Original Article

MID: a specific database and online platform for male infertility

Vickram A.S[1], Anbarasu K[2*]

[1]Department of Biotechnology, Saveetha School of Engineering, SIMATS, Thandalam, Chennai, Tamil Nadu, 602105, India
[2*]Department of Bioinformatics, Saveetha School of Engineering, SIMATS, Thandalam, Chennai, Tamil Nadu, 602105, India

Abstract

In developing countries, especially like India and China, people have a strong mindset and fully emphasis on child-bearing. Currently, human male infertility percentage is increasing drastically. Infertility is not a disease and it is treated as a condition with physiological, medical implications. Diagnosis of idiopathic males is difficult than any other category and it is very hard to find out the reasons for infertility. There are no existing databases to study easily about the various genes associated with male infertility. To elucidate the basic knowledge about semen and its composition, various causes, microelements and its role, treatments and genetic causes, as well as to retrieve the basics about the genes and proteins involved with male infertility. MID (Male Infertility Database) was implemented as a web interface using PHP scripting language at backend and HTML, CSS & JavaScript (jQuery Framework) were used at the frontend/client side. The data were collected from the bioinformatics common database like PDB, UniProt and Entrez databases. These data were appropriately filtered using specialized systematic literature and our previous knowledge on male infertility. The current information about male infertility and updated literature were retrieved from Science direct, Science alert, Goggle Scholar, PubMed and PubMed central. MID provides three modules (“Search”, “Browse” and “Statistics”) that enable searches, acquisition of contents and access to all updated statistical data. The direct links to matching external databases are also available. The database will be updated at interval corresponding to genes and protein related to male infertility. The compilation of all general information, sequence and structural data of all genes and protein in one platform is highly useful for current experts and budding researchers in human reproduction and male infertility area.

Key words: Male Infertility Database (MID), Semen Quality, Fertility Associated Proteins, Semen Parameters.

DOI:10.47750/pnr.2022.13.S04.173

INTRODUCTION

Human male infertility becomes a major problem in the evaluation of infertile couple and it is not done an impact before 50 years **(Kumar and Singh, 2015)**. But now the male infertility is treated as a predominant problem and it affects the life quality of the married couple in the developing countries **(Agarwal et al., 2015)**. There are reports that, the quality of the semen measured by number of sperm cells, active motile cells, morphologically good motile cells has been declined by almost 50% between the years 1950 to 2010 **(Johnson et al., 2015)**. Even the World health organization has reduced its own standard parameter values to access the semen quality in their new editions **(Esteves, 2014)**. This shows that overall there is a decline the semen quality throughout the world and especially in Western countries it is high **(Virtanen et al., 2017)**. The increase in prevalence is due exposure by number of environmental factors such as exposure to heavy metals **(Zafar et al., 2015)**, drugs **(Calogero et al., 2017)**, adulterated foods **(Wahab and Sultana, 2017)**, testicles heat exposure **(Durairajanayagam et al., 2015)** and lifestyle modifications **(Wright et al., 2014)**. These environmental factors also disturbs the genetic material present in sperm cells and causes the alterations and modifications in DNA structure and leads to alter the function of the specific protein encoded by the specific gene **(Carrell et al., 2016)**. Genomics and proteomics studies on human male infertility are the most advanced study that enables some proper idea for the diagnosis of human male infertility **(Ayaz et al., 2018)**. With the advance in genomic, proteomic, immunomic techniques, it is now very easy for the diagnosis and prognosis of human male infertility. As spermatogenesis is a complex process, as expected 2300 genes were involved in regulating the spermatogenesis from the initial step until the intermediate step of maturation of sperm cells to the final step in reaching female reproductive tract for fusion **(Miyamoto et al., 2015)**.

Integrative omics approach like epigenomics, genomics, and proteomics; it is very easier now to elucidate the important genes associated with human male infertility. Idiopathic type of human male infertility cannot be diagnosed by using the standard semen parameters, because idiopathic males were found with normal values for all the parameters, and some unknown factors could be the reason for that category **(Jodar et al., 2015)**. In those cases, the integrative omics approach with big data enumerates some substantial reasons for the cause. Measure of spermatozoa RNA may lead to know the paternal contribution towards giving live birth in a timed intercourse. RNA's in spermatozoa sometimes lack in their number and it could be the reasons for the male infertility in idiopathic males **(Pereira et al., 2016)**. There are many number of assumptions, important genes involved in male infertility, but there exist no database for human male infertility. So, we decided to create a male infertility database (MID) that could have very basics about the semen quality **(Gaskins et al., 2015)**, semen composition **(Byrne et al., 2017)**, the role of Zn towards male infertility **(Fallah et al., 2018)**, glucosidase and fructose in seminal fluid **(Huyen et al., 2018)**, the cause of human male infertility by environmental factors, smoking **(Sharma et al., 2016)**, and consumption of heavy metals, as a genetic cause about robertsonian translocations **(Kirkpatrick et al., 2015)** were discussed in this database.

More over important genes associated with human male infertility were retrieved from Uniprot and made to table to represent the same in the database. By this, one can easily retrieve the basic data about the protein that might involve with human male infertility by simply browsing the Uniprot ID of the protein. This database will be helpful for the researchers working with reproduction, male fertility and infertility and it will provide the basic data. The gene and protein sequences related to male infertility were retrieved from Uniprot database (Table 1).

Materials and Methods

The current database has been developed and configured usingX/WAMP server. WampServer is a Windows based web development environment. It allows us to create web applications with Apache2, PHP and a MySQL database. PhpMyAdmin, is web portal that is easy way for the admin/users to manage the database as well as the backend server settings. Most of the separation logic is written at the UI side using jQuery framework. Since our application is mostly a Content management site so keeping the logic at UI helps run our code seamless without much server-side rendering which makes application loading incredibly fast. We have separate pages for each of the type Gene Name/Protein type that gets loaded based on the search field. Searching is done using jQuery based on keypress event in input search field.

Results and Discussion

Bioinformatics, an advance field using Information technology and programming to create public available database by store, organize and analyze the vast and critical biological data in the form of information, features, sequences and structures of DNA, RNA and proteins **(Ragunath et al., 2009).** Mainly**,** biological database is actively used in two ways i) collection of biological data in a form that can be easily accessed by user ii) available to multi user (Nishant et al., 2011). The overall database scheme was shown in Figure 1. The homepage of MID contains introduction about male infertility and various icons for the sublink of the database shown in Figure 2. The general introduction of male fertility further explained in various sub links like human semen, HSP proteins, Seminal functions, Zinc and its importance, etc shown in Figure 3. The critical feature of the database was gene and protein involved in male infertility was browse and search option that can gene key information for the user shown in Figure 4. Future research on critical proteins and genes may lead to annotation of various mechanism and treatment of male infertility worldwide. The result page of protein search results in FASTA format that can leads to bioinformatics research in male infertility shown in Figure 5 .

Conclusion and future update

To best of our knowledge, MID is the first comprehensive database and online platform for the genes and proteins involved in male infertility. The main goal of the database was the researchers should able to access a free web interface with highly curated information and represented in coherent manner. We assure this platform will help researchers in understanding the genes and proteins directly and indirectly involved in cause of male infertility. In future, we will update with structural information and further novel information.

Disclosure statement

The authors declare no conflict of interest.

References

1. Agarwal A, Mulgund A, Hamada A, Chyatte MR. 2015. A unique view on male infertility around the globe. Reprod Biol Endocrinol. 13(1):37.
2. Ayaz A, Kothandaraman N, Henkel R, Sikka SC. 2018. Impact of environmental factors on the genomics and proteomics landscapes of male infertility. Bioenvironmental Issues Affecting Men's Reproductive and Sexual Health. Chapter 21. 335-353.
3. Byrne CJ, Fair S, English AM, Holden SA, Dick JR, Lonergan P, Kenny DA. 2017. Dietary polyunsaturated fatty acid supplementation of young post-pubertal dairy bulls alters the fatty acid composition of seminal plasma and spermatozoa but has no effect on semen volume or sperm quality. Theriogenology. 90:289-300.
4. Calogero AE, Condorelli RA, Russo GI, La Vignera S. 2017. Conservative nonhormonal options for the treatment of male infertility: antibiotics, anti-inflammatory drugs, and antioxidants. Biomed Res Int.. 4650182.
5. Carrell DT, Aston KI, Oliva R, Emery BR, De Jonge CJ. 2016. The “omics” of human male infertility: integrating big data in a systems biology approach. Cell Tissue Res. 363(1):295-312.
6. Durairajanayagam D, Agarwal A, Ong C. 2015. Causes, effects and molecular mechanisms of testicular heat stress. Reprod Biomed Online. 30(1):14-27.
7. Esteves SC. 2014. Clinical relevance of routine semen analysis and controversies surrounding the 2010 World Health Organization criteria for semen examination. International Braz J Urol. 40(4):433-53.
8. Fallah A, Mohammad-Hasani A, Colagar AH. 2018. Zinc is an Essential Element for Male Fertility: A Review of Zn Roles in Men’s Health, Germination, Sperm Quality, and Fertilization. J Reprod Infertil. 19(2): 69–81.
9. Huyen VT, Trang NT, Anh LT, Giang VT, Mai BB, Tung NX. 2012. The Impact of Seminal Zinc and Fructose Concentration on Human Sperm Characteristic. Journal of Medical and Biomedical Sciences. 1(1), 14-20.
10. Gaskins AJ, Mendiola J, Afeiche M, Jørgensen N, Swan SH, Chavarro JE. 2015. Physical activity and television watching in relation to semen quality in young men. Br J Sports Med. 49(4):265-70.
11. Johnson SL, Dunleavy J, Gemmell NJ, Nakagawa S. 2015. Consistent age-dependent declines in human semen quality: a systematic review and meta-analysis. Ageing Res Rev. 19:22-33.
12. Jodar M, Sendler E, Moskovtsev SI, Librach CL, Goodrich R, Swanson S, Hauser R, Diamond MP, Krawetz SA. 2015. Absence of sperm RNA elements correlates with idiopathic male infertility. Sci Transl Med. 7(295):295re6-.
13. Kumar N, Singh AK. 2015. Trends of male factor infertility, an important cause of infertility: A review of literature. J Hum Reprod Sci. 8(4):191.
14. Miyamoto T, Minase G, Okabe K, Ueda H, Sengoku K. 2015. Male infertility and its genetic causes. J Obstet Gynaecol Re. 41(10):1501-5.
15. Nishant T, Arun Kumar, Sathish Kumar D, Vijaya Shanti B. 2011. Biological Databases- Integration of Life Science Data. J Comput Sci Syst Biol. 4: 87-92.
16. Pereira N, Cozzubbo T, Neri QV, Lekovich JP, Palermo GD, Rosenwaks Z. 2016. Identifying the epigenetic basis of idiopathic infertility using next-generation sequencing of spermatozoal RNAs. Fertil Steril. 105(2):e33-4.
17. Ragunath PK, Venkatesan P, Ravimohan R. 2009. New Cur-riculum Design Model for Bioinformatics Postgraduate program using Systems Biology Approach. J Comput Sci Syst Biol. 2: 300-305.
18. Sharma R, Harlev A, Agarwal A, Esteves SC. 2016. Cigarette smoking and semen quality: a new meta-analysis examining the effect of the 2010 World Health Organization laboratory methods for the examination of human semen. Eur Urol. 70(4):635-45.
19. Virtanen HE, Jørgensen N, Toppari J. 2017. Semen quality in the 21 st century. Nat Rev Urol. 14(2):120.
20. Wahab N, Sultana F. 2017. Adulterated Food Induced Female Infertility In Bangladesh: A Hindrance Towards Achieving Sustainable Development Goal (SDGS) Nazia Wahab. Journal of Asian and African Social Science and Humanities. 3(3):12-28.
21. Wright C, Milne S, Leeson H. 2014. Sperm DNA damage caused by oxidative stress: modifiable clinical, lifestyle and nutritional factors in male infertility. Reproductive biomedicine online. 28(6):684-703.
22. Zafar A, Eqani SA, Bostan N, Cincinelli A, Tahir F, Shah ST, Hussain A, Alamdar A, Huang Q, Peng S, Shen H. 2015. Toxic metals signature in the human seminal plasma of Pakistani population and their potential role in male infertility. Environmental geochemistry and health. 37(3):515-27.

Table 1: Important proteins involved as a cause of human male infertility

Sl. No.	**Uniprot ID**	**Gene Name**	**Protein Name**
1	Q99497	PARK7	Protein deglycase DJ-1
2	Q96RN1	SLC26A8	Testis anion transporter 1
3	P31213	SRD5A2	3-oxo-5-alpha-steroid 4-dehydrogenase 2
4	P07333	CSF1R	Macrophage colony-stimulating factor 1 receptor
5	P09603	CSF1	Macrophage colony-stimulating factor 1
6	O60266	ADCY3	Adenylate cyclase type 3
7	Q8NEC5	CATSPER1	Cation channel sperm-associated protein 1

8	O95925	EPPIN	Eppin
9	Q8NEP3	DNAAF1	Dynein assembly factor 1, axonemal
10	Q8IWB6	TEX14	Inactive serine/threonine-protein kinase TEX14
11	Q8TE73	DNAH5	Dynein heavy chain 5, axonemal
12	P36969	GPX4	Phospholipid hydroperoxide glutathione peroxidase, mitochondrial
13	Q4G0P3	HYDIN	Hydrocephalus-inducing protein homolog
14	Q8IZP9	ADGRG2	Adhesion G-protein coupled receptor G2
15	Q86X45	LRRC6	Protein tilB homolog
16	O14556	GAPDHS	Glyceraldehyde-3-phosphate dehydrogenase, testis-specific
17	Q96DT5	DNAH11	Dynein heavy chain 11, axonemal
18	Q4G0X9	CCDC40	Coiled-coil domain-containing protein 40
19	O75344	FKBP6	Inactive peptidyl-prolyl cis-trans isomerase FKBP6
20	Q9UFE4	CCDC39	Coiled-coil domain-containing protein 39
21	Q9BXA6	TSSK6	Testis-specific serine/threonine-protein kinase 6
22	A0AVT1	UBA6	Ubiquitin-like modifier-activating enzyme 6
23	Q9NR20	DYRK4	Dual specificity tyrosine-phosphorylation-regulated kinase 4
24	Q8N427	NME8	Thioredoxin domain-containing protein 3
25	Q9UI46	DNAI1	Dynein intermediate chain 1, axonemal
26	Q8IW40	CCDC103	Coiled-coil domain-containing protein 103
27	Q9GZS0	DNAI2	Dynein intermediate chain 2, axonemal
28	Q86Y56	DNAAF5	Dynein assembly factor 5, axonemal
29	Q5TD94	RSPH4A	Radial spoke head protein 4 homolog A
30	O14967	CLGN	Calmegin
31	Q9BW62	KATNAL1	Katanin p60 ATPase-containing subunit A-like 1
32	Q9NVR5	DNAAF2	Protein kintoun
33	Q75WM6	H1FNT	Testis-specific H1 histone
34	Q9H1X1	RSPH9	Radial spoke head protein 9 homolog
35	Q8N9W5	DNAAF3	Dynein assembly factor 3, axonemal

36	Q9UBK7	RABL2A	Rab-like protein 2A
37	Q4LDG9	DNAL1	Dynein light chain 1, axonemal
38	Q6JVE9	LCN8	Epididymal-specific lipocalin-8
39	Q5GAN6	RNASE10	Inactive ribonuclease-like protein 10
40	Q6JVE6	LCN10	Epididymal-specific lipocalin-10
41	Q6JVE5	LCN12	Epididymal-specific lipocalin-12
42	Q9UNT1	RABL2B	Rab-like protein 2B
43	P62502	LCN6	Epididymal-specific lipocalin-6

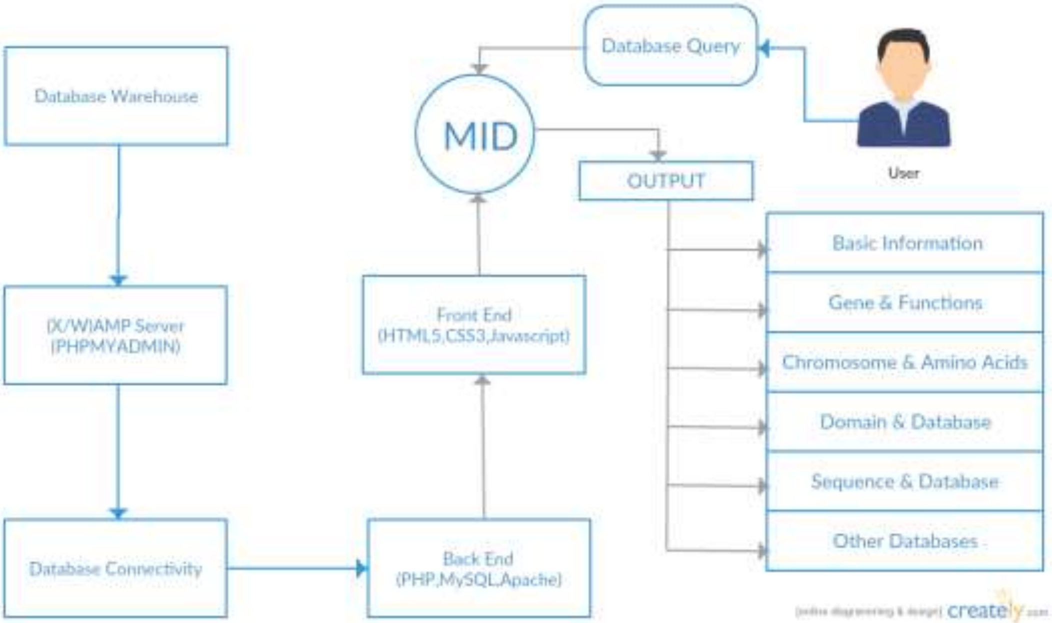

Figure 1: Flow chart of MID scheme.

Male infertility can be distinct as the inability to fulfil pregnancy subsequent to a reasonable time of sexualintercourse without contraceptive measures taken. Male infertility is accountable for more than 40 % of infertility in the world. No precise reason can be found in about 10%-15% of infertile couples. Human male infertility is found to be the stressful issue to couple as well as their families. Under these circumstances, World Health Organization (WHO, 2010) has announced human male infertility as the global problem. WHO defines infertility as biological inability of a person to contribute to conception. Approximately 10-15 of every 100 couples reported to be incapable to produce offspring. Among these, it is estimated that in about 30-40% of these cases, defects were identified among the males. Almost 30 to 50% of infertility in the couples is due to male factor and it is due to the deficiency in the sperm quality and quantity. Sperm quality represents the total number of sperm present, total motile sperms, total rapid progressive motile sperms and total number of morphologically normal sperms present in an ejaculate. The quantity represents the total volume of the ejaculate.

Figure 2: Home page of MID.

HUMAN MALE INFERTILITY

Male infertility can be distinct as the inability to fulfil pregnancy subsequent to a reasonable time of sexual intercourse without contraceptive measures taken. Male infertility is accountable for more than 40 % of infertility in the world. No precise reason can be found in about 10%-15% of infertile couples. Human male infertility is found to be the stressful issue to couple as well as their families. Under these circumstances, World Health Organization (WHO, 2010) has announced human male infertility as the global problem. WHO defines infertility as biological inability of a person to contribute to conception. Approximately 10-15 of every 100 couples reported to be incapable to produce offspring. Among these, it is estimated that in about 30-40% of these cases, defects were identified among the males. Almost 30 to 50% of infertility in the couples is due to male factor and it is due to the deficiency in the sperm quality and quantity. Sperm quality represents the total number of sperm present, total motile sperms, total rapid progressive motile sperms and total number of morphologically normal sperms present in an ejaculate. The quantity represents the total volume of the ejaculate.

Figure 3: Result page of general introduction on male infertility in MID.

Figure 4: Home page of protein search option in MID.

Figure 5: Results of the protein search for the query input in MID.