Mutations in Genes Coding for Synaptonemal Complex Proteins and Their Impact on Human Fertility

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Abstract

Human infertility is often classified as idiopathic in both males and females. Meiotic errors may account for at least part of these cases. As the synaptonemal complex (SC, a meiosis-specific protein scaffold) is essential for successful meiosis progression, in this paper, we analyzed the mutations in genes coding for SC components described in infertile patients to assess to what extent alterations in the SC can be related to human infertility. So far, mutations in SYCP3 and SYCE1 genes have been reported. While most SYCP3 mutations are heterozygous mutations with dominant-negative effect on the region encoding the C-terminal coiled coil of the protein, SYCE1 mutations are homozygous, which is consistent with a recessive inheritance. Similarities and differences between males and females as well as between mice and humans have been found and are discussed herein. The results suggest that a low percentage of human infertility cases may be explained by mutations in genes coding for SC components. The characterization of these mutations, together with available information from the study of knockout mice, will enable a deeper understanding of the underlying molecular bases for some of the cases of idiopathic infertility.

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Human infertility affects about 10–15% of the couples at reproductive age [NICE, 2013]. Male and female disorders seem to have an equal incidence in infertility [Hann et al., 2011; Esteves et al., 2012]. In about 25% of infertility cases, the reason remains unexplained, and no male or female cause can be found [NICE, 2013]; these individuals are classified as having "idiopathic infertility". For example, 50–80% of the patients with premature ovarian failure (POF) are still classified as idiopathic, which strongly suggests a genetic origin for the disease [Laissue, 2015]. Although several candidate genes for POF have started to arise, for most of them a clear confirmation is lacking [Caburet et al., 2014; Bilgin and Kovanci, 2015]. Concerning idiopathic male infertility, some genetic factors have been associated with nonobstructive azoospermia, but the number of studies that clearly relate mutations in a certain gene with a specific fertility problem is really small [Massart et al., 2012]. Moreover, it has been suggested that the causes of infertility may often be polygenic [Aston et al., 2010; Massart et al., 2012; Bilgin and Kovanci, 2015; Laissue, 2015], and, potentially, in some cases infertility can even arise as a combination of genetic and environmental factors [Massart et al., 2012]. Besides, increasing evidence implicates epigenetic changes such as expression differences in microRNAs [Wang et al., 2011; Rah et al., 2013; Abu-Halima et al., 2014], modification of DNA methylation patterns [Huo et al., 2015;
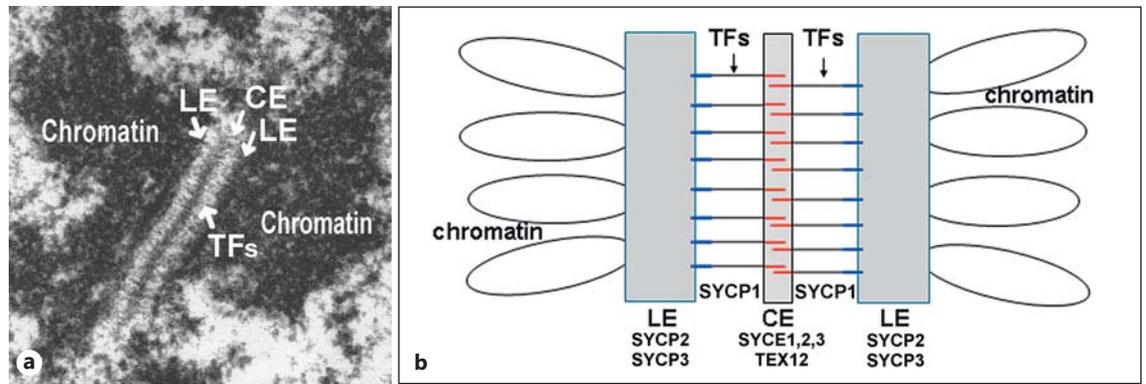
Fig. 1. Morphology and components of the SC. **a** Electron micrograph of an SC from *Mus musculus*. Lateral elements (LEs), central element (CE), transverse filaments (TFs), and chromatin are shown. **b** Diagram of a mammalian SC. The location of each of the 7 protein components is indicated. The N-terminal domains of SYCP1 are represented in red, and the C-terminal domains in blue.

Kitamura et al., 2015; Pacchierotti and Spanò, 2015], and changes in sperm histone/protamine profiles [Hammoud et al., 2011; Francis et al., 2014].

Both in males and females, meiotic errors appear to be involved in at least part of the human idiopathic infertility cases. Defects in meiosis frequently result in chromosome segregation errors that lead to cell death or aneuploidy in the gametes, which is the main cause of pregnancy loss [Handel and Schimenti, 2010]. The occurrence of partial or complete meiotic arrest during prophase I in >10% of the cases of nonobstructive azoospermia has also been reported [Topping et al., 2006]. As the 2 major events that take place in meiotic prophase I – namely homologous chromosome pairing (synapsis) and recombination (crossing-over) – have a crucial role for subsequent chromosome segregation, it is expected that the alteration of genes relevant for these processes has dramatic consequences for fertility. In studies using knockout mice, numerous genes have been identified that are required for chromosome pairing and recombination, and whose mutation affects reproductive ability. However, only for a handful of them an involvement in human fertility has been demonstrated until now [Hann et al., 2011; Quartuccio and Schindler, 2015; Yang et al., 2015].

Here, we will focus on the group of human genes that code for the framework that provides the structural support for meiotic chromosome pairing and recombination, i.e., the synaptonemal complex (SC) [Hunter, 2015; Zickler and Kleckner, 2015]. As mouse is the mammalian model where the SC has been studied most extensively, mutations in genes coding for SC components in mouse and their consequences will be also addressed. Moreover, the information acquired from mouse will be compared to the data that has started to arise from SC mutations in human idiopathic infertility cases. Interestingly, 60 years after the discovery of the SC [Moses, 1956], we are beginning to understand how mutant SC proteins can interfere with human fertility.

Brief Overview of the SC

The SC is a ladder-like, proteinaceous structure of chromosome bivalents that is formed during meiotic prophase I in sexually reproducing organisms, and whose assembly is essential for the successful advance of meiosis. It mediates the alignment and pairing of homologous chromosomes (synapsis) and acts as a scaffold for meiotic recombination (crossing-over). Besides, synapsis and recombination are essential events to ensure proper chromosome segregation during anaphase of the first meiotic division [Handel and Schimenti, 2010; Hann et al., 2011].

The SC is composed of 2 lateral elements (LEs), a central element (CE), and transverse filaments (TFs) between the LEs and the CE (Fig. 1). Together, the CE and TFs form the central region (CR) of the SC. SC assembly starts at the beginning of meiotic prophase, during leptonema, with the formation of protein axes, the axial elements (AEs), along each chromosome. During the following stage, zygonema, the AEs of homologous chromosomes, which from then on are called LEs, closely align and become connected via the CR. Then, at pachynema, the SC

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is fully assembled and crossing-over takes place [Bolcun-Filas and Schimenti, 2012; Fraune et al., 2012a]. The SC disassembly starts during the diplotene stage when components of the CR dissociate from the chromosomes, remaining only at telomeres and chiasmata. The presence of chiasmata is required for correct chromosome segregation [Handel and Schimenti, 2010].

In mammals, 7 SC protein components have been identified and characterized. Although most available data were obtained in rodents and humans, recent studies have shown a single evolutionary origin of the metazoan SC [Fraune et al., 2012b, 2013, 2014]. All 7 mammalian SC components are meiosis-specific [da Cruz et al., 2016] and contain α-helical domains that are predicted to form coiled coils, which are capable of homotypic and heterotypic protein interactions. Moreover, most SC components have been shown to be able to assemble higher order structures [Yuan et al., 1998; Öllinger et al., 2005; Davies et al., 2012; Lu et al., 2014].

The main component of the LEs is SYCP3, a 30/33-kDa protein whose coiled-coil structures span the C-terminal half of the protein [Lammers et al., 1994; Syrjänen et al., 2014]. The coiled-coil domain, together with the short C-terminal region, is required for proper polymer formation [Baier et al., 2007a, b]. In particular, human SYCP3 is a 236-amino acid protein with 66% identity to mouse SYCP3 and contains 2 coiled-coil domains that cover residues 109–144 and 172–218, respectively [Miyamoto et al., 2003] (Fig. 2a). It has been recently reported that human SYCP3 forms tetramers with amino acids 66–230 making a core helical structure that mediates tetramer assembly, and N-terminal regions that extend from the tetrameric core and are capable of binding DNA [Syrjänen et al., 2014]. The second LE component is SYCP2, a large protein that appears to be involved in LE assembly as well as in linking LEs and TFs [Offenberg et al., 1998; Yang et al., 2006; Winkel et al., 2009]. SYCP2 has a short coiled-coil domain at its C-terminal end [Offenberg et al., 1998] that can interact with SYCP3 [Yang et al., 2006] and SYCP1 [Winkel et al., 2009]. SYCP1, which is the main constituent of TFs, contains a long coiled coil-forming central part, which is flanked by globular N- and C-termini. Coiled coils would mediate SYCP1 homotypic interactions [Meuwissen et al., 1992], so that the TFs are composed of dimers or tetramers with their N- and C-termini lying in the CE and in the inner edge of the LEs, respectively [Liu et al., 1996; Schücker et al., 2015]. In the CE, 4 proteins have been identified: SYCE1 (Fig. 2b), SYCE2 [Costa et al., 2005], SYCE3 [Schramm et al., 2011], and TEX12 [Hamer et al., 2006],
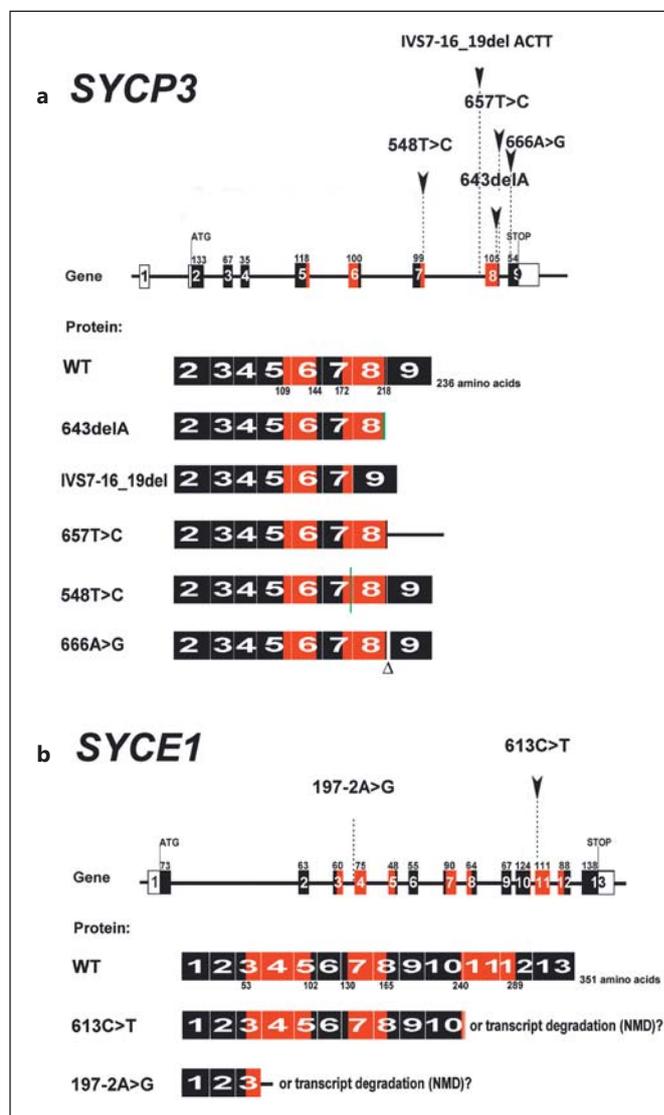

Fig. 2. Diagrams of the gene and protein structures of human *SYCP3* (**a**) and *SYCE1* (**b**) and variants identified in infertile patients. In the gene sequences, boxes represent exons whereas lines represent introns. Noncoding exon regions are depicted in white and coding exons in black. Red boxes represent the coiled-coil coding regions within the gene sequence as well as the coiled-coil domains within the protein. The number of coding nucleotides for each exon is indicated, as well as the position of the first and last amino acid in each coiled-coil domain. The positions of the identified mutations are indicated with arrowheads on the gene diagrams. Amino acid substitutions caused by 643delA and 548T>C mutations in the SYCP3 protein are represented in green. Δ designates a 3-amino acid (9-nucleotide) deletion in 666A>G mutant protein. For the 613C>T mutation in *SYCE1*, it is worth mentioning that the transcript employed as a reference by de Vries et al. [2014] was variant 1 (NM_130784.2), which uses a downstream start codon. As we used transcript variant 4 (NM_001143764) that encodes the longest SYCE1 isoform for the preparation of this diagram, the mapped mutation would be located at position 721 of the coding sequence. NMD, nonsense-mediated decay.

all of which are predicted to contain coiled-coil motifs. SYCP1, SYCE1, and SYCE3 would be essential for synapsis initiation, while SYCE2 and TEX12 would be required for synapsis propagation [Bolcun-Filas et al., 2007; Hamer et al., 2008].

Expression studies in heterologous cell culture systems, the generation of knockout mice for the different SC protein-encoding genes, and recent biophysical and biochemical studies have helped to understand the dynamics of the SC. The current picture is that chromosome loading of SYCP3 and SYCP2 during early meiotic prophase would result in AE assembly [Yuan et al., 2000; Pelttari et al., 2001; Yang et al., 2006]. Then, SYCP1 would associate with the AEs. Later on, SYCE3 and SYCE1 would be recruited [Schramm et al., 2011; Lu et al., 2014]. SYCE1 would be loaded through an interaction of its C-terminal helix with the N-terminal helix of SYCE3 [Lu et al., 2014]. SYCE1 also interacts with the N-terminal region of SYCP1, apparently stabilizing it [Costa et al., 2005]. Finally, SYCE2 and TEX12 would be recruited [Hamer et al., 2006], likely in the form of a hetero-octameric complex [Davies et al., 2012]. The SYCE2-TEX12 complex would interact with the SC through SYCE2, which would bind SYCE1/3 as well as the N-terminal region of SYCP1 [Costa et al., 2005; Bolcun-Filas et al., 2007; Schramm et al., 2011].

Mutations in Genes Coding for LE Proteins

The characterization of *Sycp2* and *Sycp3* knockout mice has shown that mutants are sexually dimorphic in relation to fertility: males are sterile, whereas females are subfertile. Mutant spermatocytes lack AEs and LEs, and recombination fails [Yuan et al., 2000; Liebe et al., 2004; Yang et al., 2006]. Hence, seminiferous tubules of homozygous male mutants exhibit meiotic arrest with a complete absence of round spermatids, elongated spermatids, and sperm, together with massive cell death during meiotic prophase [Yuan et al., 2000; Yang et al., 2006]. In contrast, in *Sycp3*−/− and *Sycp2*−/− mutant oocytes, the phenotype is less dramatic as homologous chromosomes show some degree of synapsis via assembly of CR-like structures that can support recombination [Yuan et al., 2000; Liebe et al., 2004; Yang et al., 2006]. Female null mutants are capable of gestation and birthing, although they produce fewer offspring compared to wild-type animals. In *Sycp3* null female mutants, two-thirds of the progeny are apparently healthy but one-third dies in utero because of aneuploidies [Yuan et al., 2002]. In the case

of *Sycp2*−/− females, the litter size is decreased to about half [Yang et al., 2006]. The different phenotypes of mutant males and females (i.e., infertility vs. subfertility) are likely due to differences in the stringency of the so-called pachytene checkpoint that monitors meiotic chromosome synapsis and recombination [Roeder and Bailis, 2000]. This checkpoint would be less stringent in females [Wang and Höög, 2006; Bolcun-Filas and Schimenti, 2012]. On the other hand, in *Sycp2*+/− and *Sycp3*+/− mice both males and females are fertile [Yuan et al., 2000; Yang et al., 2006].

While no patients carrying *SYCP2* mutations have been identified in humans up to the present, SYCP3 is the SC component for which more mutations have been reported in the literature. In 2003, Miyamoto et al. [2003] identified a 1-bp heterozygous deletion (643delA) in *SYCP3* in 2 out of 19 men with nonobstructive azoospermia, one Arab and the other of Hispanic origin. The mutation shifted the reading frame, resulting in a premature stop codon and truncation of the C-terminal coiled coil-forming region of the protein (Fig. 2a) [Miyamoto et al., 2003; Bolor et al., 2009]. Examination of testis biopsy samples from these patients showed complete meiotic arrest with no post-meiotic cells, early spermatocytes being the most mature cell types (Table 1) [Miyamoto et al., 2003].

The situation in the infertile patients mentioned above differs substantially from that of *Sycp3*+/− mice, which showed normal testes and, as previously stated, were fertile [Yuan et al., 2000]. An explanation for the apparent discrepancy was obtained in biochemical and ex vivo expression experiments investigating the properties of the truncated SYCP3 protein. In comparison to wild-type SYCP3, the truncated version showed defective polymerization properties. More interesting, in co-expression experiments, truncated SYCP3 interfered with normal polymerization of wild-type SYCP3. These results are consistent with the notion that the truncated SYCP3 protein has a dominant-negative effect over the wild-type protein [Miyamoto et al., 2003; Baier et al., 2007a]. Therefore, infertility in heterozygous patients would be the consequence of defective SC assembly caused by the truncated SYCP3 that in turn leads to meiosis arrest and massive spermatocyte death. In *Sycp3*+/− mice, however, no dominant-negative effect is observed as the only detectable SYCP3 protein is the one encoded by the wild-type allele [Yuan et al., 2000].

In a more recent study conducted in 26 Japanese women with idiopathic recurrent pregnancy loss, Bolor et al. [2009] identified 2 women carrying independent hetero-

Table 1. Reported SC mutations with an effect on fertility

Gene	Mutation in	Species	Heterozygous	Homozygous	Reference
SYCP3	male	mouse	fertile	meiotic arrest, absence of AEs and LEs	Yuan et al. [2000]
		human	azoospermia	NF	Miyamoto et al. [2003]
		human	miscarriages	NF	Stouffs et al. [2011]
	female	mouse	fertile	decreased fertility, aneuploidies	Yuan et al. [2002]
		human	miscarriages	NF	Bolor et al. [2009]
		human	increased predisposition to infertility?	infertility	Nishiyama et al. [2011]
SYCE1	male	mouse	fertile	meiotic arrest, synaptic failure	Bolcun-Filas et al. [2009]
		human	fertile	azoospermia	Maor-Sagie et al. [2015]
	female	mouse	fertile	meiotic arrest, synaptic failure	Bolcun-Filas et al. [2009]
		human	fertile	POF	de Vries et al. [2014]

AE, axial element; LE, lateral element; NF, not found; POF, premature ovarian failure.

zygous point mutations in *SYCP3*, neither of which was found in fertile female controls (Table 1). Expression of minigenes containing these mutations in cell culture and in mouse testis showed that both mutations affected normal splicing, generating C-terminally mutated SYCP3 proteins [Bolor et al., 2009]. One of the mutations, at the putative branch site of intron 7 (IVS7–16_19delACTT), produced skipping of exon 8. The other, 657T>C, at the end of exon 8 (and one codon after the coiled coil-coding region), although not affecting the encoded amino acid, resulted in an overlarge transcript probably due to the retention of intron 8 (Fig. 2a).

The effect of these mutations has been investigated as in the previous cases. The mutant proteins had the ability to interact with wild-type SYCP3 in vitro. In addition, co-expression of the mutant and wild-type proteins in cultured cells interfered with the formation of normal SYCP3 higher order structures. Thus, in the patients, the mutant proteins would preclude the formation of normal LEs in the SC in a dominant-negative way [Bolor et al., 2009], analogous to the situation of the 2 azoospermic men described above [Miyamoto et al., 2003].

The reports by Miyamoto et al. [2003] and Bolor et al. [2009] suggest that, as in mice, sexual dimorphism exists also in humans, with *SYCP3* male mutants exhibiting azoospermia, and female mutants presenting miscarriages. However, the identification of a *SYCP3* heterozygous mutation (548T>C) in the male partner of a couple with recurrent pregnancy loss [Stouffs et al., 2011] (Table 1) indicates that this dimorphism may not be as strict, and that problems during male meiosis might cause difficulties in maintaining pregnancies. However, it is worth noting that despite the fact that the mutation identified by Stouffs et al. falls within the coiled coil-forming region and is predicted to alter the protein functionality, it involves an amino acid substitution (Ile183Thr) and not a C-terminal protein truncation or an enlarged protein as described above (Fig. 2a). Therefore, it is conceivable that such an amino acid substitution not necessarily abrogates the SYCP3 function completely, so that some defective spermatocytes may escape the meiotic checkpoint with the consequence of aneuploid sperm production. Although the authors state that more research is required, this case suggests that a relationship between *SYCP3* mutations in men and recurrent miscarriages might also exist [Stouffs et al., 2011].

In another study, the entire coding regions as well as the exon-intron boundaries of the *SYCP3* gene from 88 Japanese women with unexplained infertility and 165 control fertile females were sequenced [Nishiyama et al., 2011]. While in all the above-mentioned reports only heterozygous *SYCP3* mutations had been found, this work identified a homozygous rare variant in exon 9 (666A>G) in 2 infertile women. Even though the nucleotide substitution does not change the encoded amino acid (Gln222Gln) nor alters the frequencies of codon usage, it potentially creates a cryptic splice acceptor site that could affect the normal splicing of intron 8, causing an in-frame 9-nucleotide deletion in the *SYCP3* transcript (Fig. 2a). Besides the fact that the homozygous variant was only found in infertile women, the frequency of the novel rare allele was significantly higher in the infertile group (Table 1). As a small number of healthy individuals also harbored the variant, it can be concluded that this variant

cannot be a sole determinant of infertility, at least in heterozygosity, but it might be one of multiple factors responsible for female infertility [Nishiyama et al., 2011]. This may suggest that, depending on the severity of the mutation, alterations in the *SYCP3* gene could either be a determining factor per se or a predisposing factor that would increase the susceptibility to nondisjunction. It should be noted, however, that attempts to demonstrate this predicted splicing anomaly by expressing minigenes carrying the variant in cell culture and in mouse testis were not successful. Nonetheless, the authors argue that these heterologous expression systems may not reflect what really happens in human oocytes.

We can point a difference between the latter case and those mentioned before. As in all the previous cases the consequence of the heterozygous mutations was infertility, they could have not been transmitted. Therefore, dominant-negative mutations would belong to the category of de novo mutations. On the contrary, in the latter case, a few healthy women were heterozygous for this variant, which indicates that it was probably inherited by the patients carrying the homozygous allele.

In summary, *SYCP3* mutations found in patients with fertility problems fall within the C-terminal coiled coil-encoding domain or are predicted to alter it. Therefore, it can be concluded that mutations that affect the coiled-coil domain of SYCP3 protein would negatively influence fertility in both sexes [Miyamoto et al., 2003; Bolor et al., 2009] (for a detailed characterization of SYCP3 domains involved in polymerization see Yuan et al. [1998] and Baier et al. [2007a, b]).

Mutations in Genes Coding for CR Proteins

In mice deficient for any of the CR proteins (i.e., SYCP1, SYCE1, SYCE2, SYCE3, TEX12), both males and females are infertile (Table 1). In the spermatocytes and oocytes of knockout animals, normal AEs are formed that show homologous alignment, but do not synapse [de Vries et al., 2005; Bolcun-Filas et al., 2007, 2009; Hamer et al., 2008; Schramm et al., 2011]. In $Sycp1^{-/-}$, $Syce1^{-/-}$, and $Syce3^{-/-}$ meiocytes, no CE structures are formed [Hamer et al., 2008; Bolcun-Filas et al., 2009; Schramm et al., 2011]. $Tex12^{-/-}$ and $Syce2^{-/-}$ meiocytes show a less drastic phenotype as they form short pieces of CE-like structures composed of SYCP1, SYCE1, and SYCE3 that are assumed to be synapsis initiation sites. However, there is no synapsis progression [Bolcun-Filas et al., 2007; Hamer et al., 2008]. Available evidence indicates that in

all CR knockout mice double-strand breaks are generated, but are not efficiently repaired. The consequences of synaptic failure are recombination block, meiotic arrest, and massive cell death of meiocytes [de Vries et al., 2005; Bolcun-Filas et al., 2007, 2009; Hamer et al., 2008; Schramm et al., 2011].

Recently, the first cases of mutations in a CR-coding gene in human infertility have been described, both in male and female patients. The anomalies were mutations in *SYCE1*, reported in siblings born to consanguineous parents of 2 Middle Eastern families [de Vries et al., 2014; Maor-Sagie et al., 2015]. In both families, the parents were heterozygous for the mutation while the patients presented homozygous mutations (Table 1), indicating a recessive inheritance [de Vries et al., 2014; Maor-Sagie et al., 2015]. In the first case, 2 daughters from first cousin parents of Israeli-Arab origin presented POF. Homozygosity mapping followed by exome sequencing and subsequent genotyping in all family members by Sanger sequencing revealed a nonsense homozygous mutation in the *SYCE1* gene (613C>T) in both affected sisters [de Vries et al., 2014]. In the second case, the affected patients were 2 azoospermic brothers of Iranian-Jewish origin, whose parents were also first cousins. A similar methodological approach to that mentioned above identified a mutation (197–2A>G) that would disrupt the acceptor site of intron 3 [Maor-Sagie et al., 2015], creating a nonsense codon (Fig. 2b). Histological examination of their testes showed maturation arrest, with primary spermatocytes as the most mature cell types. The recessive inheritance and the histological findings are consistent with the situation in the *Syce1* knockout mice (Table 1). Therefore, we would expect that in the patients cell death of meiocytes is a consequence of severe synaptic failure of homologous chromosomes.

A possible effect of both reported mutations is the production of putative C-terminal truncated proteins (Fig. 2b) [de Vries et al., 2014]. As mentioned above, the SYCE1 C-terminal helix would be involved in its recruitment to the SC by SYCE3 [Lu et al., 2014]. Thus, meiotic failure could be related to the inability of mutant SYCE1 to be loaded to the SCs. Moreover, while the regions of SYCE1 that are required for its interaction with SYCP1 and SYCE2 have not been determined yet, truncated SYCE1 proteins might not be able to bind these CR components either. Another possibility that we propose here is that mutant *SYCE1* mRNAs are targeted for degradation by nonsense-mediated decay, as both of them carry premature stop codons. If this were the case, then the sit-

uation in the infertile patients would be analogous to that of the knockout mice, infertility being a consequence of the lack of SYCE1 protein. This in turn could explain fertility of the heterozygous *SYCE1* mutation carriers, as nonsense-mediated decay would prevent potential dominant-negative effects by generating haploinsufficiency [Miller and Pearce, 2014].

Nevertheless, despite the fact that in these studies heterozygous *SYCE1* mutation carriers were fertile, we cannot ensure that this is always the case. As most CR proteins have shown the ability to form higher order structures [Öllinger et al., 2005; Davies et al., 2012; Lu et al., 2014], we cannot rule out the possibility that at least for some of the genes certain mutations with a dominant-negative effect caused by interference with normal structure assembly may be identified in the future.

Frequency of Mutations in Human SC Proteins

As summarized above, mutations in SC protein encoding genes *SYCP3* and *SYCE1* were identified as responsible of cases of idiopathic fertility disorders in humans. However, available data suggest that mutations in SC genes may account for a low percentage of idiopathic cases.

SYCP3 Mutations
Despite the above-mentioned results, several studies from different laboratories failed to detect *SYCP3* mutations in cohorts of infertile patients. A research performed in Belgium among 58 patients with maturation arrest of spermatogenesis only showed a few polymorphisms, while no *SYCP3* mutations were found [Stouffs et al., 2005]. Moreover, when the study was extended to a higher number of patients with spermatogenic arrest, no new *SYCP3* changes were detected [Stouffs et al., 2011]. Another study, carried out in 22 Mediterranean infertile men with azoospermia or severe oligozoospermia (excluding men with chromosomal aberrations or Y-chromosome microdeletions [Chandley, 1998; Stahl et al., 2010]), was also unable to find *SYCP3* mutations [Martínez et al., 2007]. A more recent work involving 75 Turkish men with nonobstructive azoospermia (excluding Y microdeletions) also failed to detect *SYCP3* mutations, only identifying polymorphisms [Gurkan et al., 2012].

Moreover, contradictory results have been reported: while a case-control study in 100 Iranian women with miscarriages of unknown causes suggests the association of the heterozygous 657T>C polymorphism with recurrent pregnancy loss [Sazegari et al., 2014], another study in 101 Japanese women could not establish a link between the 657T>C mutation and recurrent miscarriage [Mizutani et al., 2011]. Besides, a different investigation could not detect *SYCP3* mutations in western Canadian women (predominantly of Caucasian origin) that presented recurrent miscarriage and trisomic conceptions, and therefore would have a higher risk of meiotic nondisjunction [Hanna et al., 2012]. Finally, it has been suggested that ethnicity may also play a role. Apparent discrepancies between the results of the different patient cohorts might be due to polymorphisms in the different populations [Martínez et al., 2007; Gurkan et al., 2012; Sazegari et al., 2014].

SYCE1 Mutations
The described mutations dealing with *SYCE1* show a recessive mode of inheritance. This is consistent with the situation in the mouse: heterozygous animals are normally fertile, while null animals are infertile due to *SYCE1* loss of function. The fact that the only reported cases have been identified in siblings born to consanguineous parents suggests that infertility cases due to *SYCE1* mutations are rare.

Conclusions

Mutations in the genes coding for SC components might account for a small percentage of human fertility disorders by interfering with crucial processes during meiotic prophase such as double-strand-break repair, chromosome synapsis, and segregation. Among these types of mutations, only alterations in *SYCP3* and *SYCE1* genes have been reported so far in infertile patients. Most identified *SYCP3* mutations have a dominant-negative effect, while *SYCE1* changes are homozygous recessive mutations leading to loss of function. However, it has been suggested that recessive mutations in *SYCP3* might also exist. Moreover, we can presume that as the number of studied cases increases, more mutations (either dominant negative or loss of function) in *SYCP3* and *SYCE1*, as well as in the other SC component-encoding genes will be related to human infertility cases. The elucidation of the molecular basis of the pathology in each case (e.g., truncated protein or transcript degradation?) will be important for the future implementation of suitable strategies for gene therapy.

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Disclosure Statement

The authors declare no conflicts of interest.

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