Genetic causes of male infertility

Causes génétiques d’infertilité masculine

Katrien Stouffs * , Sara Seneca , Willy Lissens

Center for Medical Genetics/Research Center Reproduction and Genetics, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel (VUB), Laarbeeklaan 101, 1090 Brussels, Belgium

Abstract

Male infertility, affecting around half of the couples with a problem to get pregnant, is a very heterogeneous condition. Part of patients are having a defect in spermatogenesis of which the underlying causes (including genetic ones) remain largely unknown. The only genetic tests routinely used in the diagnosis of male infertility are the analyses for the presence of Yq microdeletions and/or chromosomal abnormalities. Various other single gene or polygenic defects have been proposed to be involved in male fertility. Yet, their causative effect often remains to be proven. The recent evolution in the development of whole genome-based techniques may help in clarifying the role of genes and other genetic factors involved in spermatogenesis and spermatogenesis defects.

© 2014 Elsevier Masson SAS. All rights reserved.

Keywords: Male infertility; Yq deletion; Chromosomal abnormalities; Whole genome-based techniques

Résumé

L’infertilité masculine, qui touche environ la moitié des couples infertiles, correspond à une situation très hétérogène. Un certain nombre de patient présente un défaut de spermatogénèse dont les causes (y compris les causes génétiques) demeuvent largement inconnues. Les seuls tests génétiques pratiqués en routine correspondent à la recherche de micro-délétions Yq et/ou d’anomalies chromosomiques. Différentes atteintes monogéniques ou des défauts polygéniques ont également été impliqués dans la fertilité masculine. Cependant, leur implication causale restent souvent à démontrer. L’évolution et le développement récent des techniques de séquençage du génome entier peuvent aider à clarifier le rôle de ces gènes et d’autres facteurs génétiques impliqués dans la spermatogénèse.

© 2014 Elsevier Masson SAS. Tous droits réservés.

Mots clés : Infertilité masculine ; Deletion Yq ; Anomalies chromosomiques ; Séquençage du génome entier


* Corresponding author.
E-mail address: Katrien.Stouffs@uzbrussel.be (K. Stouffs).

http://dx.doi.org/10.1016/j.ando.2014.03.004
0003-4266/© 2014 Elsevier Masson SAS. All rights reserved.
1. Introduction

Infertility is affecting 10–15% of couples with a desire to have children. In about half of these couples, a male factor can be assigned as the underlying cause [1,2]. Male infertility can be either acquired or of congenital origin. Despite all major efforts during the last decennia to clarify the exact nature of male infertility, a large number of men are diagnosed as having an ‘idiopathic male infertility’. Presumably, part of these cases can be explained by genetic causes. In this review, we will first give an overview of the current knowledge on genetic causes of male infertility. We will especially focus on those cases where male infertility due to an altered spermatogenesis is the only phenotypic abnormality. In a second part of this review, the focus will be on new technologies such as array comparative genomic hybridisation or next generation sequencing that allow the investigation of the whole exome/genome at once.

2. Chromosomal aberrations and Yq microdeletions.

The two most frequently observed genetic causes of male infertility are chromosomal aberrations and Yq microdeletions. In an infertile patient group, Yq microdeletions are detected in ∼7.4% of patients while karyotype abnormalities are detected in ∼5% [3]. For both aberrations, this prevalence increases when only considering men with azoospermia, to >10% or >13% for respectively Yq microdeletions or chromosomal aberrations [4,5].

The most common chromosomal abnormality detected in male infertility, is the presence of an extra X chromosome in males, resulting in a 47,XXY karyotype, referred to as Klinefelter syndrome [6]. Typically these patients present with testicular atrophy and non-obstructive azoospermia as main features. Mostly, the testicular tubuli are completely devoid of germ cells (Sertoli cell-only syndrome). However, several studies showed that mature spermatozoa can be detected in up to 44% of Klinefelter patients [7–10]. In a recent study, we have examined patients with ‘idiopathic’ Sertoli cell-only syndrome. In a group of 100 patients, we characterized 28 patients as Klinefelter syndrome affected. Consequently, the prevalence of Klinefelter syndrome may be 28% (or more) when considering a selected patient group with Sertoli cell-only syndrome.

In azoospermic males it is also possible to find a 46,XX karyotype, although less frequent than Klinefelter syndrome. In the majority of these patients, the SRY gene, normally located on the short arm of the Y chromosome is translocated to the X chromosome [11]. The SRY gene, referring to the sex-determining region of the Y chromosome, is essential for male sexual development.

It also well-known that structural defects such as Robertsonian or reciprocal translocations and inversions are more often detected in infertile men. The formation of normal bivalents during meiosis is disrupted in these patients resulting in a less efficient spermatogenesis. Therefore, it is also not surprising that the frequency of Robertsonian translocations, reciprocal translocations and inversions is higher in men with oligozoospermia compared to azoospermic men and men in the general population [5,12].

Other chromosomal abnormalities detected through karyotype analysis or array comparative genomic hybridisations are the presence of an isodicentric or a very small Y chromosome. An isodicentric Y chromosome is unstable, and might get lost during cell division. Therefore, it is often associated with Turner syndrome or mosaic Turner patients. However, an isodicentric Y chromosome has also been detected in infertile men [13]. The prevalence of a ‘small’ Y chromosome is often linked to a ‘large’ microdeletion of the Y chromosome.

Deletions on the Y chromosome (Yq microdeletions), however, are mostly not visible by karyotype analysis through G-banding. They are most often detected through PCR technologies or possibly by array comparative genomic hybridisation. Nevertheless, the first azoospermic male patients in whom a possible role of a deletion in the Yq11 region was linked to their infertility problems were identified through conventional cytogenetic analysis [14]. From then onwards > 100 papers have been published describing the frequency of Yq microdeletions, in different patient and population groups. A re-evaluation of the literature including > 13 000 infertile men showed that the prevalence of Yq microdeletions is ∼7.4% [3]. As mentioned above, Yq microdeletions are more frequent in azoospermic men compared to oligozoospermic men. In general, it is suggested that Yq microdeletions can be observed in ∼7% of infertile men. In our center, the prevalence of Yq microdeletions was 4% in a strictly selected group of infertile men [15]. In a follow-up study including >2000 infertile men, the prevalence slightly decreased to 3% [16]. The long arm of the Y chromosome (Yq) contains three “azoospermia factor” regions: AZFa, AZFb and AZFc. Deletions of the complete AZFc region are most frequently detected (69%), followed by deletions of the AZFb region (14%) and deletions of the AZFa region (6%).

3. Mutation analysis of individual genes

During the past decade, many genes have been analysed through Sanger sequencing in order to find mutations that are possibly linked to the observed fertility problem. Only a small number of disease causing mutations have been detected, mostly in patients whose sperm showed an abnormal morphology (e.g. AURKc, DPY19L2,..., reviewed in Massart et al., 2012 [3]). Moreover, some potential associations have been investigated. Nevertheless, sequencing gene after gene is time-consuming. Therefore, new technologies are currently being implemented in the field of male infertility testing. These techniques include array comparative genomic hybridisation (array CGH), single nucleotide polymorphism arrays (SNP arrays) and next generation sequencing technologies (NGS).

4. Array comparative genomic hybridisation and single nucleotide polymorphism arrays

Through array CGH and SNP arrays, deletions or gain in copy numbers – also referred to as copy number variations (CNVs) – can be detected in the whole genome of patients with...
spermatogenesis defects (and controls). In addition, SNP arrays can be used to define SNPs that are potentially associated with male infertility. Currently, few studies have been published in order to detect CNVs that are linked to male infertility [17–19]. In none of the studies, CNVs in known infertility genes have been detected. Yet, part of the detected CNVs were only present in the patient group, and therefore should require further attention in order to confirm or exclude a link with male infertility. The main limitation of array CGH or SNP arrays is defined by the resolution of the platform used: small rearrangements may be missed. Krausz et al. (2012) specifically looked at X-linked CNVs with high-resolution X-specific arrays [20]. They noticed more deletions in patients with spermatogenic impairment compared to controls. Possibly one recurrent X-linked CNV might be involved in spermatogenesis failure [21]. However, the prevalence of this CNV is low (1%) and needs further investigations, but will not be the cause of infertility problems for a large group of patients.

5. Next generation sequencing technologies

Next generation sequencing (NGS) technologies are a group of promising techniques allowing to investigate the complete exome/genome/epigenome... of patients (and controls). Moreover, (small) RNA sequencing of transcripts in testicular tissues from patients with different testicular pathologies (i.e. Sertoli cell-only syndrome, maturation arrest of spermatogenesis, normal spermatogenesis) will allow to identify genes and transcripts that are essential for each stage of spermatogenesis [22,23]. These data are also very useful to filter genes and mutations of interest from the thousands of variants obtained through exome sequencing.

6. Conclusions

Besides two well-known causes of spermatogenesis defects, the chromosomal anomalies and Yq microdeletions, only a few causal mutations have been identified in the past decennia. However, a new era has started and massive parallel sequencing technologies are promising tools for identifying genes essential for spermatogenesis and mutations involved in spermatogenesis failure.

Acknowledgements

This work was supported by Wetenschappelijk Fonds Willy Gepts of the UZ Brussel and the Methusalem grant of the Research Council of the Vrije Universiteit Brussel.

References