

Genetic risk

Leo P. ten Kate

Received: 21 July 2011 / Accepted: 4 October 2011

© The Author(s) 2011. This article is published with open access at Springerlink.com

Abstract In this paper I will review different aspects of genetic risk in the context of preconception care. I restrict myself to the knowledge of risk which is relevant for care and/or enables reproductive choice. The paper deals with chromosomes, genes and the genetic classification of diseases, and it explains why Mendelian disorders frequently do not show the expected pattern of occurrence in families. Factors that amplify genetic risk are also discussed. Of the two methods of genetic risk assessment—history taking and genetic screening—the former method is examined to some extent, and the consequences of an inadequate family history are illustrated in a case report. The paper ends with a review of the sparse literature available on the frequency of a positive family history and an outline of the challenges and rewards faced by professionals when confronted with a positive history.

Introduction

Genetic factors are of paramount importance for normal development and health. Abnormal genes and abnormal expression of genes may therefore lead to birth defects and diseases. Although the same applies for many exogenous factors, I focus here on the genetic ones. A further focus will be on genetic factors whose knowledge is of relevance for reproductive choice. Psychological and ethical issues will be discussed in the papers by Riedijk et al. (this issue)

and De Wert et al. (this issue); future methods of genetic risk assessment will be discussed in the paper by Ropers (this issue).

Relevance of knowledge of genetic risk

Two main reasons for identifying genetic risk in the preconception period are that preconception knowledge of genetic risk may influence care and also may allow informed reproductive choice. Knowledge of genetic risk may influence preconception care, prenatal care, mode of delivery and postnatal care. Previous birth of a child with a neural tube defect—a multifactorial genetic condition—indicates a higher dose of folic acid supplementation preconceptionally and in the first months of pregnancy, than for a woman without neural tube defects in her family (Grosse and Collins 2007). Preeclampsia in a sister of a pregnant woman leads to a higher level of alertness for related symptoms during prenatal care. Dexamethasone treatment in an unborn sib of a child with congenital adrenal hyperplasia has to start as soon as the pregnancy is confirmed, well before invasive prenatal diagnosis of the foetus is possible (Nimkarn and New 2010).

Preconception knowledge of genetic risk also allows informed reproductive choice. Consider a couple in which both partners are carriers of an autosomal recessive disease like cystic fibrosis. What options do they have? If they conceive normally, the child will have a 25% risk of being affected by this disease. The couple may decide to take the risk and only find out whether the child is affected after its birth, or they may consider prenatal diagnosis. If they opt for prenatal diagnosis and the foetus turns out to be affected, they must decide whether to continue or to terminate the pregnancy. However, they also may decide

Special Issue: Genetic Aspects of Preconception Consultation in Primary Care

L. P. ten Kate (✉)
Department of Clinical Genetics, VU University Medical Center,
Amsterdam, The Netherlands
e-mail: lp.tenkate@vumc.nl

not to become pregnant in the usual way, but to make use of in vitro fertilization with embryo selection, or to choose artificial insemination with donor sperm or egg cells. Of course the couple can also decide to stay childless or to adopt children. Even splitting up is an option.

It is clear that the number of reproductive options in the preconception phase is much bigger than after conception. It is also clear that these are not easy decisions to make and that every possible effort should be made to ensure that the decision of the couple is based on the principle of informed choice. Identifying a high genetic risk in a couple also has consequences for family members. In what follows I will focus mainly on genetic risk factors that are relevant for reproductive choice.

Chromosomes and genes

There are many excellent textbooks dealing with medical genetics and genetic diseases. Here I will summarise what is customary knowledge. For details, please consult the appropriate text books.

Every normal human being has 23 pairs of chromosomes in the nucleus of almost all cells of the body. One copy of each pair is of paternal origin, and the other one is maternally derived. One pair of the 23 chromosome pairs is different in males (XY) and females (XX). The other 22 paired chromosomes are called autosomes.

Approximately 25,000 genes are aligned along the chromosomes. On the autosomes there are always two copies of each gene (one on the paternally derived chromosome and one on its maternal counterpart). The same applies to the X chromosomes in females. In males there are different genes on the X and the Y chromosome, apart from a region called the pseudo-autosomal region. So, for most of the genes on the X and Y chromosome, males have only one copy. Egg cells and sperm cells have 23 single chromosomes, one copy of each pair. Red blood cells have lost their nucleus and with it their chromosomes. In addition to the approximately 25,000 genes on the chromosomes in the single nucleus of the cell, the many mitochondria in the cell each contain 37 genes.

Apart from the importance of genes for normal development and health, variation within genes is also responsible for the large variation between persons, which is what makes each of us genetically unique. Considering individual copies of genes, a practical distinction is between 'normal' genes (the wild type in biology) and altered or mutated genes with an observable effect on the phenotype including health and disease. The focus in this paper is on detrimental or pathogenic mutations. We must however realize that there are mutations that are detrimental in one situation, and neutral or even beneficial in other circum-

stances. For instance, while a particular mutation in the β -globin gene causes sickle cell disease when both copies of the gene are altered, it protects against malaria when the mutation is present in a single dose. Nevertheless, in what follows, I will use the words mutation and mutated in the negative sense, unless otherwise specified.

Mutations may be restricted to a particular gene or involve many adjacent genes or even complete chromosomes. Some mutations have only a very small effect, which only becomes manifested in conjunction with small effect mutations in many other genes and under certain environmental conditions, as in so-called multifactorial disorders; other mutations have a very big effect and become manifested even if present in a single dose; other mutations again are situated somewhere in between these two extremes. Mutations which are manifested even in a single dose are called dominant; mutations which only become manifested in a double dose but not in a single dose are called recessive. Mutations may be new, i.e., not present in the parents of the person with the mutation or inherited, i.e., present in at least one of the parents. Some mutations are present in only a proportion of all cells of a person, a phenomenon known as mosaicism.

An important distinction is made between phenotype and genotype. A person's phenotype is what we can observe, without having to study his or her chromosomes or genes. Genes and chromosomes belong to a person's genotype. For instance the disease cystic fibrosis (phenotype) can be diagnosed from its clinical presentation combined with a high concentration of salt in the patient's sweat. The disease is caused by the presence of a mutation in both copies of the so-called CFTR gene (genotype). Both terms may be used in a restrictive sense (one phenotypic aspect or one particular gene) and in a general one (the totality of one's phenotype or the totality of one's chromosomes and genes).

Genetic classification of diseases

Table 1 summarises the major modes of inheritance of human variation. Patients with numerical chromosomal disorders have either more or less than the usual number of 46 chromosomes. Figure 1 shows the chromosomal constitution of a male Down syndrome patient with trisomy 21. Patients with unbalanced structural abnormalities may have the normal number of chromosomes, but they lack parts of chromosomes or have parts in excess. Carriers of balanced structural abnormalities are in general phenotypically normal (see Fig. 2). They may however produce offspring with an unbalanced chromosomal constitution. It is difficult to recognize a chromosomal disorder just from the pattern of occurrence of affected persons in the family.

Table 1 Classification of genetic diseases

Genotype		Example of disease (phenotype)	
Major categories	Subcategories		
Chromosomal disorders	Numerical		Down syndrome
	Structural	Unbalanced	Partial deletion
Monogenic disorders	Autosomal	Balanced	–
		Dominant	Neurofibromatosis
	X chromosomal	Recessive	Cystic fibrosis
		Dominant	Rett syndrome
Mitochondrial disorders		Recessive	Duchenne muscular dystrophy
Multifactorial and complex disorders			Leber optic neuropathy
			Neural tube defects, cleft lip, several chronic diseases

Monogenic disorders are also called Mendelian disorders as they follow the Mendelian rules of inheritance. Autosomal dominant diseases for instance may show a characteristic pattern within pedigrees, showing vertical transmission, equal occurrence in males and females, transmission probability of 50% and father-to-son transmission. Autosomal recessive diseases show one or more affected sibs of either sex in a family and rare instances of affected persons elsewhere in the

family. X-linked recessive diseases may show a pattern of occurrence in males only and transmission through unaffected females in the pedigree. Mitochondrial diseases may at first sight seem to present as an autosomal dominant disease, but affected males never have affected offspring, as mitochondria are not transmitted through sperm cells. A word of warning should be given here as the situations in which it is possible to recognize the pattern of inheritance just by simple inspection

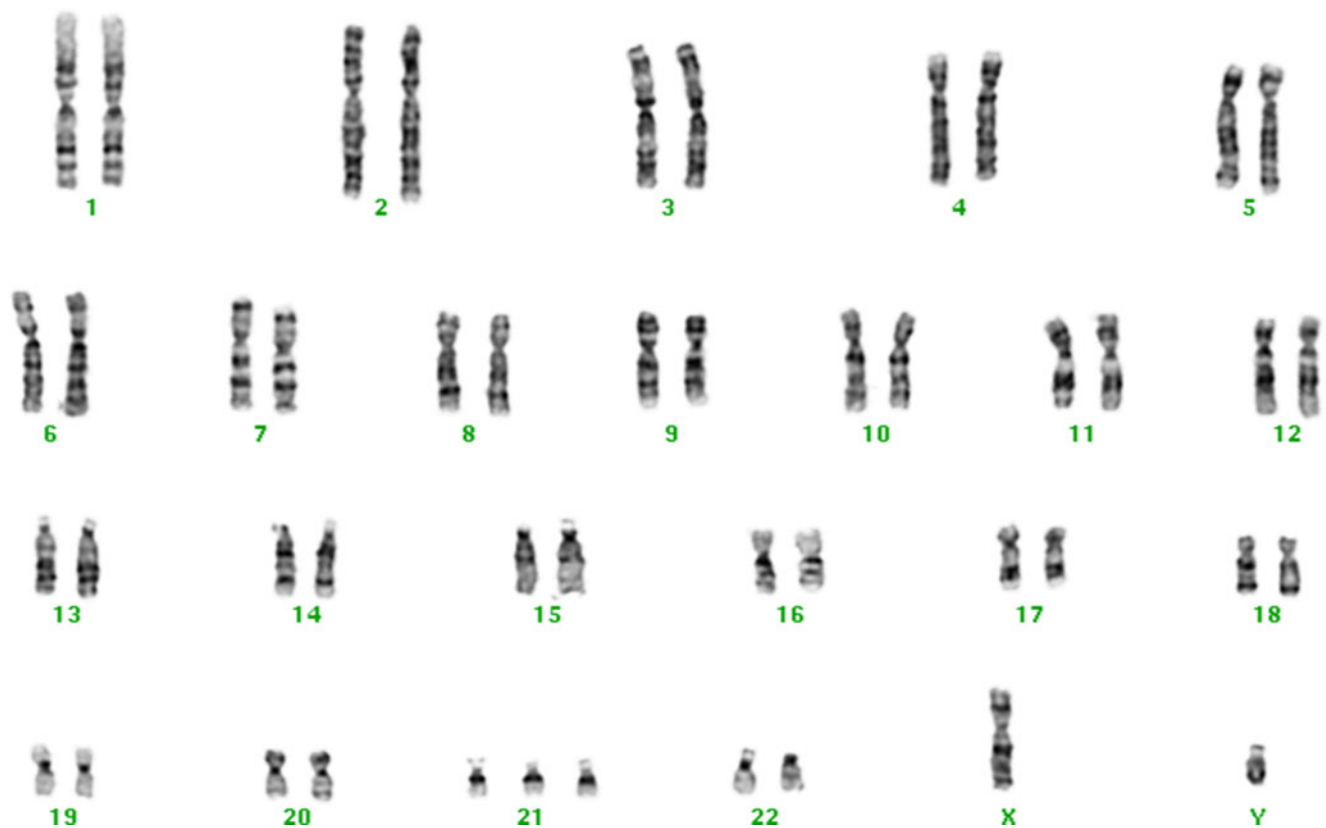


Fig. 1 Chromosomal constitution of a male Down syndrome patient with trisomy 21 (courtesy of A. Nieuwint, Cytogenetic Laboratory, VU University Medical Center, Amsterdam, the Netherlands)

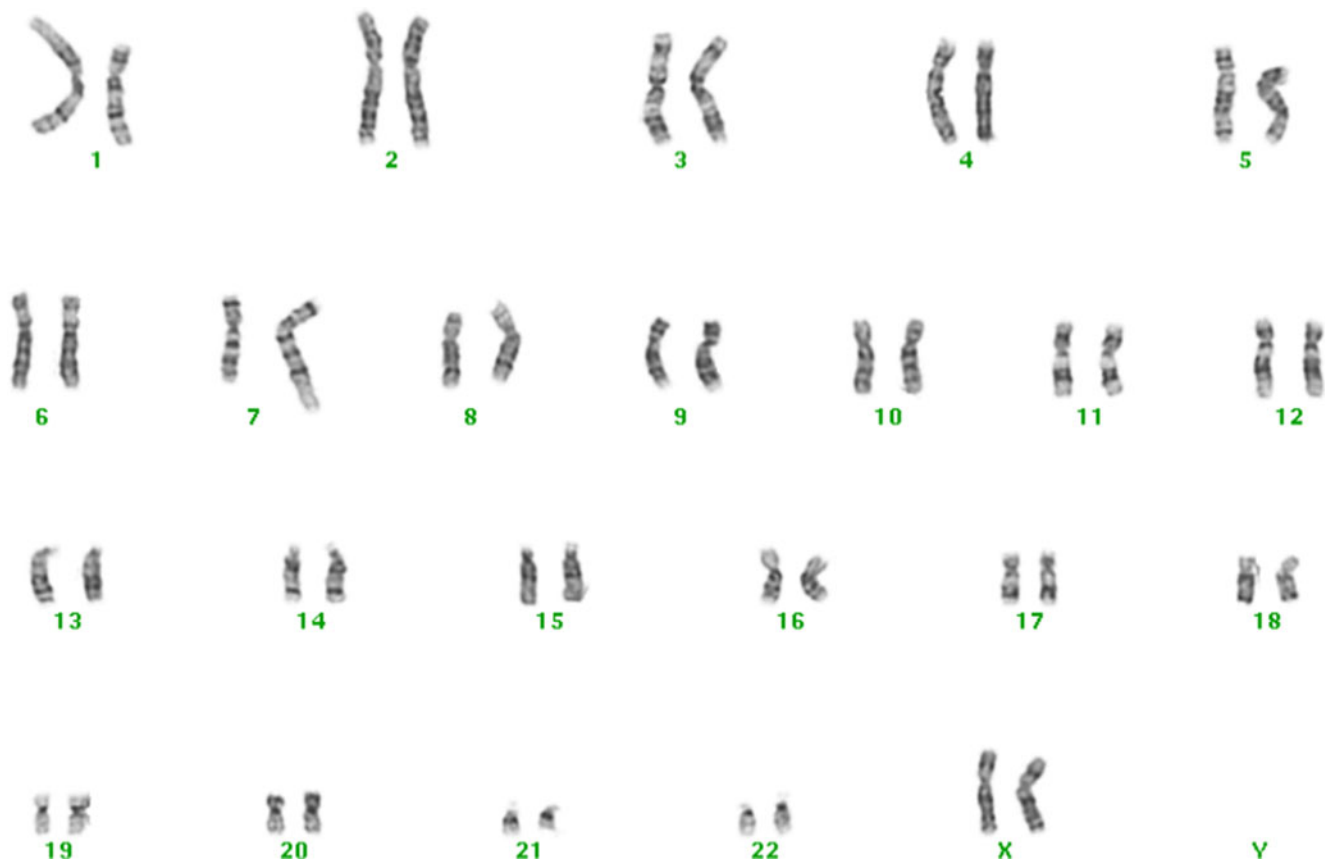


Fig. 2 Chromosomal constitution of a female person with a balanced translocation between chromosome 1 and chromosome 7 (courtesy of A. Nieuwint, Cytogenetic Laboratory, VU University Medical Center, Amsterdam, the Netherlands)

of the pedigree are rare, even when a Mendelian or mitochondrial disorder is present. Real life is much more complicated than textbook pictures claim.

Multifactorial diseases are caused by an accumulation of many mutations of small effect and environmental factors in the affected person. It is difficult to recognize a multifactorial disease just from the pattern of affected members in the family. Complex diseases combine cases with a multifactorial inheritance and with a monogenic or mitochondrial aetiology. Good examples of this are diabetes, cancer and cardiovascular diseases.

Why Mendelian disorders frequently do not show the expected pattern of occurrence in families

There are many factors which can complicate the expected pattern of occurrence of a Mendelian disorder in a family. I will mention some of them here, without claiming to present a complete picture.

When a given genotype always gives rise to an observable effect in a person's phenotype, we say that the penetrance of the genotype is complete. If the genotype leads to an observable effect in less than

100% of the cases, the penetrance is referred to as being incomplete. Incomplete penetrance may for instance give rise to the phenomenon known as skipping of a generation in a family with a well-known autosomal dominant disorder. Figure 3 shows a recently reported example of incomplete penetrance.

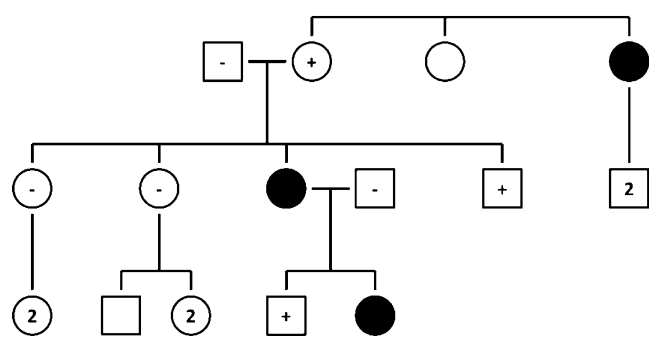


Fig. 3 Pedigree of a family with Charcot–Marie–Tooth disease, a hereditary neuropathy. Filled symbols are affected persons. They have a mutation in the so-called *TRPV4* gene. Symbols with plus sign represent unaffected carriers of the same mutation. Symbols with minus sign are persons without this mutation. As only three out of the six persons with the mutation are affected, penetrance in this pedigree is 50% (redrawn and slightly modified from Berciano et al. 2011)

Another reason why it may be difficult to deduce the pattern of inheritance directly from its occurrence in a family is the phenomenon of variable expressivity. By this we mean that a given genotype may lead to different clinical pictures in different persons. One may then assume that there are several different disorders in the family, while in fact the disorders in the family members have the same underlying genetic cause. Figure 4 shows a recently reported example of variable expressivity.

When two parents are carriers of an autosomal recessive disease, each child has a 25% chance of developing that particular disease, but this also means a 75% chance of not developing the disease. If the parents have two children, there is a 56% chance that none of them has the disease. With three children there is still a 42% chance that all will be free of the disease and so on. The chance that at least two children will be affected, thereby indicating the familial nature of the disease, is only 6% in a two-child family, 16% in a three-child family, 26% in a four-child family and so on. With smaller family sizes, the probability that an autosomal recessive disorder within a family is recognized as familial is therefore rather limited. To a lesser extent, the same restriction applies to a patient who is the first one with an autosomal dominant disorder in the family, when this person has only one child or just a few children.

There are several possible reasons why a person with an autosomal dominant disease may be the first to show this disease in the family. The disorder may be due to a new mutation, but it may also be that one of the parents already carries the mutation, either in all his or her cells, or as a mosaic. The reason for not showing the disease if a parent carries the mutation in all cells can

be a matter of incomplete penetrance or due to variable expressivity. In some disorders, whether or not a mutation is expressed, can depend on the sex of the parent who transmitted the mutation (so-called imprinting). There are also dominant and other diseases in which penetrance and expression increase from generation to generation (so-called anticipation). In this case a seemingly harmless mutation (called a premutation) develops into a full mutation by passage to the following generation.

An autosomal dominant disorder may also mimic the pattern we would expect from a recessive disease, for instance when a phenotypically normal person who is mosaic for an autosomal dominant mutation has two affected children. Conversely, an autosomal recessive disease may mimic the pattern of a dominant disorder, when the partner of a patient is a carrier of the same disorder (pseudo dominance). This situation is only possible when the severity of the disease does not prohibit reaching adulthood and procreation.

Although incomplete, this review of complications hindering a straightforward interpretation of the occurrence of a disorder in a family is meant to illustrate our earlier warning: situations in which you can recognize the pattern of inheritance just by simple inspection of the pedigree are rare, even when a Mendelian or mitochondrial disorder is present. The fact that only one person in a family is affected or that the pattern of occurrence in a family does not comply with a well-known pattern of inheritance can never exclude a genetic aetiology or a genetic risk to family members. This has important implications for risk assessment in the preconceptional phase, as we will see later on.

Amplification of genetic risk

There are a number of situations which may increase genetic risk. New mutations are more frequent in the offspring of parents of advanced age than in younger parents. The most well-known situation is the increased risk for Down syndrome and some other numerical chromosomal anomalies with maternal age. For some autosomal dominant mutations, a correlation with advanced paternal age has been demonstrated too. Originally, the increased risk for Down syndrome constituted an indication for prenatal diagnosis for pregnant women at advanced age, but nowadays, this policy has been replaced widely by the offer of prenatal screening of all pregnant women, irrespective of their age. As new mutations leading to dominant diseases are much rarer than Down syndrome, advanced paternal age has not been a reason for invasive prenatal diagnosis so far.

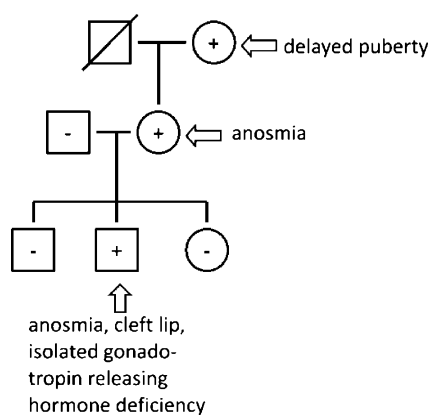


Fig. 4 Pedigree of a family with different manifestations of the presence of a mutation in the *FGFR1* gene (symbols with plus sign) in three family members (redrawn and slightly modified from Au et al. 2011)

In addition to parental age, contact with ionizing radiation or mutagenic agents, either in the medical or occupational situation, has to be considered. This will be covered in the paper by Mulvihill (this issue).

The risk of autosomal recessive disorders is greatly increased by consanguineous marriage. This subject will be dealt with in the paper by Hamamy (this issue).

If partners of a couple both originate from a place known for a high frequency of a particular autosomal recessive disease, their risk for that disorder may also be increased, even if there is no known close consanguinity between the partners. In a wider context, this also applies to partners from the same clan or with the same ethnic background. Sickle cell anaemia and thalassaemias are more frequent in persons whose ancestors came from Africa, the Mediterranean area, and countries in Southern and Western Asia, while cystic fibrosis is more frequent in persons with ancestors in Europe and the Mediterranean area (Fig. 5). Finally we may consider poor health care and genetic illiteracy as factors that contribute to genetic risk in families subject to these conditions, since recognition of genetic risk requires an appropriate diagnosis and sufficient knowledge of the genetics of the disorder in the family.

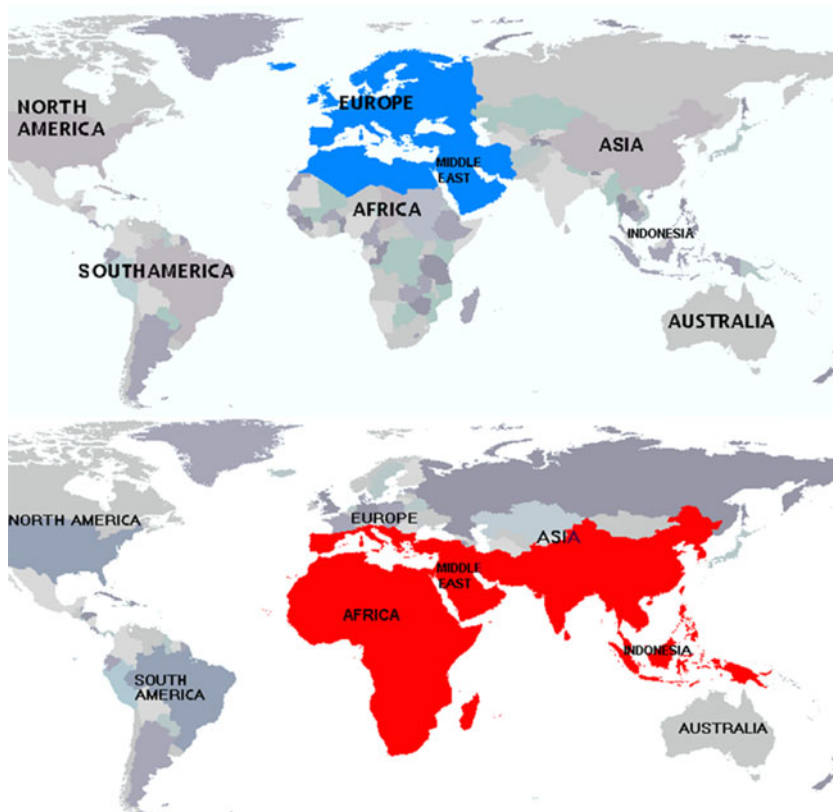
Genetic risk assessment

There are two approaches to assess genetic risk. The first one involves taking a careful medical history of the couple and their family (see the paper by Bennett in this issue), and the second one is through genetic screening (see the paper by Metcalfe in this issue).

As I have argued above, a clear-cut pattern of occurrence of a disease in the family is rather rare, so we have to base our medical history taking on other principles:

1. Every health problem in one of the partners or in a family member, either at present or in the past, may have a genetic basis, unless there are good arguments to refute this possibility. As stated before, the absence of a second patient with the disorder in the family is never a valid argument against a genetic aetiology.
2. Inquiring about the presence of a genetic disorder in the family or presenting a list of disorders that might be genetic is a sure way to miss important risks as knowledge on whether a given disorder is genetic within a family cannot be presumed and since lists of disorders that may be genetic can never be complete

Fig. 5 Global distribution according to ancestry of patients and carriers of cystic fibrosis (in blue) and the hemoglobinopathies (sickle cell disease and thalassaemias), (in red); (courtesy of Dr. P. Lakeman, Dept. of Clinical Genetics, VU University Medical Center, Amsterdam, the Netherlands)



enough. Therefore it is recommended to ask for each person in the family individually about his or her present and past health, including whether he or she was ever admitted to hospital and for what reason. This questioning can also be done by means of a written questionnaire or an electronic aid.

3. The surest way to detect genetic risk is to obtain a medical diagnosis for each health problem in the family and to check whether this diagnosis is known to point to a genetic risk. This may involve asking the permission of the patient to question his or her physician about the nature of the disorder and to consult someone with expert knowledge on the genetics of the disorder, or even to refer the couple or the patient to such an expert for further workup (see the paper by Read and Donnai in this issue).
4. Since family histories are dynamic, they need to be updated again and again (American College of Obstetricians and Gynecologists Committee on Genetics 2011; Ziogas et al. 2011).

The sad story of Peter S.

Peter S. was 10 months old when his parents became aware that the pupil of his left eye appeared pale on pictures made with flashlight (see Fig. 6). At the age of 15 months, he was referred to a local ophthalmologist, who suspected retinoblastoma and sent him to an expert centre. Here the diagnosis was confirmed, and his left eye was enucleated, since the tumour was too far advanced to warrant more conventional interventions. During the workup it became apparent that the father's left eye had been enucleated when



Fig. 6 Peter S. and his father. Notice the reflection in Peter's eye (published with written consent of Peter's father)

he was very young too, also due to a retinoblastoma. It turned out that this diagnosis was not known to this man or to his parents and that the possibility of a genetic aetiology had never been discussed with them. During his wife's pregnancy, no one had ever raised the possibility that the husband's history of an eye tumour might need closer examination. He was the first one in the family with this problem, and ideally, he should have been referred earlier for genetic testing as 15% of nonfamilial unilateral cases of retinoblastoma concern carriers of a mutation in the retinoblastoma gene. Besides the eye tumour and the reproductive risk, carriers of a retinoblastoma mutation have an increased risk of other tumours and should be checked regularly. Besides other options (Dommering et al. 2010), one option for carriers of a retinoblastoma mutation is to have their children tested very soon after birth and to closely monitor those with a mutation, to enable an intervention with more conventional means as soon as a tumour develops. If this had been done in this case, Peter would probably still have his eye.

How frequent is a positive family history?

Although there is wide consensus in literature about the importance of taking a medical family history for preconception care, data on the frequency of a positive family history are scant. The largest population studied was reported by Meschede et al. (2000), who analyzed the yield of pedigree analysis in 1,356 consecutive genetic counselling sessions of women considering invasive prenatal diagnosis for advanced maternal age or an abnormal result upon triple serum marker screening, and without a secondary indication for genetic counselling. They found 108 cases (8%) with a total of 117 disorders which they regarded as both relevant and significant. To be considered relevant, a disorder had to be manifesting congenitally or during childhood in the majority of cases and to have a major impact on the quality of life. A relevant disorder was considered significant if, after genetic workup the risk to the foetus was estimated to be 0.5% or higher. Besides these relevant and significant disorders in the family, there were 23 cases in which one of the partners had a disorder qualifying as relevant and significant, and in 16 cases, there was significant consanguinity (at least second cousins). Adding these numbers up, 147 cases (11%) had a relevant and significant risk. As this percentage is the result of interpretation and follow-up studies, the real frequency of disorders mentioned in response to taking a family and personal medical history must have been many times greater, suggesting a considerable workload.

Van der Pal-de Bruin et al. (2008) reported on the prevalence of risk factors in preconception counselling of

481 couples in primary care practices. In 42% of these couples, family history required further action by the general practitioner (GP). In 4%, following counselling by the GP, referral to a clinical genetics centre was indicated. In 38% of cases, more information was needed before a decision could be made as to whether referral to a specialist had to be considered. The authors recognize the possibility of bias introduced if the participating couples were a selected group with a higher frequency of reproductive risk factors. Since this may also apply to couples coming for preconception counselling in the future, it is safe to say that a considerable proportion of couples qualifying for preconception care have genetic risk factors in their personal and family history and deserve an adequate response.

Challenge and reward

The above sad story of Peter S. is a perfect illustration of the importance of an adequate family history and an appropriate follow-up of that history. It is possible that history taking by the professionals attending this family was inadequate, leading to the surgery for an eye tumour at a young age in the father to be being missed. It is also possible that they were aware of the eye tumour but failed to identify precisely what had happened or to establish the possible consequences of the precise diagnosis.

Taking a family history implies a commitment to follow-up on that history in two directions: what is the precise diagnosis and what are the consequences of that diagnosis for this couple. The levels of competences of primary care professionals in these matters are probably highly variable, which implies that consulting with a colleague with more expertise on the particular subject or referral is a wise policy.

Given the numbers of relevant and significant disorders in the family histories of preconception couples, combined with the numbers for which more information is needed before a decision can be made, genetic risk assessment in preconception consultation is a real challenge. However, the results of this effort can be very rewarding for the

couple, their children and other family members, and for the professional involved.

Declaration The author declares that he has no conflict of interest.

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

References

- American College of Obstetricians and Gynecologists Committee on Genetics (2011) Committee Opinion No. 478: family history as a risk assessment tool. *Obstet Gynecol* 117(3):747–750
- Au MG, Crowley WF Jr, Buck CL (2011) Genetic counseling for isolated GnRH deficiency. *Mol Cell Endocrinol* 346(1–2):102–109
- Berciano J, Baets J, Gallardo E, Zimoń M, García A, López-Laso E, Combarros O, Infante J, Timmerman V, Jordanova A, De Jonghe P (2011) Reduced penetrance in hereditary motor neuropathy caused by *TRPV4* Arg269Cys mutation. *J Neurol* 258(8):1413–1421
- Dommering CJ, van den Heuvel MR, Moll AC, Imhof SM, Meijers-Heijboer H, Henneman L (2010) Reproductive decision-making: a qualitative study among couples at increased risk of having a child with retinoblastoma. *Clin Genet* 78(4):334–341
- Grosse SD, Collins JS (2007) Folic acid supplementation and neural tube defect recurrence prevention. *Birth Defects Res A Clin Mol Teratol* 79(11):737–742
- Meschede D, Albersmann S, Horst J (2000) The practical importance of pedigree analysis in women considering invasive prenatal diagnosis for advanced maternal age or abnormal serum screening tests. *Prenat Diagn* 20(11):865–869
- Nimkarn S, New MI (2010) Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: a paradigm for prenatal diagnosis and treatment. *Ann N Y Acad Sci* 1192:5–11
- Van der Pal-de Bruin KM, le Cessie S, Elsinga J, de Jong-Potter LC, van Haeringen A, Neven AK, Verloove-Vanhorick SP, Assendelft P (2008) Pre-conception counselling in primary care: prevalence of risk factors among couples contemplating pregnancy. *Paediatr Perinat Epidemiol* 22(3):280–287
- Ziogas A, Horick NK, Kinney AY, Lowery JT, Domchek SM, Isaacs C, Griffin CA, Moorman PG, Edwards KL, Hill DA, Berg JS, Tomlinson GE, Anton-Culver H, Strong LC, Kasten CH, Finkelstein DM, Plon SE (2011) Clinically relevant changes in family history of cancer over time. *JAMA* 306(2):172–178