Journal of Assisted Reproduction and Genetics (2020) 37:451–458
https://doi.org/10.1007/s10815-019-01660-1

GENETICS

The second mutation of *SYCE1* gene associated with autosomal recessive nonobstructive azoospermia

Mahdieh Pashaei[1] · Mohammad Masoud Rahimi Bidgoli[1] · Davood Zare-Abdollahi[1] · Hossein Najmabadi[1] · Ramona Haji-Seyed-Javadi[2] · Farzad Fatehi[3] · Afagh Alavi[1]

Received: 9 September 2019 / Accepted: 12 December 2019 / Published online: 8 January 2020

Abstract

Purpose It is estimated that 40–50% of infertility among human couples is due to male infertility. Azoospermia is estimated to occur in 1% of all men and to be the cause of 10–20% of male infertility. Genetic defects, including single gene effects, maybe cause of azoospermia in 20–30% of affected males. Here, we aim to identify the genetic cause of azoospermia in a man who is also affected by hereditary spastic paraplegia.

Methods The proband was subjected to whole-exome sequencing, followed by a comprehensive in silico analysis to identify the azoospermia causative gene.

Results A novel splice site mutation c.375-2A > G in *SYCE1* that is thought to be the cause of azoospermia was identified. This variant co-segregated with azoospermia status in the family that has three additional affected males.

Conclusion *SYCE1* gene encodes synaptonemal complex (SC) central element 1 protein which contributes to the formation of the synaptonemal complex during meiosis. Syce1 null male and female mice have been shown to be infertile. There have only been two reports on the effects of *SYCE1* mutations in humans; it was shown as the cause of primary ovarian failure (POI) in one and as the cause of nonobstructive azoospermia (NOA) in another. We suggest that the mutation 375-2A > G, which affects the acceptor splice site within intron 6 of *SYCE1*, is the likely cause of azoospermia and subsequent infertility in the family studied. The finding constitutes the third report of *SYCE1*mutations that affect infertility in humans and further supports its contribution to this condition.

Keywords Azoospermia · Infertility · Synaptonemal complex · *SYCE1* gene · Whole-exome sequencing (WES)

Introduction

Infertility is the inability of a couple to become pregnant naturally after 1 year of regular and unprotected intercourse, based on criteria of International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) [1]. Infertility affects approximately 10–15% of couples worldwide [2], and male infertility is responsible for 40–50% of all cases [3, 4]. Among male infertile cases, more than half and 10–20% of affected individuals are idiopathic and azoospermic, respectively [5, 6]. Azoospermia (absence of sperm in the semen) is categorized into two subgroups, obstructive or nonobstructive (NOA) forms [7]. Almost 60% of azoospermic cases are NOA which is a consequence of defective spermatogenesis (lack of sperm production) and can cause by primary or secondary testicular failure [8]. While in obstructive azoospermia, sperms are produced but unable to reach the emitted semen [8].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10815-019-01660-1) contains supplementary material, which is available to authorized users.

✉ Farzad Fatehi
f-fatehi@tums.ac.ir

✉ Afagh Alavi
afaghalavi@gmail.com; af.alavi@uswr.ac.ir

[1] Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

[2] Department of Radiation Oncology, Winship Cancer Institute of Emory University, Emory University School of Medicine, Atlanta, GA 30322, USA

[3] Department of Neurology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

At least 15% of infertile male cases and 21–29% of all azoospermic cases results from genetic defects [9–12]. However, most of the genetic factors affecting azoospermia still remain unknown.

Mutations in the *CFTR* gene, as well as some chromosomal abnormalities such as aneuploidies and microdeletions of chromosome Y, are among the most relevant genetic causes of azoospermia [8, 9, 13, 14]. Copy-number variations (CNVs) and mutations in several genes have also been detected as the other genetic causes of azoospermia [15]. It has been previously reported that mutations in several genes including *USP26*, *DAZL*, *MTHFR*, *INSL3*, *AR*, *StAR*, *SYCP3*, *SYCP2*, *SYCE1*, *XRCC2*, and *DMC1* affect spermatogenesis and cause nonobstructive azoospermia [8, 11, 16–19]. Some of these genes – *SYCP3*, *SYCP2*, and *SYCE1* – encode major components of the synaptonemal complex (SC) which plays a critical role in homologous chromosome synapsis formation during the meiotic division, gametogenesis [8, 16, 17]. Therefore, it has been suggested that human infertility can be related to the disruption of the SC. Confirming this finding, so far, mutations in the *SYCP3*, *SYCP2*, and *SYCE1* genes, encoding synaptonemal complex protein 3 and 2 and synaptonemal complex central element protein 1, respectively, have been reported as the rare causes of male infertility. Most of the *SYCP3* and *SYCP2* mutations are heterozygous, which is consistent with the autosomal dominant mode of inheritance, whereas *SYCE1* mutations are homozygous and have shown a recessive pattern of inheritance [8, 16, 17]. Mutations in the *SYCE1* gene have only been reported twice in humans, a nonsense homozygous mutation which was shown as cause of primary ovarian insufficiency (POI) in two sisters of an Israeli Arab consanguineous family and a splice site homozygous mutation as cause of nonobstructive azoospermia (NOA) in two brothers of a consanguineous Iranian-Jewish family [8, 20].

Here, we report the clinical evaluation and results of genetic analysis of the second NOA family originating from Iran with a novel mutation in *SYCE1*.

Subjects and methods

This research was performed in accordance with the Declaration of Helsinki and the approval of the ethics board of the University of Social Welfare and Rehabilitation Sciences in Iran. All patients and family members were informed of the nature of research, and the consent forms were signed.

Subjects

An Iranian patient presenting with azoospermia (proband; AZO-III13), born to consanguineous parents, was referred to our lab for genetic analysis (Fig. 1). There were three other affected individuals (AZO-II2, AZO-II3, and AZO-III15) in the family. The mode of inheritance of azoospermia in this family (AZO-100) was consistent with the autosomal recessive pattern, as four affected individuals were born to unaffected consanguineous parents. All affected and unaffected family members of the proband were informed and recruited when available.

Proband: AZO-III13

AZO-III-13 was a 37-year-old man with a history of weakness and spasticity of lower limbs for more than 15 years (started at age 22). The deep tendon reflexes in lower limbs were 4+ and in upper limbs were 2+ with bilateral upward plantar reflexes and normal sensory exam. On brain and spinal cord magnetic resonance imaging (MRI), he had increased signal intensity on T2-weighted images in corticospinal tracts in internal capsules and basis pontis. Serum B12, copper, and vitamin E were in the normal range, and the laboratory evaluation for HTLV1/II was negative. Considering negative findings for acquired causes, he was diagnosed with pure hereditary spastic paraplegia (HSP) by a neurologist (FF).

At the age of 25 years, he married his cousin (AZO-III14). After 4 years, they recognized that they had problems in achieving pregnancy. Given that the patient had two azoospermic uncles (AZO-II2, AZO-II3), he suspected azoospermia in himself. Clinical examinations demonstrated that the size of the testicles was approximately normal and there was no varicocele. He had no history of cryptorchidism, infections, genital trauma, and chemotherapy or radiation therapy. His endocrine measurement results, including levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, and prolactin, were all normal. He had a normal 46, XY karyotype, and no chromosome Y microdeletions were detected. Investigations on a biopsy from the patient's testes had been performed 8 years earlier, and the results were documented as nonobstructive azoospermia (NOA) in his medical records. Consistent with this, recent seminogram analysis showed no detectable sperms. With this background, in vitro fertilization (IVF) using donor sperms was performed for this couple.

Genetic analysis

Exome sequencing

DNA was isolated from peripheral blood according to the salting-out method. Exome sequencing was performed on the DNA of proband by an Illumina HiSeq 2500 platform (Illumina). Sequence alignment and variant calling were performed against human reference genome UCSC NCBI37/hg19. Preliminary filtering was done to identify all homozygous variations. Then nonfunctional variants that did not affect amino acid sequence or splicing were filtered out.

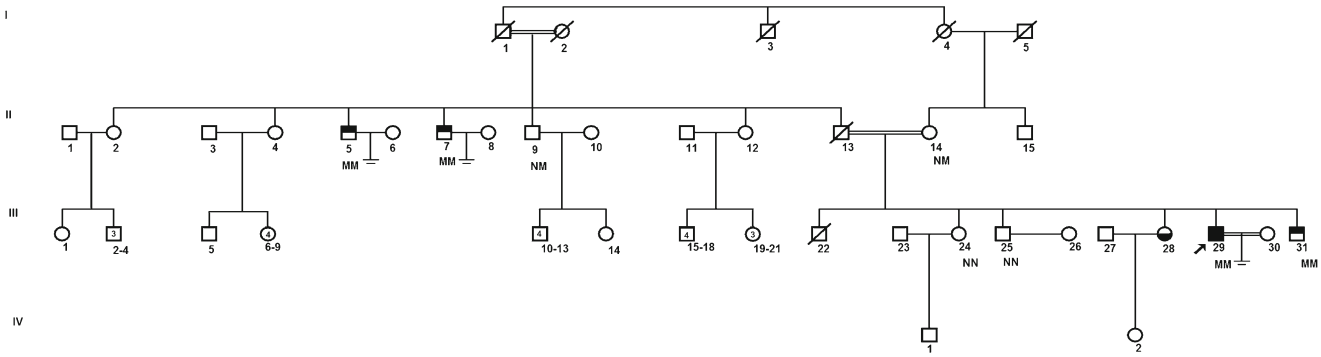

Fig. 1 Iranian azoospermia pedigree with mutation c.375-2A > G in the *SYCE1* gene recruited in this study. Genotypes of *SYCE1* are shown when individuals were assessed. Arrow shows proband. Unfilled circles and squares, not azoospermia affected; ▬ indicates azoospermia-affected; ◒ indicate HSP-affected; ■ indicate azoospermia and HSP-affected. Abbreviations: *HSP* hereditary spastic paraplegia; *M* mutated allele; *N* wild-type allele

Subsequently, SNPs with a reported minimal allele frequency (MAF) greater than 0.01 in the 1000 Genomes database (www.1000genomes.org), ENSEMBL (https://www.ensembl.org/index.html), the Trans-Omics for Precision Medicine program (https://www.nhlbiwgs.org/), the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/), the Exome Aggregation Consortium database (http://exac.broadinstitute.org/), the Genome Aggregation Database (http://genomad.broadinstitute.org/), the Greater Middle East Variome Project (http://igm.ucsd.edu/gme/), the Healthy Exomes database (https://www.alzforum.org/exomes/hex), the Al mena database (http://clingen.igib.res.in/almena/), and the Iranome database (http://iranome.com/), or observed in in-house exome data of 100 unrelated Iranians affected with non-infertility diseases, were removed. The remaining variants were examined to identify those within any of the known male infertility-causing or susceptibility genes (Supplementary Table S1).

In silico analysis

The potential pathological effects of the variants on the encoded proteins were predicted using in silico tools including SIFT (https://sift.bii.a-star.edu.sg/www/Extended_SIFT_chr_coords_submit.html), Polyphen2-HVAR (http://genetics.bwh.harvard.edu/pph2/), PROVEAN (http://provean.jcvi.org/seq_submit.php), SNAP (http://www.rostlab.org/services/SNAP/), LRT (http://www.genetics.wustl.edu/jflab/lrt_query.html), MutationTaster (http://www.mutationtaster.org/), Mutation Assessor (http://mutationassessor.org), FATHMM (http://fathmm.biocompute.org.uk/), GERP (http://mendel.stanford.edu/sidowlab/downloads/gerp/index.html), PhyloP (http://hgdownload.cse.ucsc.edu/goldenPath/hg18/phyloP44way), as well as combined annotation dependent depletion (CADD; http://cadd.gs.washington.edu) webserver.

Finally, the deleterious effects of variants on splicing were assessed using NNSPLICE 0.9 (http://www.fruitfly.org/seq_tools/splice.html) and Human Splicing Finder version 3.1 (HSF 3.1) (http://www.umd.be/HSF/HSF.shtml) software. NNSPLICE predicts novel splice sites based on known splice site sequences of the drosophila and human genomes [21]. HSF software evaluates potential splice sites strong sites by a designated consensus value (CV); strong splice sites are given CV values > 80, whereas less strong sites have a CV < 80 [22]. For assessment of effect of the identified *SYCE1*mutation on splicing, sequences spanning exons 6 through exon 8 (inclusive of introns 6 and 7) of the wild type and mutated gene were submitted to the software for prediction of donor and acceptor splice sites.

Screening of candidate variant

A candidate disease-causing variant c.375-2A > G in the *SYCE1* gene was amplified from DNA of the proband using the forward: 5-TTCAGCTCTTTGGGAAAACG-3 and reverse: 5-GTCTCTGCTCCACTGGGAAC-3 primers by polymerase chain reaction (PCR). The PCR products were sequenced using the Sanger method (BigDye kit and the Prism 3130 sequencer; Applied Biosystems, Foster City, CA, USA). Sequences were analyzed by CodonCode Aligner 8.0.2 software. Sequence variation was assessed by comparison with the reference sequence available at NCBI: NC_000010.10, NM_001143763.1, and NP_001137235.1 for the *SYCE1* gene. After confirmation of this variant in the proband, all available affected and unaffected individuals of the family were sequenced in order to co-segregate analysis of the variant with the disease status.

Results

Clinical evaluations showed that our proband and other affected members of this family suffered from NOA. Whole-exome sequencing was performed for AZO-III13, and 105,186

variants were found. Preliminary filtering of WES data based on the mentioned criteria reduced the number of candidate variants to 16 (Fig. S1 and supplementary Table S2). The genes in which these16 sequence variants were located were compared with known male infertility-causing or susceptibility genes (Supplementary Tables S1 and S2). *SYCE1* was the only gene associated with the observed variants that was included in the list of the known candidate male infertility genes. The genes associated with the remaining 15 sequence variations had no obvious role in infertility (Supplementary Tables S2). *SYCE1* is located on chromosome 10 (g.135,370,662), and the observed variant in *SYCE1* was c.375-2A > G. The variant was not found in any of the public exome databases including IRANOME which reports exome sequence data on 800 Iranians or in the 100 individual's in house exome data on Iranians. MutationTaster predicted that this variant is a "disease-causing." NNSPLICE and HSF software both predicted that this intronic variant would result in the disruption of the acceptor (3') splice site of intron 6 of the *SYCE1* gene (Supplementary Tables S3 and S4). NNSPLICE predicted that the acceptor site of intron 6 would ligate to the donor site of exon 8, resulting in deletion of exon 7 in the mature mRNA and in frame deletion of 30 amino acids in the encoded protein (Supplementary Tables S3 and Fig. 3). HSF predicted the same effect and also the possibility that the 3'end of exon 6 would ligate to c.394 which is nucleotide 20 within exon 7. The latter event is predicted to result in frameshift and premature translational termination (p.K126Sfs*8) and/or nonsense-mediated decay (NMD) of the mutated mRNA (Fig. 3). Unfortunately, the predicted effects on splicing using appropriate primers could not be confirmed as RT-PCR (reverse transcription–polymerase chain reaction) amplification of mutated *SYCE1* transcripts on RNA isolated from patient blood was unsuccessful (not shown). Amplification of control genes was achieved using the same RNA.

Finally, the variant was co-segregated with azoospermia in the family. All affected members carried homozygous mutations, whereas all unaffected individuals carried at least one normal allele, consistent with autosomal recessive inheritance (Fig. 1 and Fig. 2). Hence, we considered that homozygous variant c.375-2A > G in *SYCE1* would be an azoospermia-causing variant in this family.

Discussion

Synapsis of homologous chromosomes during meiosis division is necessary for the occurrence of crossing over and production of germ cells. Synaptonemal complex is a three-

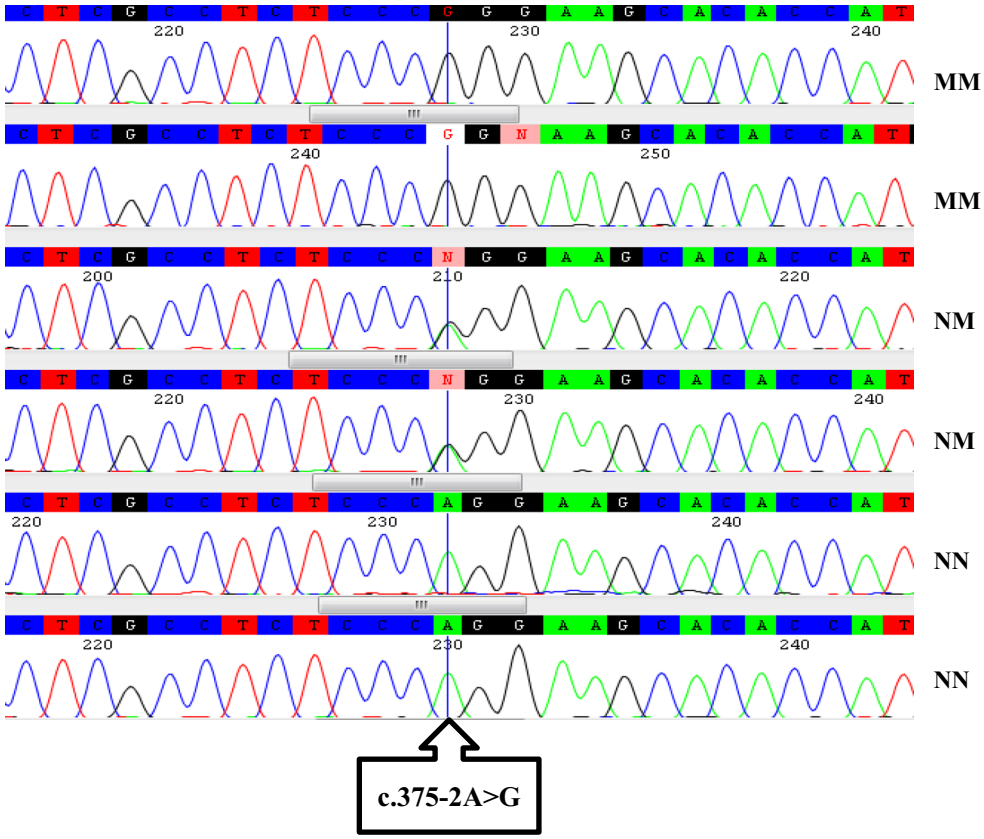

Fig. 2 Sequence chromatograms showing the homozygous and heterozygous c.375-2A > G mutation in the *SYCE1* gene and the wild-type sequence. *M* mutated allele; *N* wild-type allele

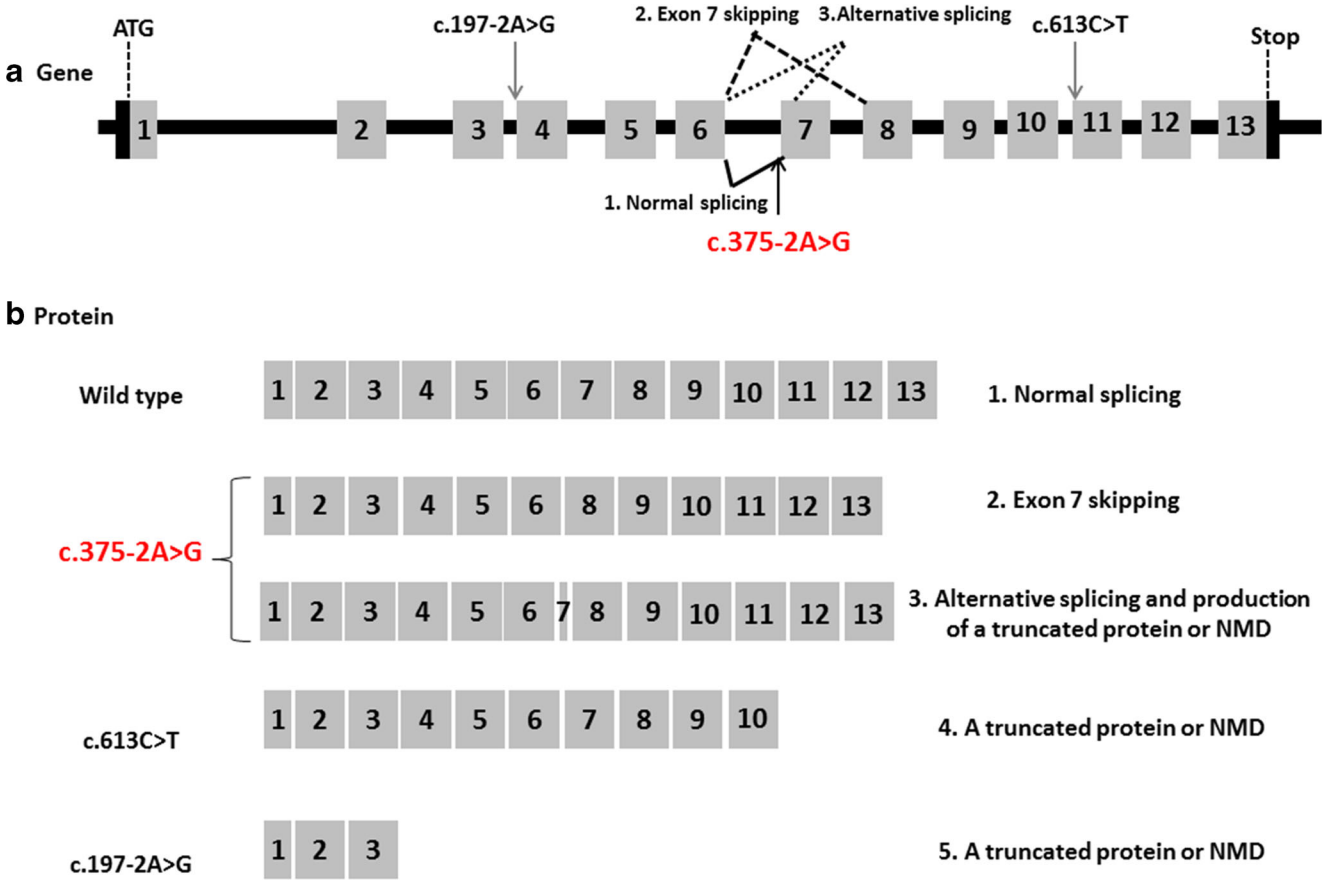

Fig. 3 Schematic view of the human *SYCE1* gene and its protein and three identified variants among nonobstructive azoospermia and primary ovarian insufficiency patients (including this study). (A): exons, noncoding exons. The number of each exon has been shown within the boxes. Gray arrows indicate positions of the two previously identified variants in the *SYCE1* gene. (1) Black lines "—" show normal splicing, (2 & 3) "– – – –" and "·····" indicate exon skipping and usage of an alternative 3′-splice site, respectively. The black arrow shows the situation of the *SYCE1* variant in this study. (B) Wild type [1] and three predicted mutant SYCE1 proteins up to now [2–5]. NNSPLICE and human splice finder software predict after occurance of c.375-2A > G mutation, the acceptor site of intron 6 would ligate to the donor site of exon 8, resulting in deletion of exon 7 in the mature mRNA and in frame deletion of 30 amino acids in the encoded protein [2]. HSF predict also the possibility that the 3'end of exon 6 would ligate to c.394 which is nucleotide 20 within exon 7. The event is resulted in frameshift and premature translational termination (p.K126Sfs*8) and/or nonsense-mediated decay (NMD) of the mutated mRNA [3]. c.613C > T is resulted in producing a premature stop codon (p.Gln205*) [4], and c.197–2A > G disrupts the splice sites introns 3 and subsequently premature translational termination and/or NMD of the mutated mRNA [5]

dimensional proteinaceous structure that facilitates these processes. The SC structure is constituted from a central region containing a central element (CE) and transverse filaments (TFs) and two lateral elements (LEs) which are located on both sides of the central region. The main components of this higher-order structure in mammalians include SYCP3, SYCP2 in the LEs, SYCP1 in the TFs, and SYCE1, SYCE2-TEX12, SYCE3, and SIX6OS1 in the CE [23–32]. SYCE1, SYCE3, and SIX6OS1 are synapsis initiation factors, whereas two remaining CE proteins (SYCE2-TEX12) are considered as synapsis elongation factors [24, 30, 33].

Previous studies, including expression analysis, SC encoding genes knockout mice, and biophysical and biochemical studies, have revealed the dynamics of the SC and investigated its role in fertility. Briefly, *Sycp2* and *Sycp3* knockout male mice ($Sycp3^{-/-}$ and $Sycp2^{-/-}$) were infertile, and recombination could not occur; consequently, they exhibited meiotic arrest and spermatogenesis was blocked. Whereas, *Sycp2* and *Sycp3* knockout female mice ($Sycp3^{-/-}$ and $Sycp2^{-/-}$) were fertile but presented a lower recombination rate and produced fewer offspring compared to wild-type mice. On the other hand, these mice were subfertile. Mutations in other SC genes (*SYCP1*, *SYCE1*, *SYCE2*, *SYCE3*, and *TEX12*) were also related to infertility in both male and female mice [26, 32–35].

In humans, mutations in *SYCP3* and *SYCP2* were identified in 2003 and 2019, respectively, in azoospermic individuals [16, 17]. While no infertile females carrying *SYCP2* mutations have been reported in humans up to now, but *SYCP3* mutations were also found in infertile females [36]. Mutation in the central region of coding genes was not reported up to 2014,

when de Vries et al. for the first time described two sisters affected with primary ovarian insufficiency (POI) type 12 who carried a nonsense homozygous mutation (c.613C > T; p.Gln205*) in the *SYCE1* gene. Thereafter, in 2015, Maor-Sagie et al. reported two azoospermic brothers (spermatogenic failure 15) with homozygous mutation c.197–2A > G in the *SYCE1* that would result in the disruption of 3′-splice site of intron 3. This mutation was the first report of the effect of *SYCE1* mutation in human male infertility. Both described families were originated from the Middle East (Israeli-Arab and Iranian-Jewish families, respectively) [8, 20].

Here we presented the second azoospermic family with a novel mutation c.375-2A > G in the *SYCE1* who has again originated from a Middle East country, Iran. This mutation is the third mutation of the *SYCE1* gene, which has been associated with human infertility. Although a low percentage of human infertility cases with mutations in the SC encoding genes have been found, but as Maor-Sagie et al. assumed, it seems the rate of mutations in *SYCE1* as well as in the other SC encoding genes is more than it appears [8, 20], especially *SYCE1* mutations among the Middle Eastern and Iranian infertile patients. Two out of three reported mutations in *SYCE1* have been identified among Iranian families so far [8, 20]. On the other hand, all *SYCE1* mutations in mice and humans, including the variation reported in the present study, show a recessive pattern of inheritance. Therefore, it is expectable that *SYCE1* mutations will be more common in populations with a high degree of consanguineous marriage such as the Middle Eastern countries.

Previous studies have shown that the C-terminal of the protein interacts with SYCE3, which contributes to its tether to the SC. Accordingly, if SYCE1 cannot be loaded to the SC, the SC assembly is blocked, and a meiotic arrest may occur [23, 37]. In addition to the importance of C-terminus of SYCE1 in the SC assembly, Dunne et al. in 2019 showed that amino acids 25–179 of SYCE1, located within the N-terminus, constitute core structure of the protein. This part of the protein has an α-helix that forms a coiled-coil structure and contributes to dimerization/self-association of SYCE1 in order to form an anti-parallel configuration or a rigid scaffold in SC [24]. Therefore, it seems both predicted effects of the reported variant c.375-2A > G in this study are notably deleterious. The mutated gene may encode a protein with a deletion of 30 amino acids (residues 126–155; p.K126_R155del) encoded by exon 7. The deleted amino acids constitute part of a critical coiled-coil region of the wild-type protein that promotes the dimerization of SYCE1 within SC [23, 24]. Alternatively or in addition to the described effect, the mutation may result in an altered splicing pattern in which a potential cryptic acceptor splice site in exon 7 is used. This would result in the deletion of 19 nucleotides in the mRNA product and the creation of a premature stop codon. This in turn would result in NMD or production of a truncated protein (p.K126Sfs*8) significantly shorter than the wild-type protein with 318 amino acids (Fig. 3). Ultimately, SC structure and function disruptions, meiotic arrest, abnormal germ cell production, and infertility may ensue.

Interestingly, among other reported *SYCE1* mutations, c.197–2A > G disrupts the splice sites of introns 3 and c.613C > T is resulted in producing a premature stop codon (p.Gln205*). On the other hand, both would also produce a truncated SYCE1 protein lacking a part of the C-terminus region or result in NMD (Fig. 3) [8, 20].

As mentioned above, azoospermia is a heterogeneous condition. It is assumed that more than 500 genes might be associated with this condition. For diseases presenting with genetic heterogeneity, identification of the causative gene by direct sequencing is a time-consuming and costly process. Whole-exome sequencing in a medical setting is generally used for gene discovery and also as a diagnostic powerful tool to elucidate the genetic etiology of heterogeneous disorders. Here, using the WES facility, we identified the causative gene in a large azoospermic family. Identification of novel genes and mutations helps further understanding of the genetic bases of the disease that would provide a better opportunity for early intervention, as well as discover direct potential targets for suitable future therapies.

In conclusion, we suggest that the rate of *SYCE1* mutations may be higher than it appears among Iran and the Middle Eastern countries and screening of these genes among large cohorts of infertile male and female patients from these populations is reasonable.

Acknowledgments We acknowledge the Iran National Institute for Medical Research Development (NIMAD; grant number 963846) and the University of Social Welfare and Rehabilitation Sciences for funding the research and thank the patients and their family members for participating in the study.

Authors' contributions Mahdieh Pashaei: tertiary analysis of exome sequencing data and contributed to writing of manuscript

Mohammad Masoud Rahimi Bidgoli: analysis of exome sequencing data, mutation screening of *SYCE1* in azoospermic proband, segregation analysis pertaining to azoospermia, and amplification of cDNA in order to analysis of splice site variant

Farzad Fatehi: clinical evaluations and editing of manuscript

Davood Zare-Abdollahi: karyotyping, RNA extraction, cDNA synthesis, and editing of manuscript

Hossein Najmabadi: advisor of MP

Ramona Haji-Seyed-Javadi: primary analysis of exome sequencing data

Afagh Alavi: designed and supervised the research and wrote the manuscript

Funding information National Institute for Medical Research Development (NIMAD) and the University of Social Welfare and Rehabilitation Sciences.

Compliance with ethical standards

Conflict of interest All authors claim the absence of financial interests and the absence of conflicts of interest.

Ethical standards All participants, after being informed of the nature of the research, consented to participate to the study. This research was performed in accordance with the Declaration of Helsinki and with the approval of the ethics board of the University of Social Welfare and Rehabilitation Sciences.

References

1. Zegers-Hochschild F, Adamson G, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. Technology ICfMAR, organization WH. The international committee for monitoring assisted reproductive technology (ICMART) and the world health organization (WHO) revised glossary on ART terminology, 2009. Fertil Steril. 2009;92(5):1520–4.
2. Rapino C, Battista N, Bari M, Maccarrone M. Endocannabinoids as biomarkers of human reproduction. Hum Reprod Update. 2014;20(4):501–16.
3. Di Spiezio SA, Di Carlo C, Minozzi S, Spinelli M, Pistotti V, Alviggi C, et al. Efficacy of hysteroscopy in improving reproductive outcomes of infertile couples: a systematic review and meta-analysis. Hum Reprod Update. 2016;22(4):479–96.
4. Miyamoto T, Minase G, Shin T, Ueda H, Okada H, Sengoku K. Human male infertility and its genetic causes. Reprod Med Biol. 2017;16(2):81–8.
5. Jarow JP, Espeland MA, Lipshultz LI. Evaluation of the azoospermic patient. J Urol. 1989;142(1):62–5.
6. Gudeloglu A, Parekattil SJ. Update in the evaluation of the azoospermic male. Clinics. 2013;68:27–34.
7. Rowe PJ, Comhaire FH, Hargreave TB, Mahmoud AM. WHO manual for the standardized investigation, Diagnosis and Management of the Infertile Male. 1rd ed. Cambridge: Cambridge University Press; 2000.
8. Maor-Sagie E, Cinnamon Y, Yaacov B, Shaag A, Goldsmidt H, Zenvirt S, et al. Deleterious mutation in SYCE1 is associated with non-obstructive azoospermia. J Assist Reprod Genet. 2015;32(6):887–91.
9. Krausz C, Riera-Escamilla A. Genetics of male infertility. Nat Rev Urol. 2018;15(6):369–384.
10. Oud MS, Volozonoka L, Smits RM, Vissers LE, Ramos L, Veltman JA. A systematic review and standardized clinical validity assessment of male infertility genes. Hum Reprod. 2019;34(5):932–41.
11. Hamada AJ, Esteves SC, Agarwal A. A comprehensive review of genetics and genetic testing in azoospermia. Clinics. 2013;68:39–60.
12. Lee JY, Dada R, Sabanegh E, Carpi A, Agarwal A. Role of genetics in azoospermia. Urology. 2011;77(3):598–601.
13. Vog P, Edelmann A, Kirsch S, Henegariu O, Hirschmann P, Kiesewetter F, et al. Human Y chromosome azoospermia factors (AZF) mapped to different subregions in Yq11. Hum Mol Genet. 1996;5(7):933–43.
14. Harton GL, Tempest HG. Chromosomal disorders and male infertility. Asian J Androl. 2012;14(1):32–9.
15. Eggers S, DeBoer KD, van den Bergen J, Gordon L, White SJ, Jamsai D, et al. Copy number variation associated with meiotic arrest in idiopathic male infertility. Fertil Steril. 2015;103(1):214–9.
16. Schilit SL, Menon S, Friedrich C, Kammin T, Wilch E, Hanscom C, et al. SYCP2 translocation-mediated dysregulation and frameshift variants cause human male infertility. bioRxiv. 2019;pii: S0002–9297(19)30434–3.
17. Miyamoto T, Hasuike S, Yogev L, Maduro MR, Ishikawa M, Westphal H, et al. Azoospermia in patients heterozygous for a mutation in SYCP3. Lancet. 2003;362(9397):1714–9.
18. He W-B, Tu C-F, Liu Q, Meng L-L, Yuan S-M, Luo A-X, et al. DMC1 mutation that causes human non-obstructive azoospermia and premature ovarian insufficiency identified by whole-exome sequencing. J Med Genet. 2018;55(3):198–204.
19. Zhang YX, Li HY, He WB, Tu C, Du J, Li W, et al. XRCC2 mutation causes premature ovarian insufficiency as well as non-obstructive azoospermia in humans. Clin Genet. 2019;95(3):442–3.
20. de Vries LBD, Smirin-Yosef P, Lagovsky I, Tzur S, Basel-Vanagaite L. Exome sequencing reveals SYCE1 mutation associated with autosomal recessive primary ovarian insufficiency. J Clin Endocrinol Metab. 2014;99(10):E2129–E32.
21. Reese MG, Eeckman FH, Kulp D, Haussler D. Improved splice site detection in genie. J Comput Biol. 1997;4(3):311–23.
22. Desmet F-O, Hamroun D, Lalande M, Collod-Béroud G, Claustres M, Béroud C. Human splicing finder: an online bioinformatics tool to predict splicing signals. Nucleic Acids Res, 2009. 37(9):e67.
23. Geisinger A, Benavente R. Mutations in genes coding for synaptonemal complex proteins and their impact on human fertility. Cytogenet Genome Res. 2016;150(2):77–85.
24. Dunne OM, Davies OR. Molecular structure of human synaptonemal complex protein SYCE1. Chromosoma. 2019:128(3):223–236.
25. Liu J-G, Yuan L, Brundell E, Björkroth B, Daneholt B, Höög C. Localization of the N-terminus of SCP1 to the central element of the synaptonemal complex and evidence for direct interactions between the N-termini of SCP1 molecules organized head-to-head. Exp Cell Res. 1996;226(1):11–9.
26. Bolcun-Filas E, Costa Y, Speed R, Taggart M, Benavente R, De Rooij DG, et al. SYCE2 is required for synaptonemal complex assembly, double strand break repair, and homologous recombination. J Cell Biol. 2007;176(6):741–7.
27. Hamer G, Gell K, Kouznetsova A, Novak I, Benavente R, Höög C. Characterization of a novel meiosis-specific protein within the central element of the synaptonemal complex. J Cell Sci. 2006;119(19):4025–32.
28. Yang F, De La Fuente R, Leu NA, Baumann C, McLaughlin KJ, Wang PJ. Mouse SYCP2 is required for synaptonemal complex assembly and chromosomal synapsis during male meiosis. J Cell Biol. 2006;173(4):497–507.
29. Yuan L, Liu J-G, Zhao J, Brundell E, Daneholt B, Höög C. The murine SCP3 gene is required for synaptonemal complex assembly, chromosome synapsis, and male fertility. Mol Cell. 2000;5(1):73–83.
30. Costa Y, Speed R, Öllinger R, Alsheimer M, Semple CA, Gautier P, et al. Two novel proteins recruited by synaptonemal complex protein 1 (SYCP1) are at the centre of meiosis. J Cell Sci. 2005;118(12):2755–62.
31. Davies OR, Maman JD, Pellegrini L. Structural analysis of the human SYCE2–TEX12 complex provides molecular insights into synaptonemal complex assembly. Open Biol. 2012;2(7):120099.
32. Schramm S, Fraune J, Naumann R, Hernandez-Hernandez A, Höög C, Cooke HJ, et al. A novel mouse synaptonemal complex protein is essential for loading of central element proteins, recombination, and fertility. PLoS Genet. 2011;7(5):e1002088.
33. Bolcun-Filas E, Speed R, Taggart M, Grey C, de Massy B, Benavente R, et al. Mutation of the mouse Syce1 gene disrupts synapsis and suggests a link between synaptonemal complex structural components and DNA repair. PLoS Genet. 2009;5(2):e1000393.
34. de Vries FA, de Boer E, van den Bosch M, Baarends WM, Ooms M, Yuan L, et al. Mouse Sycp1 functions in synaptonemal complex assembly, meiotic recombination, and XY body formation. Genes Dev. 2005;19(11):1376–89.

35. Hamer G, Wang H, Bolcun-Filas E, Cooke HJ, Benavente R, Höög C. Progression of meiotic recombination requires structural maturation of the central element of the synaptonemal complex. J Cell Sci. 2008;121(15):2445–51.
36. Nishiyama S, Kishi T, Kato T, Suzuki M, Bolor H, Nishizawa H, et al. A rare synaptonemal complex protein 3 gene variant in unexplained female infertility. Mol Hum Reprod. 2010;17(4):266–71.
37. Lu J, Gu Y, Feng J, Zhou W, Yang X, Shen Y. Structural insight into the central element assembly of the synaptonemal complex. Sci Rep. 2014;4:7059.