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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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, synopsis 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 leptotene, 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
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],...
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-coiling 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-

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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

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**Table 1.** Reported SC mutations with an effect on fertility

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

AE, axial element; LE, lateral element; NF, not found; POF, premature ovarian failure.
cannot be a sole determinant of infertility, at least in het-
erozygosity, but it might be one of multiple factors re-
sponsible 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 infertil-
ity, they could have not been transmitted. Therefore,
dominant-negative mutations would belong to the cate-
gory 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 Bai-
er 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 *Syce1*–/–, *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 synopsis initiation sites. However, there
is no synopsis progression [Bolcun-Filas et al., 2007;
Hamer et al., 2008]. Available evidence indicates that in
all CR knockout mice double-strand breaks are generat-
ed, 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; Sch-
ramm 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 (Ta-
ble 1), indicating a recessive inheritance [de Vries et al.,
2014; Maor-Sagie et al., 2015]. In the first case, 2 daugh-
ters from first cousin parents of Israeli-Arab origin pre-
sented POF. Homozygosity mapping followed by exome
sequencing and subsequent genotyping in all family
members by Sanger sequencing revealed a nonsense ho-
mozygous 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 matu-
ration arrest, with primary spermatocytes as the most
mature cell types. The recessive inheritance and the hist-
ological findings are consistent with the situation in the
*Syce1* knockout mice (Table 1). Therefore, we would ex-
pect that in the patients cell death of meiocytes is a con-
sequence of severe synaptic failure of homologous chro-
mosomes.

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 recruit-
ment 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 com-
ponents either. Another possibility that we propose here
is that mutant SYCE1 mRNAs are targeted for degrada-
tion 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 study 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 [Szegari 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; Szegari 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 synopsis, 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

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