Review Article

Genetics of Azoospermia: Current Knowledge, Clinical Implications, and Future Directions
Part I

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Introduction: We reviewed the most recent advances in the genetics of male infertility focusing on karyotypic abnormalities, obstructive azoospermia, and idiopathic hypogonadotropic hypogonadism.

Materials and Methods: To update our previous review, we searched the literature using PubMed and skimmed articles published from January 1998 to November 2006. There were 52, 30, and 41 relevant articles to our subject on karyotypic abnormalities, obstructive azoospermia, and idiopathic hypogonadotropic hypogonadism. The full texts of these articles and their bibliographic information were reviewed and a total of 93 were used to contribute this review.

Results: The frequency of sperm aneulpoidy in karyotypic abnormalities such as 47,XXY and 47,XYY is higher than that in the healthy individuals, but transmission of the abnormalities to the offspring is rare and the outcomes of assisted reproductive techniques are encouraging. Mutations in the cystic fibrosis gene are detectable in up to 80% of men with congenital bilateral absence of the vas deferens. However, there is a considerable diversity among different populations and the role of other potential causes is not ruled out yet. Autosomal and X-linked genetic aberrations in men with idiopathic hypogonadotropic hypogonadism are now well known. As hormone replacement therapy can provide the chance of fathering in these patients, the risk of mutations' transmission, especially the autosomal dominant ones, is high.

Conclusion: In the recent decade, a parallel progress has been made in the genetics of men with azoospermia and the treatment modalities for these patients. Assisted reproductive techniques can help most of the patients, but there are several genetic abnormalities that must be considered before decision making for treatment of their infertility.

Keywords: male infertility, azoospermia, genetic diseases, Kallmann syndrome, chromosome aberrations, Klinefelter syndrome

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INTRODUCTION

Genetic aberrations account for a significant proportion of male-factor infertility. These abnormalities cover a wide spectrum including chromosome number and structure, the Y chromosome and azoospermia factor, the hypothalamic-pituitary gonadal axis, the morphogenesis of the internal ductal system, sperm function, and other nonspecific disorders with variable effects on the reproductive axis.[1] With the advent of intracytoplasmic sperm injection (ICSI) for the treatment of severe male factor infertility, an understanding of the genetic etiology of a patient-specific disorder is critical for proper counseling and decision-making. In the recent

decade, a significant number of reports have been published on ICSI in men with specified genetic aberrations with encouraging outcomes. To provide the newest knowledge, we reviewed the literature published in the recent 9 years and updated our previous paper published in 1997.[2] This 2-part article will review the most recent advances pertaining to some of the main genetic etiologies of syndromes resulting in azoospermia. The first part (in this issue) encompasses karyotypic abnormalities, obstructive azoospermia, and idiopathic hypogonadotropic hypogonadism. The next part will cover the other topics including Y chromosome microdeletion.

KARYOTYPIC ABNORMALITIES

Karyotypic analysis of the azoospermic or severely oligozoospermic men may reveal genetic abnormalities that warrant concern. Up to 14% of patients in this population may have abnormalities of chromosome number or structure.[3-5] In a cytogenetic study of 694 infertile men, Van Assche and colleagues found that infertile men were eight times more likely than fertile men to harbor some kinds of chromosome abnormalities.[3] Karyotypic abnormalities are either structural or numerical found in sex or autosomal chromosomes. Less than 10% of the major chromosome anomalies in this group involve the autosomes.[6] The most common chromosome abnormalities in infertile male subjects are Klinefelter syndrome (numerical sex chromosome disorder) and Y chromosome microdeletions (structural, not detected by karyotype analyses).

Klinefelter Syndrome

The most common cytological anomaly in azoospermic men is 47,XXY (Klinefelter Syndrome), representing 82.5% of the total number of sex chromosome abnormalities.[7] Klinefelter Syndrome is found in approximately 1 in 500 to 1 in 1000 live births in boys.[6,8] It is found in 3% of infertile men,[8] 3.5% to 14% of azoospermic men,[6,9] and in 1% of couples referring for ICSI.[9]

Both maternal and paternal origins are described for Klinefelter syndrome. The incidence of 47,XXY increases with maternal age and is due to nondisjunction in either the meiotic division of the oocytes/spermatocytes or cleavage division of an early embryo. Paternal age may increase the percent of XY aueuploid sperm and subsequently the risk of fathering boys with Klinefelter syndrome.[10] Arnedo and colleagues showed that sperm aneuploidy was more frequent in the fathers' sperm of Klinefelter patients with paternal origin.[11] In this group, the age of the fathers correlated with XY sperm frequency.

The prototypical Klinefelter male presents with spermatogenic and androgenic failure. However, there is great variability and many affected individuals have normal virilization and are diagnosed by karyotype analysis for infertility.[12] Eighty-five percent of Klinefelter men have a pure 47,XXY karyotype while 15% are mosaics (46,XY/47,XXY).[8] Almost all 47,XXY men are azoospermic while mosaic patients may have the capacity for a minimal amount of spermatogenesis.

Successful sperm retrieval procedures are reported in 16% to 49% of nonmosaic Klinefelter men,[13-16] and this rate is higher in mosaic patients.[17] Contradictory results have been reported on predictor factors of successful testicular sperm extraction (TESE) in Klinefelter patients.[14] Larger testicular volume, higher serum levels of testosterone, and younger age are suggested as the predictors of successful sperm recovery,[18,19] but most authors have found no predictive parameters.[16,17,20] Yamamoto and colleagues suggested that men who exhibit both 46,XY and 47,XXY spermatogonia in their sminiferous tubule have a greater probability of testicular foci of spermatozoa than men who exhibit only 47,XXY spermatogonia type in their seminiferous tubules. They also suggested that men with a higher degree of Sertoli cell secretory dysfunction have a poor prognosis for having testicular foci of spermatozoa.[13]

High fertilization rates have been reported with ICSI in mosaic Klinefelter cases,[21-23] and to date, 46 healthy children have been the result of ICSI from nonmosaic Klinfelter men.[14,24,25] However, several cases of abortion and 1 offspring with Klinefelter syndrome were reported.[14,23,24] Thus, concerns remain about the risk of producing offspring with chromosome aneuploidies. Since only about half of the embryos with 47,XXY karyotype have the chance of survival to birth,[26] abortions in couples with Klinefelter syndrome can be due to the transmission of the disease. Furthermore, it is shown that the frequency of other genetic defects in Klinefelter

syndrome, such as Y chromosome microdeletions, is high.[27] Thus, other genetic infertility factors should not be neglected.[27]

Autosomal and gonosomal aneuploidies in the spermatozoa of 47,XXY men are more frequent than in healthy men,[9,28] and mosaic patients have a comparable frequency of sex chromosome abnormalities with mosaics in their extracted sperm cells.[14] Nonetheless, the percentage of 47,XXY karyotype in the peripheral lymphocytes of these men do not predict the percentage of hyperhaploidy in sperm cells.[14,22] Hyperploid sperm cells are seen in 0.9% to 7.5% of the patients.[14] This suggests two possibilities. The first is that the supernumerary X chromosome is lost during spermatogenesis and does not enter meiosis such that all spermatozoa are either 23,X or 23,Y. The second possibility is of low level gonadal mosaicism where a markedly reduced population of 46,XY spermatogonia are actually the direct precursors of the few whole spermatozoa present in those selected patients. However, the proportion of XY and XX spermatozoa in 47,XXY patients are not consistent with the expected proportions that can be derived from a segregation of abnormal cells during meiosis.[29] In a prospective analysis of meiosis, Blanco and associates found that the abnormal cells are unable to enter meiosis in 47,XXY males.[29] They speculated that the higher proportion of aneuploid spermatozoa than that found in healthy males is a result of nondisjunctional events induced by an abnormal testicular environment (eg, elevated follicle-stimulating hormone). However, as concluded in previous studies, the presence of 47,XXY germ cells and their completion of spermatogenesis process cannot be rejected.[29]

Overall, assisted reproductive techniques (ARTs) are recommended for Klinefelter patients, but professional genetic counseling including the options of prenatal diagnosis and preimplantation genetic diagnosis must be offered.[14] Early detection of Klinefelter patients and cryopreservation of their sperm may be of help, since a depletion in spermatogenesis occurs with age.[15,30] However, Wikstrom and colleagues demonstrated that in adolescent boys with Klinefelter syndrome, the older ones did not have testicular germ cells while their hormonal profile was still normal and testicular volume was increasing. Thus, early puberty may not be the unique opportunity to preserve the sperm these patients for their future fathering potential.[31]

Finally, Okada and colleague showed that serum testosterone concentrations decline after conventional or microdissection TESE, requiring potential androgen replacement therapy.[32] However, in another report of microsurgical testis sperm extraction with cryopreservation, Damani and colleagues found no alteration of testosterone levels.[33] A large scale study of the impact of TESE on testicular function in azoospermic men documented relative reversibility of changes in long term follow-up. Specifically, although there was an initial drop in serum testosterone levels to 80% of pre-TESE levels at 3 to 6 months after surgery, the levels rose to 95% after 18 months.[34] Regarding the declining trend of testosterone levels in men with Klinefelter syndrome, it seems that even a slight alteration caused by TESE can influence the treatment of these patients and should not be neglected.

Other Numerical Abnormalities

Of numerical autosomal anomalies, only trisomy 21 may allow survival into puberty, but all of the patients are azoospermic.[26] Numerical sex chromosome abnormalities other than 47,XXY may be found including 47,XYY and 45,X/46,XY. The 45,X/46,XY mosaism is a rare entity and most infertile males of this type are low-level mosaics (less than 10% abnormal cells).[9] Recently, successful ICSI and delivery of a healthy female was reported from an infertile man with 46,XX/46,XY karyotype.[35]

A 47,XYY sex chromosome constitution is the second most common chromosome anomaly causing infertility, after Klinefelter syndrome.[36] Men with an extra Y chromosome are mostly fertile, but azoospermia may be seen in some cases. Sperm aneuploidy has been reported in 0.11% to 10% of the spermatozoa of 47,XYY males.[37] Autosomal chromosome abnormalities are also seen in the spermatozoa of these patients (such as disomic 18 spermatozoa).[37] The 24,XY spermatozoa are specially increased[37]; thus, 47,XXY progeny production can be more frequent, with a 50% probability of survival to birth, explaining the contribution of 47,XYY men to recurrent abortion.[26]

There is increasing evidence that, although an elimination mechanism reduces the number of 47,XYY germ cells in humans, a variable number of them can become viable spermatozoa.[29] Rives and colleagues showed the presence of the extra Y chromosome in more then 50% of primary spermatocytes in a nonmosaic 47,XYY infertile patient and concluded that a high rate of germ cell degeneration must be responsible for spermatogenesis impairment and the low rate of aneuploid spermatozoa.[36]

Structural Abnormalities

The Y chromosome-specific structural irregularities that may be detected upon cytological analysis include pericentric inversion of the Y, dicentric Y, ring Y, and truncated Y.[3] The X-autosome and Y-autosome translocations in men are usually associated with azoospermia, but successful ICSI and birth of healthy offspring have been reported.[9] The XX male syndrome is another rare type of structural chromosome abnormality seen in 0.9% of azoospermic men.[9] Two mechanisms are proposed: translocation of a fragment containing the sex determining region (SRY) on Y chromosome to the X chromosome, and a mutation in an X region necessary for inhibition of an autosomal testis determining gene.[6]

Autosomal chromosome abnormalities are usually structural (rather than numeric) in infertile males.[7] These include reciprocal and Robertsonian translocations, inversions, insertions, and ring chromosomes. In the oligozoospermic population, autosomal anomalies, especially Robertsonian and reciprocal translocations, are more frequent than sex chromosome abnormalities.[3,9] Robertsonian translocations are found in about 0.1% of newborns.[26] They are mostly fusions between chromosomes 13 and 14.[38] A Robertsonian translocation between two of the same chromosome, for example a t(13q;13q) homozygote, would produce only disomy 13 or nullisomy 13 spermatozoa. In such cases, ICSI would not be an option.[38] Variable rates of unbalanced spermatozoa is seen in structural reorganization carriers.[26] Reciprocal translocations, for example, are associated with repeated pregnancy losses and varying degrees of unbalanced sperm.[39]

Finally, autosomal inversions are 8-fold more frequent in infertile men than in normal population. Particularly, inversions in chromosome 9 are associated with azoospermia and severe oligospermia.[6]

OBSTRUCTIVE AZOOSPERMIA

Congenital Bilateral Absence of Vas Deferens

Congenital bilateral absence of the vas deferens (CBAVD) is found in 6% of obstructive azoospermia cases and in 1% to 2% of all infertile men.[40] Mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) are responsible for CBAVD and cystic fibrosis (CF). The CFTR is a protein (chloride selective ion channel regulated by cAMP) encoded by the *CFTR* gene.[41,42] Located on chromosome 7 (7q31.2), the *CFTR* gene is 250 kb in length and contains 230 000 base pairs and 27 exons. More than 1000 different mutations and 200 polymorphisms have been identified in this large gene.[43] Of these, approximately 50% to 80% are ΔF508, a three-base pair deletion in exon 10.[40] Although there is no absolute genotype-phenotype correlation, some general principles do apply. When the patient possesses two *severe* aberrations in *CFTR*, eg, homozygous for ΔF508, clinical cystic fibrosis is recognized which is the most common autosomal recessive disease among the Caucasian population. Over 95% of all CF males are infertile due to obstructive azoospermia. If two *mild* mutations are inherited, congenital absence of the vas deferens (CAVD), epididymal obstruction, or bilateral ejaculatory duct obstruction, namely the genital forms of CF, may be the only clinical manifestation.[40,43] The ultimate phenotypic expression depends upon the level of functionally normal CFTR present. In cases of ΔF508 homozygosity, there is little, if any, CFTR that is functionally adequate and the diseased respiratory, pancreatic, and reproductive ductal systems all reflect this. In other cases of severe/mild, mild/mild, sever/-, or mild/- mutations, a relatively mild set of *CFTR* anomalies, pulmonary and pancreatic function may be entirely normal while vasal aplasia persists as the only recognizable consequence. It appears that anatomical vasal deficiency is the most subtle expression of CFTR protein dysfunction.

Approximately 60% to 80% of men afflicted with

CBAVD will have at least one easily detectable, standard, CFTR mutation.[44-46] Among the Iranian CBAVD men, 80% harbor a mutation or variant.[47] The ΔF508 (32% to 82%) and R117H (~30%) are the 2 most common gene mutations in CBAVD patients.[43,48-50] Up to 30% of the mutations will be *compound* heterozygotes.[51] Of the *simple* heterozygotes, in whom only one CF mutation exists, up to 40% may harbor the 5T variant on the opposite allele. In intron 8, there is a poly-T tract that is variably comprised of 5, 7, or 9 thymidine bases. Splicing efficiency is optimal with a 9T sequence, but markedly reduced in the 5T variant. Exon 9 bears the brunt of this inefficiency, its mRNA sequence being lost from the final message in a significant percentage when a 5T series is present.[52,53] Therefore, while some qualitatively normal CFTR protein still results from a 5T allele, the ultimate amount is quite low. The combination of mutation/5T allele variant leads to a quantitative deficiency in functional CFTR, a level too low for proper male reproductive ductal morphogenesis. Overall, the 5T variant is seen in 12% to 27% of *CFTR* alleles from CBAVD patients.[43] In a study on 106 Iranian patients by Radpour and colleague, the combination of the 5T allele in one copy of the *CFTR* gene with a CF mutation in the other copy was the most common cause of CBAVD.[47] Recently a 3T allele in the CFTR gene was found associated with CBAVD.[54]

In a considerable proportion of CBAVD patients (20% to 40%), *CFTR* mutations are not found.[40,47] Some authors suggested that the etiology of the CBAVD in this group is secondary to causes other than an abnormal CF gene.[46,55] On the other hand, the standard screening tests for *CFTR* mutations may not recognize all abnormalities,[56] because of the wide-ranging allelic heterogeneity.[47] Variable mutations reported from different countries emphasizes the necessity of designing population-specific panels.[47,57,58] However, the most extensive mutation analyses can detect aberration in nearly 82% of CBAVDs, reserving the other potential etiologies for further investigation.[51] Wang and colleagues used a panel of 100 *CFTR* mutations analysis and could increase the percentage of mutation-positive CBAVD patients only up to 67%.[51]

The presence of subclinical CF symptoms such as elevated sweat chloride concentrations, polyps, rhinosinositis, bronchitis, and sinusitis in CBAVD men supports the concept of incomplete forms of CF.[59,60] Defining lower values for the upper limit of normal sweat chloride concentrations, the diagnosis of some CBAVD cases can be changed into CF.[59] Josserand and colleagues reported sweat chloride values and *CFTR* aberrations in 50 patients with CBAVD. A mutated allele was more frequent in the group of elevated sweat chloride concentrations (> 60 mmol/L, 47%; 40 to 59 mmol/L, 41%; and < 40 mmol/L, 35%). There were 10 patients with no mutation/5T variant in whom the sweat chloride concentration was less than 60 mmol/L. The 5T variant was not associated with sweat concentration.[59] Dumur and colleagues found a high frequency of *CFTR* mutations in the group with high sweat chloride values.[61] A second group of patients with equivocal sweat chloride values had a high frequency of the 5T variant with or without the ΔF508 mutation. No abnormalities of the CF gene could be detected in a third group of patients who had low chloride values and other congenital abnormalities of the urogenital tract.

With specific attention to the pulmonary function, Colin and colleagues evaluated the clinical status of 18 patients with CBAVD.[62] They found *CFTR* mutations in 58% of the CBAVD patients with 26% being ΔF508 mutations. All patients had normal pulmonary function tests (except one with asthma) and normal general anthropomorphic and physical examinations. The authors concluded that patients with CBAVD without any other clinical features of CF should not be considered to have a *mild* form of CF, because the two diagnoses, although constituting different ends of a spectrum, have completely separate clinical and prognostic characteristics.

Concerning the reproductive characteristics, there is no genotype-phenotype consonance. Mennicke and coworkers found that abnormally low semen pH, normal FSH, normal testicular volume, and azoospermia are predictive of *CFTR* mutations.[43] But, the sensitivity for the combination of these factors was low.

Most patients with CBAVD have completely normal spermatogenesis and a small subgroup have impaired spermatogenesis.[49] The underlying cause can be the *CFTR* gene mutations, other genetic/nongenetic conditions, and the impact of chronic obstruction.[63]

Van der Ven and coworkers tested the interesting hypothesis that the *CFTR* gene might be responsible for reduced sperm quality in otherwise healthy men with no evidence of CBAVD.[64] They found at least 1 mutation in 14.3% of healthy azoospermic men and a significantly higher frequency of mutations in their sample of infertile males (17.5%) than that expected in a random sample of the population ($P = .001$), suggesting that the CFTR protein may have a role in the normal processes of spermatogenesis. Furthermore, the frequency of 5T allelic variant was reported to be similar in obstructive azoospermic men and the general population, but higher in nonobstructive azoospermic patients.[40] Nonetheless, Meng and colleagues found no higher frequency of 5T allele in those with impaired spermatogenesis. They found other abnormalities (Y deletions and varicocele) in this group of patients. Thus, they concluded that impaired spermatogenesis in CBAVD may be mostly related to other causes than *CFTR* mutations.[63]

A proportion of patients with CAVD may suffer from concomitant urogenital abnormalities, mainly unilateral renal aplaisa. In addition, cryptorchidism, dysplastic seminal vesicles, and inguinal hernia are reported.[60,65] However, the association of *CFTR* muatations with these urinary tract abnormalities is controversial. The rate of urinary tract abnormalities in CBAVD is about 10%, mostly seen in the group without *CFTR* gene aberrations.[46,66] The physical separation of renal/ureteral system and the ipsilateral vas deferens, seminal vesicle, and distal epididymis occurs at the week 7 of gestation. The CFTR protein impacts the latter part in CBAVD males with normal renal system. Thus, it seems to act after this separation and cannot be the mere etiology of CBAVD with renal agenesis. McCallum and coworkers evaluated 17 CBAVD men with urinary tract abnormalities and 97 isolated CBAVD men. No differences in physical examination, laboratory assay, and ultrasonographic assessment were detected. But, *CFTR* mutations were found in 19% and 100% of the 2 groups, respectively. This emphasizes the possible role of a mesonephric duct gene anomaly rather than the *CFTR* mutations.[66] In line with the above hypothesis, males with a unilateral form of CAVD have a lower frequency of *CFTR* mutations and higher frequency renal agenesis.[60] However, Casals and colleagues found *CFTR* mutations in one-third of CAVD patients with renal agenesis using an extensive genetic analysis.[60] A multifunctional or polygenic point of view may explain the coexistence of CAVD and renal anomalies.[60]

Thanks to advances in ART, men with CAVD can enjoy parenting their own children. Josserand and colleagues reported 8 successful pregnancies by ICSI and birth of 10 healthy children among 28 CBAVD who attempted ICSI.[59] McCallum and coworkers reported 10 fetuses conceived by ICSI, but one had bilateral renal agenesis, emerging prenatal ultrasonography.[66] Because of a high frequency of *CFTR* gene carriers in the general population and the high frequency of ΔF508, a severe mutation, both in CBAVD men and general population, the probability of the birth of an offspring with CF is high. Thus, careful counseling before IVF or ICSI is recommended.[48] Stuppia and associates studied *CFTR* mutations in 1195 couples counseling for IVF in Italy. A total of 11% had mutations or 5T allele. Among 16 CBAVD males, 62.5% had only a 5T allele and 37.5% were heterozygote (5T variant/mutation).[50] Since the prevalence of *CFTR* mutations was not higher than those in the general population, they concluded that it is sufficient to analyze only one partner (preferably the infertile) and perform screening in the second one only when a mutation or 5T allele is found in the first one.[50] However, the wide spectrum of mutations may lead to a false-negative result in the routine screening tests done for one partner. Thus, testing both partners to increase the possibility of case finding can be rational.

HYPOGONADOTROPIC HYPOGONADISM AND KALLMANN SYNDROME

Idiopathic hypogonadotropic hypogonadism (IHH) and anosmia are the most prominent clinical features of Kallmann Syndrome. This syndrome has an incidence of 1:10 000 to 1:60 000.[67] Some of the genetic defects described for Kallmann syndrome are also associated with normosmic IHH. Consequently, the current idea that Kallmann syndrome and IHH are two distinct entities is disputed.[68,69] There are families with individuals having cases of typical Kallmann syndrome, normosmic IHH, and isolated anosmia, corresponding to a heterogeneity with different phenotypes.[70]

About 30% to 60% of men with IHH have anosmia.[67,71] Delayed puberty is a usual presentation.[72] Other clinical features include renal agenesis (seen in X-linked Kallmann syndrome), pes cavus, cerebellar ataxia, microphallus, cryptorchidism, high-arched palate, color blindness, hearing loss, midline craniofacial abnormalities, and bimanual synkinesia (mostly X-linked).[71-75] Magnetic resonance imaging (MRI), as well as karyotype analysis, measurement of sexual hormones, and gonadotropin releasing

hormone (GnRH) stimulation test is useful for diagnosis. On MRI, absence of olfactory bulbs and hypoplasia or absence of olfactory sulci are usually observed, but hypoplasia of the anterior pituitary may not be present in all cases.[76] Thus, MRI may not be able to differentiate Kallmann syndrome from the normosmic form of GnRH deficiency.[77]

Most patients with Kallmann syndrome present as sporadic cases.[73] The disease may also be inherited in an autosomal dominant (64%), autosomal recessive (25%), or X-linked fashion (11%).[78] Autosomal genes account for the majority of familial and sporadic Kallmann syndrome cases.[67]

X-linked Kallmann Syndrome

KAL1 is the gene responsible for the X-linked form of Kallmann syndrome and has been localized to Xp22.3.[79] Mutations or deletions in *KAL1* are seen in 10% to 14% of all Kallmann syndrome cases,[73,80] mostly seen in familial ones.[67,73] The GnRH-synthesizing neurons normally migrate from the olfactory epithelium to the forebrain along the olfactory nerve pathway.[81] Cariboni and colleagues demonstrated the direct action of anosmin-1 on the migratory activity of GnRH-synthesizing neurons. Anosmin-1 (namely, KAL protein) is encoded by *KAL1*.[82]

There is a lack of genotype-phenotype correlation in *KAL1*-positive patients.[67] There are patients who have normal gonadal function.[83,84] For instance, *KAL1* mutations were reported in 3 brothers, 2 with Kallmann syndrome and 1 with isolated partial anosmia.[85] On the other hand, Sato and coworkers found 2 cases of normosmia and asymptomatic borderline olfactory function. However, hypoplastic olfactory bulbs on MRI were observed.[68] Different phenotypes have been found even in monozygotic twins with Kallmann syndrome and a same mutation of the *KAL1* gene.[86] These indicate a spectrum of clinical manifestations in mutation-positive patients and emphasize the role of putative modifier genes and/or epigenetic factors in the expressivity of the X-Linked Kallmann syndrome.[87] To explain the discrepancy between the degrees of anosmia and hypogonadism, de Roux found another mutation in *Gln66X*, responsible for complete inactivation of the *KAL1* gene.[85]

Autosomal Dominant Kallmann Syndrome

The autosomal dominant (AD) form of Kallmann syndrome is more frequent than X-Linked and most familial cases are inherited in an autosomal fashion.[67] Dode and colleagues described for the first time loss-of-function mutations in fibroblast growth factor receptor 1 gene (*FGFR1*) on 8p12 which were responsible for the AD form of Kallmann syndrome.[75] This gene is required for initial olfactory bulb evagination and its mutation accounts for 8% to 10% of all Kallmann syndrome cases.[67,80,88] It is shown that *FGFR1* mutations can cause both Kallmann syndrome and normosmic IHH.[69,74] Of the associated anomalies, cleft palate and dental agenesis are only seen in *FGFR1* mutated cases.[73,81,85]

Pitteloud and colleagues reported a case of Kallmann syndrome with mutation in *FGFR1* who had spontaneous recovery after discontinuation of testosterone therapy. They suggested that despite the disruption of the olfactory bulbs, GnRH neuronal migratory defects in *FGFR1* mutations are not always complete and milder cases of AD forms of Kallmann syndrome may bee seen.[72]

Autosomal Recessive Kallmann Syndrome

Genes responsible for autosomal recessive (AR) inheritance have only been reported in normosmic IHH. In 1997, de Roux and colleagues reported gonadotropin releasing hormone receptor gene (*GNRHR*) mutation in a man with the AR form of IHH and his sister.[89] Further investigation demonstrated this mutation in 1.6% of IHH men,[71] 40% of AR forms of IHH, and 16% of sporadic IHH.[90] de Roux and colleagues also identified a mutation in *GPR54* as an AR form of isolated IHH.[91] The phenotypes resulting from mutations in *GNRHR* and *GPR54* are similar and do not have

a significant diversity. *GPR54* seems to be involved in regulating hypothalamic GnRH secretion, but an effect at the pituitary level is not discounted. These 2 genes may act in concert to regulate the gonadotropic axis, thereby also regulating the onset of puberty.[85]

Treatment and Paternity

Patients with Kallmann syndrome and IHH can benefit from hormonal therapy. Life-long physiological doses of gonadotropins or pulsatile GnRH is required to achieve and maintain sexual maturity. Spontaneous recovery after discontinuation of testosterone therapy was also reported.[72] The size of the testes might be a predictor of response to hCG/hMG administration and production of sperm.[92] However, the testes may remain of infantile volume despite hormone replacement therapy. Ferro and associates transferred one testis to the contralateral hemiscrotum and placed a testicular prosthesis instead to normalize the appearance of the genital area while presenting testicular function.[93]

Treatment of Kallmann syndrome can directly induce fertility. Thus, patients with Kallmann syndrome, especially those with AD genetic defects, are at the risk of transmission of mutations to their next generation. Nevertheless, there are few reported cases in this regard. Sato and colleagues showed transmission of *FGFR1* mutation in 3 patients who received gonadotropin therapy to their offspring. They concluded that transmission of Kallmann syndrome, especially the AD forms, to the next generation may occur following therapy.[74]

CONFLICT OF INTRESEST

None declared.

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