of several simulation studies are described for investigating the unbiasedness and accuracy of the new estimation method. Also, a situation is considered in which not all mutations can be detected.

An application of the maximum likelihood method using real data is described in Chapter 7. In this chapter this method is applied to estimate the allele frequencies of bi-allelic autosomal recessive *MEFV* mutations in Tunisia and Morocco based on data from 293 Tunisian patients and 199 Moroccan patients with familial Mediterranean fever (FMF). The data were partly inconclusive, as in FMF patients molecular testing often fails to show two *MEFV* mutations. First, *q* was estimated based on individuals with bi-allelic mutations. Second, a fictive allele was modelled for all missing alleles and used for estimating *q*. The two estimates of total allele frequency for autosomal recessive *MEFV* FMF in Tunisia are 0.01040 (95% CI: 0.00381-0.02540) and 0.00949 (95% CI: 0.00460-0.01831). For the Moroccan data these estimates equal (by lack of bi-allelic heterozygous patients) 0.00000 (95% CI: 0.00000-0.01326) and 0.002866 (95% CI:0.00042-0.0118). These results show that by using a maximum likelihood method, the total allele frequency of an autosomal recessive disorder can be estimated, provided that sufficient and reliable data are available, even if some mutations are not identified.

THE PERSPECTIVE OF THE TARGET POPULATION

Chapter 8 presents a study that aimed to gain more insight into the attitudes of people belonging to ethnic groups in Western society towards consanguinity and their understanding of risk for offspring. Also, their attitudes regarding reproductive information targeted at consanguineous couples was investigated. Dutch Moroccans and Turks were invited to complete an online questionnaire by snowball sampling and by placing a link on two popular Dutch Moroccan/Turkish forum websites between September and October 2011. The questionnaire was completed by 201 individuals who were, on average, neither positive nor negative towards consanguinity. Respondents with a consanguineous partner were more positive, estimated the risk for the offspring lower, and were less positive about the provision of risk information to consanguineous couples when compared to respondents without a consanguineous partner. Participants of Turkish origin had a more negative attitude towards consanguinity and estimated the reproductive risk higher than Moroccan participants. More than half of the respondents thought that information should be given before marriage, whereas only 10% thought it should never be provided. The general practitioner was most often

mentioned (54%) as the designated professional to inform people. Information about genetic risks related to consanguinity should be offered early, preferably before marriage. The diversity of the target population requires various strategies to disseminate information and reach consanguineous couples with the offer of genetic counselling.

THE PERSPECTIVE OF PRIMARY HEALTH CARE PROVIDERS

Chapter 9 presents the results of a study exploring the experiences, attitudes and beliefs of primary health care professionals regarding their care for consanguineous couples. Sixteen semi-structured interviews were conducted with midwives and general practitioners.

Although most primary care professionals considered it their task to inform couples about the risks of consanguinity, during consultations the topic was generally only briefly touched upon and quickly abandoned. Important reasons for this were professionals' beliefs about religious and social values of couples, their low perception of the couples' reproductive risk and expected limited feasibility of referral. Feelings of embarrassment regarding addressing consanguinity did not seem to play a significant role. Primary care professional beliefs about their clients' religious and social values, their attitudes toward the risk, and perceived limited options for referral seem to conflict with the professional norm to address the topic of consanguinity.

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.

In conclusion, although the genomic approach of determining the amount of DNA IBD in consanguineous couples was not proven to be useful for prospective risk assessment, advances in genetic technology are likely to change the available preconception genetic counselling options. Implementation of such a genetic risk tool requires a paradigm shift: simultaneously with the development of a new risk tool, it is necessary to attune positions between the different actors involved and, above all, the target population. If primary care professionals play an active role and/or the tool is offered on a large scale, infrastructure, skills and facilities will need adaptation. Depending on the way the genetic counselling and risk tool is offered, it may be important to address the knowledge and skills of health professionals regarding genetics and parental consanguinity in particular. A decision must be made about how primary care professionals will be empowered with the necessary knowledge and skills to be responsible for referring consanguineous couples. Moreover, the possibility of community-oriented approaches should be further investigated. Finally, the ethical issues raised in the context of developing and offering a consanguinity risk tool aimed at

a minority group will also need to be identified and elaborated, especially as they concern a marriage tradition that is considered controversial in Western society.