ARCHIVES OF BIOINFORMATICS AND COMPUTATIONAL BIOLOGY
Jan-Jun 2024, VOL. 1, ISSUE 1, pp. 1-2
https://doi.org/10.61577/abcb.2024.100001

RESEAPRO JOURNALS

EDITORIAL

OPEN ACCESS

Role of bioinformatics in the diagnosis of female infertility

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ARTICLE HISTORY
Received 29 August 2023; Revised 12 September 2023; Accepted 19 September 2023

Introduction

Infertility has been increased globally as a common health problem which affects 18% of couples at the reproductive stage [1]. Abnormalities in anatomical, physiological, genetic, endocrine, and immunological aspects of the therapeutic system can affect a woman's fertility rate [2], while the major female infertility influencing factors include age, onset of puberty, developmental programming, diseases like endometriosis, polycystic ovarian syndrome (PCOS), environment, and lifestyle [3]. However, 10% of infertility cases still have unexplained reasons and remain undiagnosed [1,4]. In spite of reproductive pathology, many exceptional, poorly understood difficulties have been seen in women to conceive babies. In these cases, the connection of genetic elements may play a major character in the clinical infertility phenotypes, including dysregulation of meiotic processes such as defects or abnormalities in aneuploidy, gonadal differentiation, ovary development, folliculogenesis, oocyte maturation, and gamete recognition or early embryogenesis [5], whereas the non-meiotic female infertility represents altered ovarian reserve and/or ovarian function, defective follicle activation or growth and syndromic associated infertility.

In spite of reproductive pathology, many exceptional, poorly understood difficulties have been seen in women to conceive babies. In these cases, the connection of genetic elements may play a major character in the clinical infertility phenotypes, including dysregulation of meiotic processes such as defects or abnormalities in aneuploidy, gonadal differentiation, ovary development, folliculogenesis, oocyte maturation, and gamete recognition or early embryogenesis [5], whereas the non-meiotic female infertility represents altered ovarian reserve and/or ovarian function, defective follicle activation or growth and syndromic associated infertility. Dysregulation of DNA damage or repair has also been added to the causes list of female infertility [6]. Understanding the mysterious genetic relationship of female infertility may be the key to unlocking the origins of aneuploidy [6]. However, genomic approaches like next-generation sequencing (NGS) have been implemented to identify the association between clinical infertility phenotypes and maternal gene variants, which reported the involvement of some genes like *SYCP3, SYCE1, TRIP13, PSMC3IP, DMC1, MCM8, MCM9, STAG3, PATL2, TUBB8, CEP120, AURKB, AURKC, WEE2,* etc. in the dysregulation of meiotic process, oocyte maturation, zygotic cleavage failure, embryo development arrest, etc. and leads to female infertility [6,7].

In the field of reproductive medicine, the identification of causative pathogenic/ likely pathogenic genetic variants can improve the IVF cycle outcomes and enhance the knowledge of better patient counseling through effective advanced diagnosis processes of unexplained infertility [3]. Genetic screening is the newly approved and widely used NGS technology to discover pathogenic genetic mutations in patient cohorts and has been implemented in reproductive centers [7]. The applications of genome-wide association studies (GWAS) have heightened the understanding of genetic architecture, including epidemiological observations, pathogenic gene mutations, pathways, etc., of female reproduction and associated infertility through high throughput sequencing methods, especially metagenomic, whole genome sequencing (WGS) and whole exome sequencing (WES) for genetic counseling/testing [3].

Metagenomics

The study of metagenomics improves the knowledge of microbial diversity like vaginal microbial diversity associated with human health and disease like infertility. Metagenomic profiling can help understand the reproductive tract's microbiome and provide more precise diagnostic criteria [4].

Women with abnormal bacterial colonization in the vaginal cavity or bacterial vaginosis have the capability of causing an increased risk of pathological conditions like infertility, pregnancy loss, sexually transmitted diseases, failure of IVF therapy, etc. According to the Human Microbiome Project, 9% of the whole human microbiota is present in the female reproductive organ. Gardnerella vaginalis grows in the reproductive tract during the reproductive age of women and is the common cause of bacterial vaginosis, infertility, endometriosis, etc [4]. Along with Gardnerella, some other bacterial communities like Lactobacilli, Prevotella, Bifidobacterium, Atopobium, Megasphaera, Sneathia, and Anaerococcus etc, have been involved in different reproduction phases like gamete formation, fertilization, pregnancy establishment and maintenance [8].

Incorporation of more effective and less costly NGS insights in the human microbial research has been a great approach to finding the associated infectious disease and infertility causal high-risk microbial communities in the human being's semen, vagina, and urethra, which can help to establish a healthy female reproductive system microbiome [4]. The infertility-related microbial community needs to be analyzed through advanced NGS sequencing technologies like 16S rDNA sequencing, which has revealed the abundance of anaerobic bacterial populations in females with bacterial vaginosis [4].

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Whole genome sequencing

The identification of unrecognized genetic abnormalities, including single nucleotide variants, copy number variations, single gene mutations, structural variants, etc., have been simplified and easily explained by applying WES simultaneously. WGS has been used to analyze the genetic association or involvement in embryonic loss, fetal death, and stillbirth of recurrent unexplained pregnancy loss in many families [9]. Personalized therapeutic treatment insights can be provided to infertile females according to the individual's genotype, along with novel biomarkers analyzed through WGS [10]. As per the reported study, WGS has also been used for genetic disease screening, denovo mutations, and transmitted variants identification in preimplantation embryos [11].

Whole exome sequencing

Whole exome sequencing (WES) is an advanced and cost-effective sequencing method than WGS [7] of the NGS era, which targets the novel and unknown etiology of causative genetic mutations in the protein-coding regions of genes to provide an appropriate and safe diagnostic rate [12,13]. The implementation of WES has shown genetic consequences of various important causes of female infertility, which happen without any obvious risk factors such as diminished ovarian reserve (DOR), endometriosis, premature ovarian insufficiency (POI), failed IVF, etc. The unknown and/or poorly understood genetic etiology, associated candidate gene variants, genetic association of DOR, failed IVF patients, endometriosis, POI or early loss of ovarian function, etc., have been identified and understood during the reproductive age or young age of reproduction of women by the advanced NGS sequencing method like WES [12-16]. There have been many genes involved in ovarian development and function, including gonadogenesis (*LRR4, PRDM1*), meiosis (*CPEB1, KASH5, MCMDC2, MEIOSIN, NUP43, RFWD3, SHOC1, SLX4, and STRA8*) and folliculogenesis and ovulation (*ALOX12, BMP6, H1-8, HMMR, HSD17B1, MST1R, PPM1B, ZAR1, ZP3*), etc. [16]. This targeted genetic analysis of WES may improve the potential insights of genetic screening to be used as a candidate diagnostic approach in female infertility.

Conclusions

The discovery of causative genes, associated variants, and common genetic risk factors could help to interpret the basic relationship and actual sources in the regulation of reproductive lifespan, fertility, and related traits. The NGS allows essential interrogation of diverse genetics of reproductive biology, especially female infertility, through advanced bioinformatics tools and algorithms. The increased role of NGS in the field of reproductive clinical genetics can make genetic diagnostics a usual part of medical diagnosis.

Disclosure statement

No potential conflict of interest was reported by the authors.

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https://doi.org/10.61577/abcb.2024.100001