A New Approach to Genetic Factors of Men's Infertility: A Case Study

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Abstract— Infertility is one the most prevalent hygienic problems in the world which about 15% of couples are subjected to this problem. Male factor is effective in half of these cases. The etiology of infertility in men is multi-dimensional and many genetic and environmental factors are affected the infertility problem. The genetic factors including chromosomal malformations and single gene mutations are responsible for 10 to 15 % of factors in infertile men. In the current paper, we have discussed about genetic aspects (chromosomal and single gene malformation and polymorphism of effective genes), the role of mitochondrial mutations, the relationship between miRNA and infertility and reports of new effective genes in infertility problem during recent years.

Index Terms— Environmental factors, Single gene, Genetic factors, Infertility, Spermatogenesis, Chromosome Malformation, Epigenetic

1 INTRODUCTION

According to the definition of World Health Organization, infertility is inability of couples in productivity after one year of sexual intercourse without any prevention [1-8]. Infertility is one the most prevalent problems in the world which is seen in about 15% of couples [9, 10]. Depending on the sex type, there are different factors which can be effective in infertility [11-15]. For women, these factors are including endometriosis, ovulation problems, low quality of ovum, polycystic ovary syndrome and blockage of Fallopian tubes [16-23]. However, these factors for men are blockage of vas, sperm problems (low number, low mobility, dis-morphology) and sperm allergy [24]. In addition, some percent of infertility cases are related to unexplained factors of infertility [25, 26].

Male factor is effective in half of the infertility cases. The presence of male factor is frequently based on the unnatural sperm parameters (azoospermia to oligozoospermia) [27]. Generally, the infertility factors are in three types: acquisitive, congenital and unexplained factors [28-30]. Congenital factors may be originated genetically or produced from genetic malformation. In spite of vast studies to find the natural origination of infertility in men, unexplained factors are mostly recognized as the origin of infertility in men [31-38]. It is suggested that the infertility may be resulted from mutations and or other changes in genes of spermatogenesis [39, 40].

2 CHROMOSOMAL MALFORMATIONS

The prevalence of chromosomal malformations among sterile men is high and degree of malformation is conversely related to the number of sperms. According to the published results, the general frequency of chromosomal factors is between 2 and 8 % with average of 5 %. However, it can be raised up to 15 % in azoospermia men which mostly are XXY men [41]. The malformation of chromosome Y such as microdeletion is the important factor of azoospermia cases and sever oligozoospermia cases (number of sperms as low as 20 million per m.litre) [42-43].

Aneuploidy is the most frequent reason of chromosomal malformation among sterile men [44]. Particularly, men with non-blockage azoospermia are more subjected to aneuploidy [45], especially in sexual chromosomes [46]. Although an aneuploid sperm is of changed genetic materials, it can be successfully inseminate the ovum and transported uncorrected number of chromosomes to offspring [47].

Klinefelter syndrome and Mozaism of XXY: Klinefelter syndrome is the most prevalent aneuploid sexual chromosome in men so that it is happened in 0.1 to 0.2 % of new births. The frequency of the syndrome is very high in sterile men between 5 % in sever oligospermia to 10 % in azoospermia cases. The syndrome is a type of primary deficiencies of testicle along with hypertrophy of testicle and the increase of plasmatic level of gonadotropins and is the most frequent reason of hypogonadism in men. Although it is supposed that about 90 % of non-mosaic syndrome cases have fully azoospermia, it may be possible that some level of spermatogenesis are presented in seminiferous tubules in men with Klinefelter syndrome [48]. The mosaic XY, XXY/46, 47 have different levels of sperm production but the percentage of men which have sperm in semen is not clear. Such patients can be experience the pregnancy with ICSI (Intracytoplasmic sperm injection). However, the risk of having a child with chromosomal malformation is high in this situation [49, 50].

Another source of aneuploidy is chromosomal translocation [51]. Translocations can lead to loss of genetic material in the breakage location of chromosome and hence, breakage of genetic message [52]. The autosomal translocation in sterile men is about 4 to 10 cm more than natural men [52, 53]. The Robertsonian translocation which is happened in acrocentric chromosomes is the most frequent structural chromosomal malformation in human and affects the productivity of 1 in each 1000 men [54-61]. Although the prevalence of this type of translocation is only 0.8 % in sterile men, this number is 9 times more than natural population [62-65]. The translocations can lead to a spectrum of phenotypes in sperm production from the natural production of sperm to incapability in production of spermatogenesis [66].

3 THE Y CHROMOSOME

The Y chromosome is critically studied in the field of infertility due to having many of necessary genes for spermatogenesis and genesis of gonads [41]. Microdeletion in the Y chromosome is one of the important factors in infertility of men. It is described as the deletion of chromosome which is included some genes but such deletion cannot be recognized by customary cytogenetic techniques [42]. The studies show that microdeletion is usual in men with azoospermia and or severe oligozoospermia [43]. It is more happened in long arm of the chromosome (Yq) and the deletion in this region is accompanied by deficiency in spermatogenesis [44, 45]. The considered region is named as AZF (Azoospermia factor region) due to having some genes which are necessary for growing of sperm. The region is subdivided to three sections named as AZFa, AZFb and AZFc [46].

The most deficiencies in these sections are multi-genes deletions in AZFb and AZFc which can lead to a spectrum of infertility phenotypes [47]. Microdeletion is found in sections of AZF in azoospermia and oligozoospermia men with natural karyotype [48].

AZFa: two important genes in this section are USP9Y (Ubiquitin specific peptidase 9, Y-linke) and DBY. The deletions of both genes are led to Sertoli cell-only syndrome in which sertoli cells are complete in testicle but there are not any sperm in semen [49, 50].

In a research program for men subjected to sertoli-cell only syndrome it is shown that the description level of DBY is reduced but other investigated genes are in natural level [51].

USP9Y also is critical in spermatogenesis and its deletion can result to azoospermia, oligozoospermia and oligoasthenozoospermia [52, 53].

AZFb: the deletion in this section is a key factor in stopping of spermatogenesis in the first steps of spermatocyte which is clearly shows the importance of the gene in fertility [54]. The important gene of this section is RBMY which there are 6 copies of the gene in the Y chromosome [55]. The gene codes an attaching protein to RNA which is a proprietary splicing factor in testicle and is explained in the core of spermatogenesis, spermatocyte and spermatid [56]. The description of this gene is reduced in azoospermia men [57]. There is also a family of PRY genes in AZFb. They are interfered in the regulation of programmed cell dead (apoptosis) which is a necessary process in deletion of unnatural sperms in the population of spermatozoa [58].

AZFc: the deletion in this section also leads to a wide spectrum of phenotypes which most of them included reducing of sperms due to reduce in spermatogenesis [59]. The deletion in the section is responsible for 12 % of non-blockage azoospermia and 6 % of severe oligozoospermia cases [60]. AZFc is prone to many tiny deletions which are resulted due to intra chromosomal new composition [61]. Such deletions interact with environmental factors and genetic potential which can be lead to a spectrum of phenotypes from natural production of sperm to azoospermia [62]. DAZ (Deleted in azoospermia) which has 4 copies of the Y chromosome has different roles in spermatogenesis and describes in all steps of growing of prolific cells [63].

4 OTHER GENES IN Y CHROMOSOME

CDY: the other important gene in spermatogenesis is CDY in Yq which codes a chromodomain protein. The gene is exclusively describes in testicle and make the replacement of histones in spermatogenesis easier. In addition, it allows easy access for proteins which regulate copies via histone acetylation [64]. The gene has differently performed compared to its homologue autosoma (CDYL gene in chromosome 6) during evolution process and hence, it migrates to the Y chromosome. It is a considered gene since there is imply to a hypothesis that explained the genes which are interfered in spermatogenesis are tend to populate in the Y chromosome [65].

TSPY (Testis-specific protein Y): this gene is located on the short arm of the Y chromosome and has some copies on the long arm [66]. The gene is explained in testicle and its protein is interfered in spermatogenesis [67]. It seems that the gene characterize the time of spermatogenesis with sending a signal to the spermatogonia for entering of meiosis [68].

5 AUTOSOMAL GENES AND POLYMORPHISMS

Many of autosomal genes can have a role in infertility of men. CFTR (Cystic fibrosis transmembrane conductance regulator) is presented in the chromosome 7 of 60 to 90 % of patients subjected to mutated congenital bilateral absence of the vas deferens (CBAVD) [50-66]. CBAVD is a type of non-blockage azoospermia in which the lack of relation between Epididymis and Ejaculatory duct lead to infertility. Men subjected to CBAVD have mostly two soft mutations in CFTR and or a composition of severe mutation or soft mutation in the gene. The most frequent severe mutation is F508del which is found in 60-70 % of patients subjected to CBAVD [69].

SHBG (Sex hormone-binding globulin): this gene in chromosome 17 has been studied for possible role in spermatogenesis. The role of its product is transmission of sexual hormones to the target location and control of androgens concentration in testicle [70]. Androgens have a critical role in sexual differentiating and spermatogenesis process. If the level of androgens experiences some disorder, it can be affect fertility. An investigation about the role of polymorphism n SHBG (TAAAA) in fertility of men concluded that shorter alleles of SHBG are along with increase in spermatogenesis levels. The shorter alleles of SHBG with increase in level of SHBG lead to increase in level of free androgens and hence, incitement of spermatogenesis [71].

ESR1 (Estrogen receptor) and ESR2: the studies about the relation of unnatural spermatogenesis and insufficient estrogens led to more studies about the estrogen receptor genes [72]. ESR1 in chromosome 6 has high polymorphism which their role in infertility, especially about severe oligozoospermi,

has been studied and the results have been different [73]. The differences may be due to interaction of gene with environment since the differences are mostly between various descents.

FSHR (Follicle-stimulating hormone receptor): this gene is located on the chromosome 2 and codes the receptor of FSH hormone (necessary hormone for natural activity of gonads). It is shown in a study that the relative deletion of this gene leads to ignorable effects on spermatogenesis [74]. In addition, it is found that the single nucleotide polymorphism affect the activity of gene [75].

MTHFR (Methylenetetrahydrofolate reductase): this gene is located on the short arm of chromosome 1 and codes an enzyme which interfered in folate metabolism and has an important role in DNA methylation and spermatogenesis process [76]. Polymorphism of 677C ➔T is the reason of replacing alanine to valine which reduces the activity of enzyme [77]. Reduction of activity in MTHFR leads to mis-regulation of folate metabolism and hence, inaccuracy in methylation of DNA and some effects on spermatogenesis [78]. This polymorphism is related to infertility of African, South East Asian and Indian men [79, 80] but such results are not validated for European population [81].

6 Dependent genes to X

Numerous genes located in the X chromosome are explained in testicle and hence, have role in gametogenesis [81]. The androgen receptor (AR) is located on the long arm of X and is interfered in meiosis and conversion of spermatocyte to spermatide in spermatogenesis process [82]. In a study on the sterile men, it was recognized that about 2 % of them have mutation in AR while such mutation was not seen in testimonial group [83].

USP26: it is located on the long arm of the X chromosome and is explained during the elementary steps of spermatogenesis in testicle [84]. It seems that this gene has a role in histonic deletion process in spermatogenesis [85]. The previous results have been shown that there is a relationship between this gene and infertility, such as discovering of gene variants in azoospermia men [84].

KS (Kallmann syndrome): one of the other genetic diseases which is the reason of infertility in men and have both portion of autosomal and related to X. The syndrome is defined as IHH (Idiopathic hypogonadotropic hypogonadism) along with anosmia. IHH with low levels of sexual steroids is recognized in composition with low to natural levels of FSH and LH hormones [83]. Patients can be subjected to a spectrum of IHH from complete to incomplete which leads to a spectrum of sexual growing malformations [82]. The genetic deletions of FGFR1 (Fibroblast growth factor receptor) and KAL1 are related to the syndrome [81]. KAL1 is located on the short arm of the X chromosome and is interfered in migration of neurons of Gonadotropin-releasing hormones (GnRH) and codes Anosmin-1 protein which is a cohesion cell molecule [80]. The deletion of this gene is seen in 30 to 70 % of KS patients. The deletion of FGFR1 also results anosmia types in KS patients.

7 Epigenetics error and Telomere

Spermatogenesis is a complex process which is resulted from a set of events, each of them are prone to mutations which can affect the process [79]. In addition, sperm shall be accurately categorized to transmission of genetic and epigenetic information to accurate growth of embryo. Epigenetic information means the changes of genetic codes which not affect DNA sequence; such as adding different molecules to DNA structure which changed the copy regulation and hence, gene explanation [78]. The chromatin packing is a critical case for genesis of sperm and it is believed that the compressed structure of chromatin transmitted urgent messages for genesis of embryo [76]. During the chromatin packing, 85 % of histones replace by protamines [74, 75].

In mid steps of this replacement, transitional protein entered to the chromatin structure [73]. The studies in mouse are shown that the destruction of genes that codes these proteins (TP1 and TP2) can lead to infertility phenotype [71, 72]. In addition, the performances of two different proteins of protamine P1 and P2 are recognized in human so that if mRNA related to P1 explained very soon, the spermatogenesis stopped in spermatide step [70]. Histones are another important factor in epigenetic transmission and they are highlighted imprinting control regions during the production of spermatogenesis. Explanation regulation control of genes is performed by adding acetyl, methyl, ubiquitin and phosphate to histones [69]. The histone malformation is a potential candidate for germinal malformation and their roles in infertility are still under investigation [68].

Imprinting of DNA methylation determined what gene is explained by father or mother genome. The imprinted regions in DNA are repeatedly imprinting during each sexual cycle and allow stabilizing the parental imprints in cells with prolific level [67]. Kobayashi et al. studied the validity of imprinting in sterile men. In prolific men with natural ejaculation, differentiated regions of father should be methylated while mother regions should be un-methylated. The study showed that about 14 % of sterile men have malformation in differentiated regions of father and 21 % of sterile men have malformation in differentiated regions of mother. Most of patients having malformation in both regions are oligozoospermia. In addition, assisted reproductive techniques (ART) are of low rate of success in men with imprinted DMRs malformation. Moreover, it is found that oligozoospermia men are highly subjected to risk of transmission of imprint mistakes to their children [66]. Telomere can be a potential candidate in outbreak of infer tility phenotype. Telomere protects the genetic information in chromosomes and localizes the chromosome in the core and plays a role in simulating of DNA [65]. Unnatural shortening of telomere is related to infertility in men [64]. Hemann et al. studied about the length of telomere in knock out mouse and found that there is a mechanism in telomerase enzyme which lead to destruction of spermatocytes in short telomeres and hence, prevent from maturity of them [63]. However, the mechanism is not perfect. Liu et al. shown the spermatocytes that are able to path from control regions and reach to meiosis 1

without any failure whiles the telomere is short [62]. At the other hand, study about the length of telomere in different infertility phenotypes including blockage and non-blockage azoospermia and oligozoospermia patients have not shown a clear difference in activity of telomerase [61]. As a result, the effect of telomere length shall be more studied as a productivity factor.

8 MITOCHONDRION DNA

A field of genetic research about the infertility which is not interested for researchers until recent years is the role of mitochondrion and its genome in infertility. Mitochondrion has an important role in all biochemical paths which one of them is the motility of sperm [60]. Motility of sperm is strongly related to production of ATP by mitochondrion. This case is performed by oxidative phosphorylation. During recent years, there found some mutations in mitochondrion genome which are related to some diseases. Most of mitochondrion mutations lead to special type of nervous - muscular and nervous analysis diseases.

Since the motility of sperm is needed to high amount of ATP to move the flagellin system, deficiency in respiratory chain of mitochondrion can lead to stagnancy of sperm and hence, infertility. About 70-80 % of mitochondrion is presented in mid section of sperm in mammals. Each mitochondrion has a copy of mitochondrion's genome [59]. Since the bioangetic performance of sperm is critical for motility, any quantitative or qualitative deviation affects the cell performance of sperm. Firstly, infertility due to asthenozoospermia and oligoasthenozoospermia (no to low sperm motility cases) in patients with mitochondrion malformations resulted from point mutation and deletion reported in some studies [58]. Secondly, it was shown that sperm is prone to deletion mutations in mtDNA and these mutations are related to decrease in motility of sperm. Thirdly, there found a relationship between respiratory chain performance in mitochondrion sperm and semen quality. In addition, it found that point mutations and single nucleotide polymorphism are effective in semen quality.

Use of assisted reproductive techniques such as ICSI may be transmitted the mitochondrion malformation to the child since sperm is completely inseminated to the ovocyte but other studies explained anomalous information which complicates the role of mitochondrion DNA in infertility of men. Marchington et al. reported that mitochondrion DNA of father in child produced by ICSI is not recognizable [57]. This finding confirms the hypothesis of breakup of mitochondrion DNA of father after zygosis [56].

9 microRNA AND INFERTILITY

miRNA are members of small not codeable RNA (mostly between 19 to 23 nucleotides) which have a critical role in regulation of explanation after translation and silence of gene explanation via constitution of open pair with target mRNA [55]. Numerous miRNAs are explained in testicle of mouse, exclusively or preferentially, which is representative of their important role in spermatogenesis [54]. The role of miRNA in anchoring of translation during spermatogenesis is suggested with aggregation of biogenic paths of miRNA in chromatid bodies [52, 53]. It was found that transition protein 2 which is an exclusive gene of testicle is regulated via miR-122a [51]. In addition, in testicles that dicer deleted spermatogenesis is postponed during reproduction and or differentiation steps [50]. In a testimonial case study, Lian et al. compared the profile of miRNA in sound men and sterile men with semen malformation using microarray technique. Totally, explanation of 52 miRNA differed in two groups of sterile and sound men. The results confirmed by qRTPCR (quantitative real-time polymerase chain reaction) and northern blot and it found that miR-574-5p, miR-297, miR-122, miR-1275, miR-373, miR-185 and miR-193b are of increase in explanation and miR-100, miR-512-3p, miR-16, miR-19b, miR-23b and miR-26a are of decrease in explanation in semen of sterile men [49]. More studies in this field can lead to finding new cases and role of miRNA in infertility.

10 DISCOVERING OF NEW EFFECTIVE GENES IN INFERTILITY

DPY19L2: during an international cooperation, one the effective genes in infertility of men discovered. This gene is named as DPY19L2 and is related to a case named as round headed sperm or globozoospermia which is a factor of infertility in low percent of sterile men (lower than 1 % of sterile men). This situation is explained by presence of 100 % of non chromosome sperms in semen analysis via optical microscope. In this study that performed in a Jordanian family, 5 brothers recognized as fully globozoospermia which 4 of them are of hemozygote deletion 200 kb in chromosome 12. This region is only consists of DPY19L2. Similar deletions in non-related patients is showed that delete of this gene is one of the important factors of globozoospermia and hence, infertility in men [48].

GLUT3 and CASPR5: in 2012, researchers of Baylor medical college in Texas recognized the factor of infertility in a group of sterile men. They studied DNA genome of environmental blood for 22 men with non-blockage azoospermia and 4 reproductive men using array CGH technique to compare the copy number variation. The added and missed copies recognized and candidate genes selected. After supplementary tests, it found that among 22 sterile patients, 2 of them are of extra copy number in GLUT3 and one of them is of extra copy number in CASPR5. The supplementary investigation on more 43 sterile men showed that there are extra copy number in GLUT3 of 5 patients and missed copy number in CASPR5 of one patient. The frequency of copy number variation in GLUT3 and CASPR5 in general population of reproductive and sterile men are about 5 and 0.002 %, respectively, while in this study they are about 16 and 4 %, respectively [47]. It should be noted that GLUT3 is a protein which cause to transmission of glucose from plasmatic membrane in mammals. This is named as neuron transporter due to its exclusive role in neuron cells. The role of GLUT3 in cells which have need to glucose, such as sperm also studied. The production of CASPR5 is belonged to neuroxin family which some of its members act as cohesion cell molecules and receptor in nervous system of vertebrates.

Mutation in NR5A1: in cooperation between Pastor Institute of Paris and children health institute of London in a study of 315 men, it found that mutation in NR5A1 can be an unexplained factor of infertility in men. This gene codes a protein that is of an important role in genesis of sexual organ [46].

SRPK: the researchers of Edinburgh University with study of hundreds of sterile vinegar houseflies shown that the lack of SRPK performance can be lead to chromosomal unaggregation and hence, infertility and decrease in level of productivity. This phenomenon is also seen in mammals and human cells [45].

11 CONCLUSION

With continuing progress of different aspects of life sciences, researchers are able to understand the interactions of genetic, environmental and descent factors in infertility. Although there are still many works to accurately complete the effective genetic factors in infertility, recent studies are signified the need to accurate transmission of epigenetic information along with genetic factors to correct pregnancy. More studies in neglected fields of infertility such as mitochondrion genetics and miRNA may be caused to finding other regulatory factors in the gametogenesis process. Using the whole of these information, clinics will be more capable to infertility remediation and they will be able to make better decision in use of assisted reproductive tools.

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