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Citation for published version:
Adams, IR & Davies, O 2023, 'Meiotic Chromosome Structure, the Synaptonemal Complex, and Infertility', *Annual Review of Genomics and Human Genetics*, vol. 24, pp. 35-61. https://doi.org/10.1146/annurev-genom-110122-090239

Digital Object Identifier (DOI):
10.1146/annurev-genom-110122-090239

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Annual Review of Genomics and Human Genetics

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ANNUAL REVIEWS

Annual Review of Genomics and Human Genetics

Meiotic Chromosome Structure, the Synaptonemal Complex, and Infertility

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Annu. Rev. Genom. Hum. Genet. 2023. 24:35–61

First published as a Review in Advance on May 9, 2023

The *Annual Review of Genomics and Human Genetics* is online at genom.annualreviews.org

https://doi.org/10.1146/annurev-genom-110122-090239

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Keywords

meiosis, synaptonemal complex, fertility, azoospermia, primary ovarian failure, recurrent pregnancy loss

Abstract

In meiosis, homologous chromosome synapsis is mediated by a supramolecular protein structure, the synaptonemal complex (SC), that assembles between homologous chromosome axes. The mammalian SC comprises at least eight largely coiled-coil proteins that interact and self-assemble to generate a long, zipper-like structure that holds homologous chromosomes in close proximity and promotes the formation of genetic crossovers and accurate meiotic chromosome segregation. In recent years, numerous mutations in human SC genes have been associated with different types of male and female infertility. Here, we integrate structural information on the human SC with mouse and human genetics to describe the molecular mechanisms by which SC mutations can result in human infertility. We outline certain themes in which different SC proteins are susceptible to different types of disease mutation and how genetic variants with seemingly minor effects on SC proteins may act as dominant-negative mutations in which the heterozygous state is pathogenic.

THE ROLE OF THE SYNAPTONEMAL COMPLEX IN MAMMALIAN MEIOSIS

Meiosis, the process of reductive cell division, involves an extraordinary chromosome choreography in which homologous chromosomes exchange genetic material by crossing over and then segregate to generate haploid germ cells (180). This necessitates elaborate chromosome dynamics and structures that are unique to, and essential for, fertility in sexually reproducing organisms. The structural hallmark of meiosis is the synaptonemal complex (SC), a zipper-like proteinaceous assembly that synapses homologous chromosomes together to facilitate the formation of recombination-mediated crossovers (24, 180) (**Figure 1*a***). The SC was first identified in 1956 through its iconic tripartite appearance in electron micrographs of crayfish spermatocytes (114). Subsequently, the same tripartite SC structure was identified in almost all meiotic organisms, spanning animal, plant, and fungal kingdoms (115, 172). Hence, the SC is a fundamental structural

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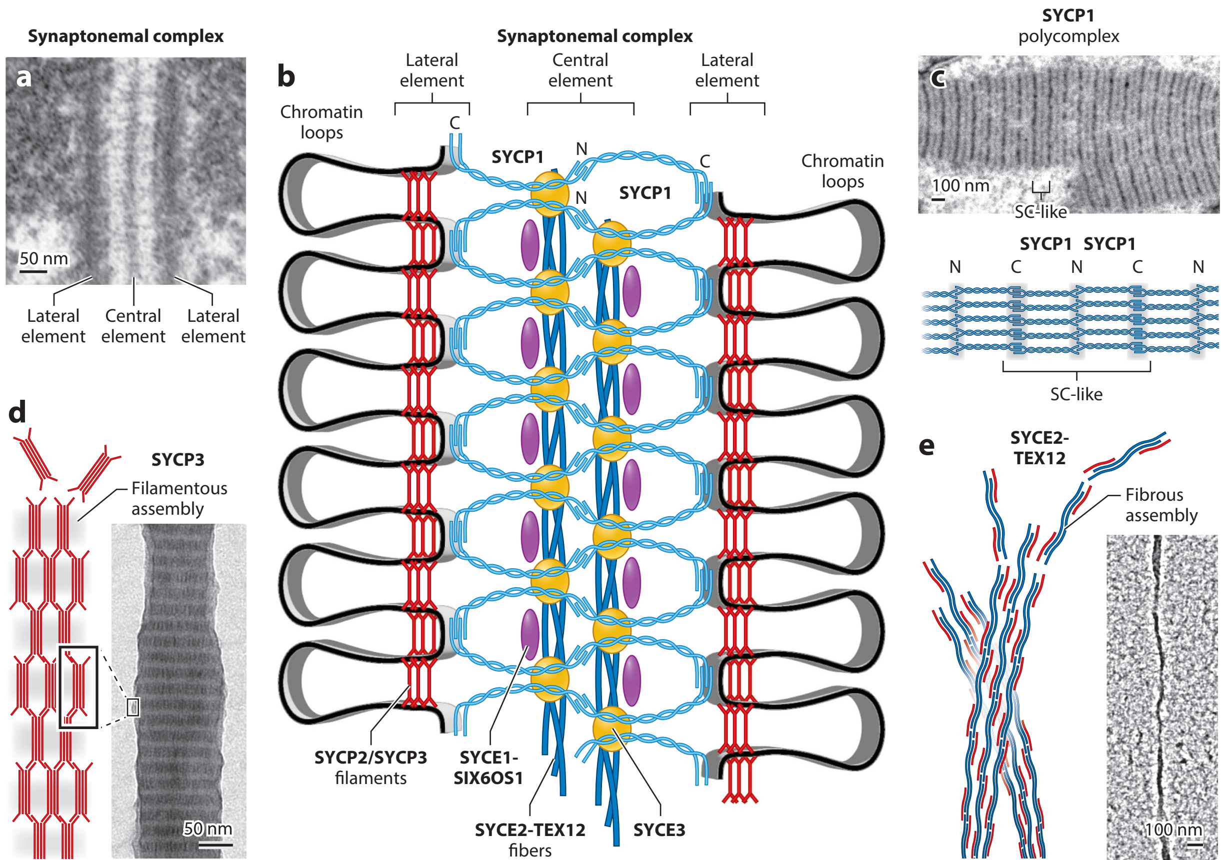

Figure 1

The mammalian synaptonemal complex (SC). (*a*) Electron micrograph of the mouse SC. Panel adapted from Reference 81 (CC BY 3.0). (*b*) Schematic model of the mammalian SC, highlighting transverse filament protein SYCP1, lateral elements formed of SYCP2 and SYCP3 filaments, and the central element consisting of SYCP1-binding SYCE3, SYCE1-SIX6OS1 complexes, and SYCE2-TEX12 fibers. (*c*) Electron micrograph of SYCP1 polycomplexes formed upon expression of eGFP-SYCP1 in COS7 cells. Unpublished data provided by James Dunce and Owen Davies. (*d*) Electron micrograph and schematic of SYCP3 self-assembly into filaments. Panel adapted from Reference 160 (CC BY 4.0). (*e*) Electron micrograph and schematic of SYCE2-TEX12 self-assembly into fibers. Panel adapted from Reference 30 (CC BY 3.0).

component of the molecular program of meiosis that has been conserved throughout evolution. Mice that fail to form an SC have defects in chromosome synapsis and crossover formation and are infertile (81). Furthermore, numerous mutations of SC components have been identified as causing human infertility and recurrent miscarriage (13, 52, 178), which is the subject of this review.

Meiotic chromosome synapsis and crossover formation are driven by interhomolog recombination searches that establish physical links between the same regions of homologous chromosome pairs (24, 74, 180). After chromosomes are replicated to generate sister chromatids held together at their centromeres, meiotic chromosomes adopt distinctive structures during prophase I in which chromatin is looped around proteinaceous cores such that the linearity of their genetic sequence is projected onto linear axes (57, 102). This proteinaceous core is composed of cohesins, ring-like protein complexes involved in chromosome architecture that mediate cohesion between sister chromatids in both meiotic and nonmeiotic cells (10, 119). Interestingly, meiotic cells express meiosis-specific cohesin subunits (75, 92, 93, 129, 133), at least some of which have evolved to carry out meiosis-specific roles (14). The telomeres at both ends of each chromosome become tethered to the nuclear envelope by the meiotic telomere complex (37, 152), where they are subjected to microtubule forces that drive their rapid movement throughout the nucleus (51, 68, 91). These rapid prophase movements facilitate interhomolog recombination searches from the approximately 200–400 programmed DNA double-strand breaks (DSBs) that are generated in each cell (8, 95, 127). Interhomolog repair of these programmed DSBs drives pairing of homologous chromosomal regions and then, through assembly of the SC, their synapsis (9, 104, 138, 139). SC assembly converts and extends the discrete physical links between homologous chromosomes provided by recombination intermediates into a single continuous and close alignment along the entire length of the chromosome axis (35, 162). It is within the three-dimensional context of the SC that early recombination intermediates mature and resolve, with approximately 10% forming crossovers and 90% undergoing noncrossover resolution (5, 67, 113, 162). The SC is then dissolved, leaving crossovers as the sole physical connections between homologs (35). Once the SC has disassembled, a subpopulation of chromosome-associated cohesin needs to be maintained to retain these physical connections between homologous chromosomes until metaphase I (66, 131, 161). Subsequent separase-dependent cleavage of cohesins along the chromosome arms allows the physical connections to resolve and homologous chromosomes to segregate at the end of meiosis I (42, 86, 87, 93). Removal of cohesin from centromeres then finally allows sister chromatids to segregate in meiosis II (58, 109).

The SC's enigmatic tripartite structure is formed of two lateral elements separated by approximately 100 nm, which coat the homologous chromosome axes, and a midline central element (114, 115, 172) (**Figure 1*a***). These proteinaceous structures extend along the entire chromosome length, which is between 4 and 24 μm in humans (155), and are held together by a series of interdigitated transverse filaments that form the teeth of the SC zipper (31). Electron microscopy and super-resolution immunofluorescence imaging have demonstrated that the mammalian SC has a depth of approximately 100 nm (149, 151, 156). Hence, combining these measurements suggests that entire SCs may be between 6 and 154 GDa (38), placing them among the largest supramolecular protein structures in the cell.

BUILDING THE MAMMALIAN SYNAPTONEMAL COMPLEX

Over the last three decades, the mammalian SC's protein components have been identified and localized through combined mouse genetics, immunofluorescence, and electron microscopy studies (**Figure 1*b***). This research has uncovered that transverse filaments are formed of SYCP1

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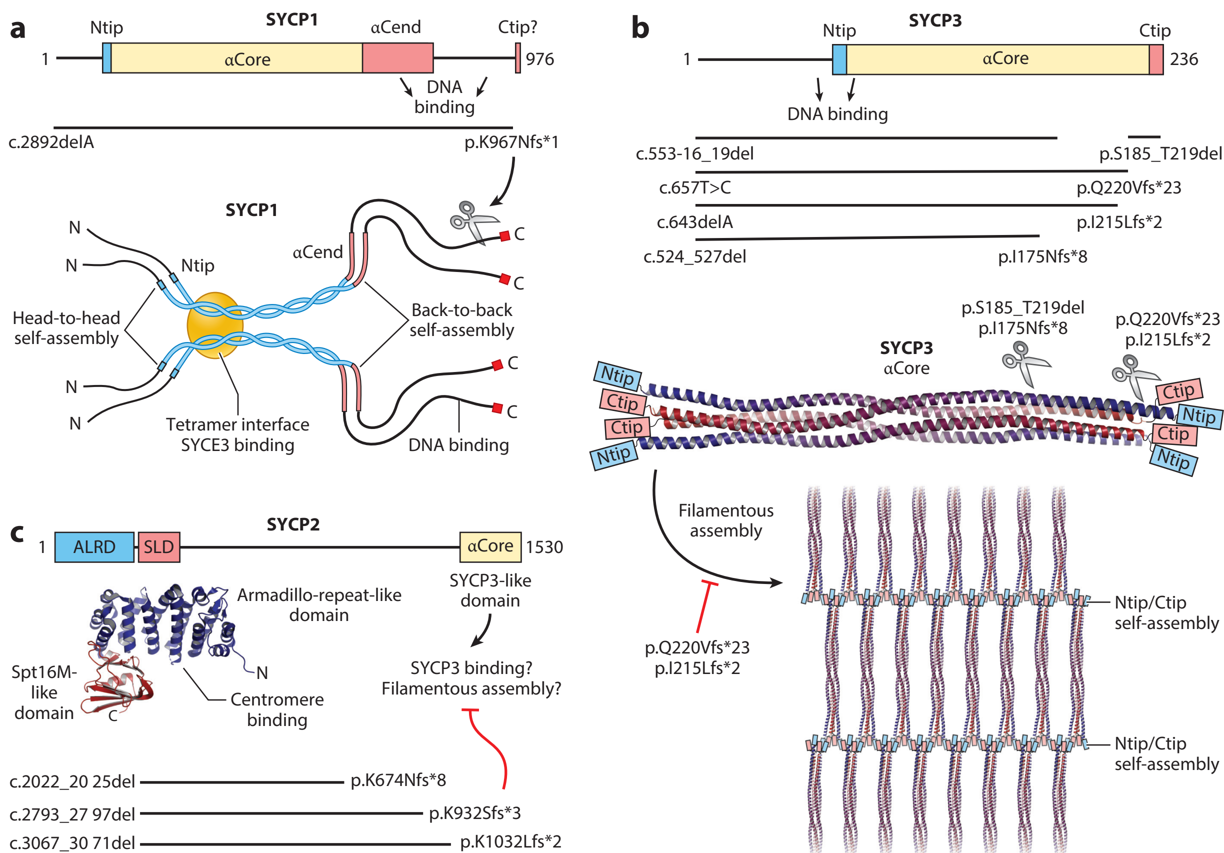

Figure 2

Structure and infertility mutations of synaptonemal complex transverse filament and lateral element proteins. (*a*) SYCP1 is a tetramer that undergoes lattice-like self-assembly through Ntip and αCend sites at either end of its α-helical core (αCore) and binds to DNA through sites toward its C terminus (36). The tetramer interface mediates interactions with SYCE3 that result in remodeling of the lattice and recruitment of central element proteins (28). (*b*) SYCP3 is a tetramer (Protein Data Bank accession 4CPC) that undergoes self-assembly through Ntip and Ctip sites at either end of its αCore, forming filaments in which DNA is bound at regular 23-nm repeating intervals (160). (*c*) SYCP2 contains an N-terminal globular domain that consists of associated armadillo-repeat-like and Spt16M-like domains (Protein Data Bank accession 5IWZ), which interact with centromeric proteins (45). Its C terminus contains an SYCP3-like domain that may interact and form filamentous assemblies with SYCP3 (171).

coiled-coil proteins (110), which are organized with their N and C termini located with the central and lateral elements, respectively, such that the length of two juxtaposed SYCP1 molecules dictates the 100-nm separation between lateral elements (97, 148) (**Figures 1*b*** and **2*a***). The lateral element contains SYCP2 and SYCP3 (118, 146, 173, 176) (**Figure 2*b*,*c***) and assembles on a core of meiosis-specific and generic cohesins that define the axis of a meiotic chromosome (42, 75, 92, 93, 128, 129, 133). These structures are often referred to as axial elements when they assemble on unsynapsed axes prior to synapsis and as lateral elements when they are part of a fully assembled tripartite SC (118, 146, 173, 176). Lastly, the central element is formed of SYCE1, SYCE2, SYCE3, SIX6OS1, and TEX12 (15, 16, 56, 60, 61, 150) (**Figure 3*a–d***).

In recent years, substantial progress has been made in understanding the structure and function of mammalian SC proteins at the molecular level (18, 28, 30, 36, 38–41, 45, 99, 159, 160,

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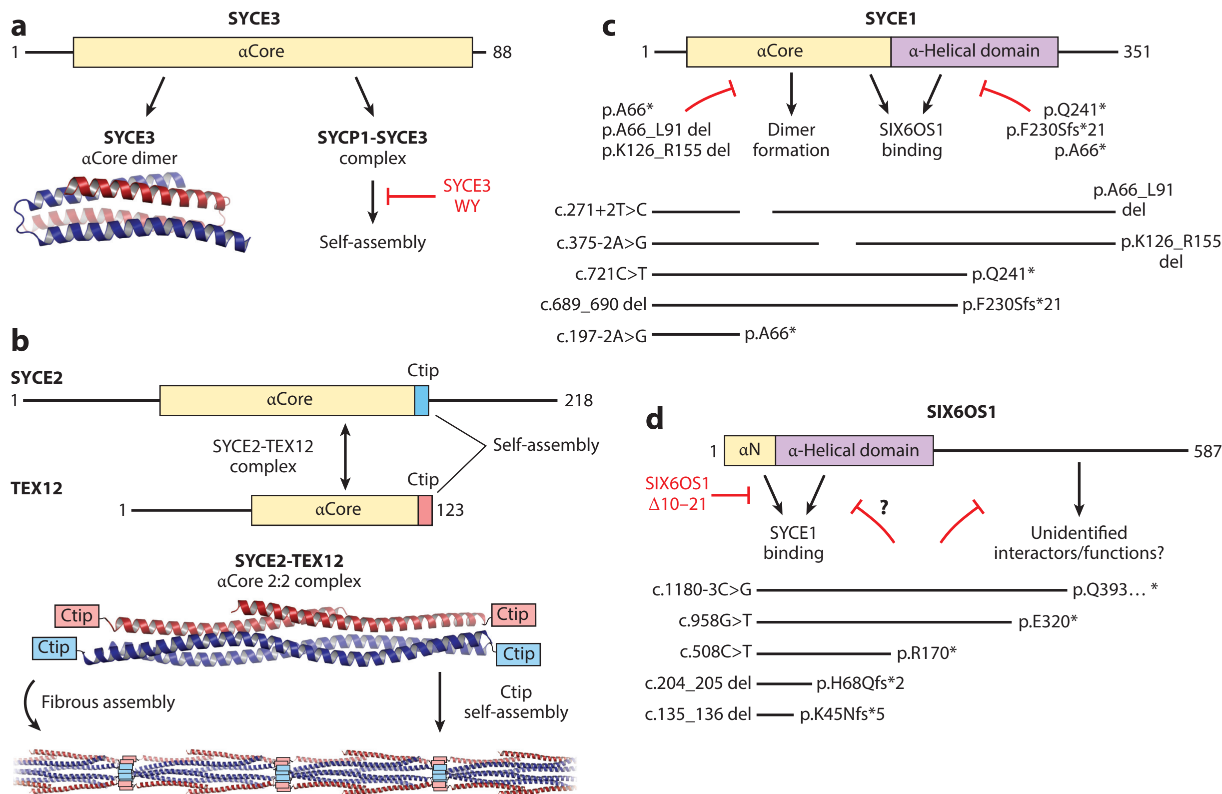

Figure 3

Structure and infertility mutations of synaptonemal complex central element proteins. (*a*) SYCE3 forms a dimer in isolation (Protein Data Bank accession 6H86) and binds to SYCP1 in a 2:1 complex that undergoes self-assembly, which is specifically blocked by the mouse SYCE3 WY mutation (28). (*b*) SYCE2 and TEX12 interact in a 2:2 complex that undergoes fibrous assembly through Ctip sites at the C-terminal ends of their α-helical cores (αCores) (38). (*c*) SYCE1 forms a dimer in isolation (41) and binds to SIX6OS1 in a 1:1 complex (143). The *SYCE1* c.721C>T (p.Q241*) mutation can also be described as c.613C>T (p.Q201*) (33), reflecting its position in an alternative *SYCE1* transcript. (*d*) SIX6SO1 has N-terminal α-helical regions that interact with SYCE1, the first binding site of which is disrupted by the mouse SIX6OS1 Δ10–21 mutation (143). This is followed by an extensive C-terminal unstructured region of unknown function.

171) (**Figure 1*b***). This work has revealed several important underlying themes. First, SC proteins are predominantly α-helical coiled coils, which typically have dimeric or tetrameric structure to provide flexible or rigid tethering/scaffolding, respectively. Second, the coiled-coil building blocks formed by SC components and complexes undergo self-assembly, through short sequences at the termini of their α-helices, into structures that provide the SC's distinct architectural elements. These themes are clearly apparent within three self-assembling systems of the mammalian SC (**Figure 1*c*–*e***).

SYCP1 is a tetramer that self-assembles at N- and C-terminal ends into a lattice-like array to provide the underlying architectural role of the SC in tethering chromosome axes (36) (**Figure 2*a***). The intrinsic capacity of SYCP1 for self-assembly has been demonstrated by the formation of SC-like polycomplexes upon SYCP1 expression in somatic cells (120) (**Figure 1*c***). SYCP1 assemblies are modified by the central element protein SYCE3, which interacts with SYCP1 to form an integrated SYCP1-SYCE3 lattice, in which other central element components are recruited by integrated SYCE3 molecules (28, 40, 99) (**Figures 2*a*** and **3*a***).

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Within the lateral element, the SYCP3 tetramer assembles into paracrystalline fibers in which its DNA-binding sites are separated by 23-nm distances along the longitudinal axis to facilitate the compaction of the meiotic chromosome axis (18, 159, 160) (**Figures 1*b*** and **2*b***). SYCP3 fibers have been observed in the recombinant protein in vitro (160) (**Figure 1*d***), upon heterologous cellular expression (177), and within the native mammalian SC in vivo (121), indicating that their formation is an intrinsic property of the underlying protein sequence (**Figure 2*b***). The other lateral element protein, SYCP2, has an unusual structure of an N-terminal globular domain that binds to centromeric components, followed by a large predicted unstructured region and a C-terminal SYCP3-like coiled-coil domain (45) (**Figure 2*c***). The latter domain has been reported to interact with SYCP3, and truncated constructs form thin fibrils that may represent early intermediates of the full 23-nm fibers observed in full-length SYCP3 (171). Hence, it is possible that SYCP2 and SYCP3 form integrated fibers within the lateral element. After the rest of the SC disassembles in diplotene, SYCP2 and SYCP3 persist at centromeres in spermatocytes, although not in oocytes (11, 65, 130). SYCP2 and SYCP3 are not required to maintain cohesion at centromeres at this stage of meiosis in spermatocytes (82), and it remains unclear whether these persistent SC proteins have roles at later stages of meiosis after synapsis has occurred.

In the central element, SYCE2 and TEX12 form a seemingly constitutive 2:2 complex that undergoes hierarchical self-assembly in a manner reminiscent of intermediate filament proteins, through a 4:4 intermediate, into fibers up to 40 nm in width and several micrometers in length (30, 38) (**Figures 1*b*,*e*** and **3*b***). These SYCE2-TEX12 assemblies seemingly form a fibrous backbone that enables SC growth along the up to 24-μm length of meiotic chromosomes (30, 38). Hence, three self-assembling systems define the principal architectural features of the SC. By contrast, the remaining SC proteins, SIX6OS1 and SYCE1, form a 1:1 complex that does not appear to self-assemble or form an architecturally significant structure (41, 56, 143) (**Figure 3*c*,*d***). Thus, we may hypothesize that this Cinderella complex of mammalian SC proteins either has essential structural interactions with hitherto unidentified SC components or has critical functional roles in regulating SC assembly and crossover formation.

Although the structure of the SC has been conserved through evolution, there is almost no primary sequence homology between mammalian SC components and those in yeast, flies, worms, or plants (24, 49). Functionally equivalent SC proteins from these different species can have similar domain organizations, lengths, and structural features but show no higher sequence similarity with one another than with other coiled-coil proteins, such as myosin. Furthermore, the genes encoding most mammalian SC proteins (*SYCP2*, *SYCP3*, *SYCP1*, *SYCE2*, and *TEX12*) likely arose early in metazoan evolution, with some SC genes (*SYCE3*) not arising until the emergence of vertebrates (47, 48). Therefore, much of our understanding of mammalian SC genes and their genetics comes from studies of mouse models.

MUTATIONS IN SYNAPTONEMAL COMPLEX COMPONENTS CAUSE INFERTILITY IN MALE AND FEMALE MICE

Loss-of-Function Mutations in Lateral Element Components in Mice

The lateral element of the SC contains two known components, SYCP2 and SYCP3 (35, 64, 89, 118) (**Figure 2*b*,*c***). SYCP2 and SYCP3 assemble onto meiotic chromosomes that contain a cohesin core, and severe depletion of meiotic cohesin can disrupt assembly of SYCP2 and SYCP3, causing defects in axial element formation (42, 98). Modest depletion of meiotic cohesin can alter the length of the chromosome axis and can reduce sister chromatid cohesion to the extent that axial elements on individual sisters can be distinguished and allow the SC to assemble between them (2, 98, 134). Severe depletion of meiotic cohesin results in meiotic defects, asynapsis, cell

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death during meiosis, and infertility (2, 98, 134). Though defects in SC assembly likely contribute to the meiotic phenotypes in these cohesin mutants, their impact on meiosis potentially extends beyond defects in SC assembly.

Loss-of-function mutations in *Sycp2* and *Sycp3* have both been shown to cause infertility in male mice (173, 176). Homozygous loss-of-function mutations in either of these SC genes result in azoospermia, with extensive cell death observed as spermatocytes go through meiosis (173, 176). In both *Sycp2*$^{-/-}$ and *Sycp3*$^{-/-}$ male mice, chromosome synapsis during prophase I is defective, resulting in a failure to repair programmed meiotic DSBs (173, 176) and activation of the robust checkpoint present in pachytene mouse spermatocytes (21). *Sycp2*$^{-/-}$ and *Sycp3*$^{-/-}$ spermatocytes each fail to assemble electron-dense axial elements, and SYCP2 and SYCP3 depend on each other to localize to meiotic chromosomes (126, 173, 176). The meiotic chromosomes in these two mutants still assemble a cohesin core and, interestingly, can assemble reasonably long regions of SYCP1, likely between paired chromosomal regions (126, 173, 176).

In contrast to the strong meiotic arrest and infertility seen in *Sycp2*$^{-/-}$ and *Sycp3*$^{-/-}$ male mice, oogenesis is able to progress to completion in both *Sycp2*$^{-/-}$ and *Sycp3*$^{-/-}$ female mice (173, 175). At least some oocytes generated by these animals are functional, as *Sycp2*$^{-/-}$ and *Sycp3*$^{-/-}$ female mice are subfertile (173, 175). The basis for the sexual dimorphism in these phenotypes partly reflects molecular differences in the SC between males and females (126, 173, 175, 176). In contrast to *Sycp3*$^{-/-}$ spermatocytes, some SYCP2 is recruited to meiotic chromosomes in *Sycp3*$^{-/-}$ oocytes, and chromosomes synapse and assemble SYCP1 along their length, albeit with some axial gaps (175). Similarly, some SYCP3 is recruited to meiotic chromosomes in *Sycp2*$^{-/-}$ oocytes, primarily as foci located at the ends of the chromosomes, and chromosomes synapse and assemble SYCP1 along their length with some axial gaps (173). The sexually dimorphic effects of *Sycp2*$^{-/-}$ and *Sycp3*$^{-/-}$ mutations on SC assembly potentially reflect differences in meiotic chromosome organization and SC structure between male and female gametogenesis, with females having shorter chromatin loops, longer chromosome axes, and a narrower SC than males (1, 101, 163). The difference in the width of the SC between males and females is potentially caused, at least in part, by the C terminus of SYCP1 associating with different regions within the lateral element in male and female meiosis (1).

In addition to sexual dimorphism in the SC itself, differences in SC mutant phenotypes between male and female mice also partly reflect differences in the way that spermatocytes and oocytes respond to defects in chromosome synapsis during meiosis (21). These sex-specific responses relate to differences in the behavior of the sex chromosomes in spermatocytes and oocytes during normal meiosis: In oocytes, the X chromosome has a homologous partner with which to pair and synapse, whereas the heterologous X and Y chromosomes in spermatocytes remain mostly unsynapsed and become organized in a transcriptionally silent compartment in the nucleus called the sex body (21). In spermatocytes, asynapsis involving the autosomes triggers a robust response involving three components. First, the asynapsed autosomal regions accumulate persistent unrepaired DSBs that sequester the transcriptional silencing machinery away from the sex chromosomes, causing aberrant expression of Y-encoded genes, which in turn triggers spermatocyte death (103, 165). Second, transcriptional silencing of endogenous genes in these asynapsed autosomal regions likely contributes to the pachytene checkpoint recognizing a single pair of asynapsed autosomes but not a single additional nonessential chromosome (29, 103). Third, some persistent DNA repair intermediates can also contribute to the pachytene checkpoint independently of asynapsis (7, 29, 103, 106, 124). Thus, even relatively modest defects in chromosome synapsis in SC mutant spermatocytes typically elicit a robust pachytene checkpoint response and cell death at this stage of meiosis, resulting in azoospermia. By contrast, the pachytene checkpoint in oocytes lacks the aberrant gene

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expression of the Y-encoded gene component and is less robust (21). Both silencing of endogenous genes in asynapsed regions and persistent DNA repair intermediates triggering DNA damage responses likely contribute to the cell death associated with asynapsis in oocytes (17, 25, 34, 137). Depending on the extent of asynapsis, asynapsed oocytes can undergo cell death during late fetal or early perinatal development, with some oocytes able to progress to maturity (17, 25, 34, 83, 137). Thus, asynapsis in oocytes typically depletes the number of oocytes in the ovary, resulting in primary ovarian failure (POF, also known as primary ovarian insufficiency), with the extent of asynapsis influencing the severity and timing of this depletion.

Though chromosome synapsis is largely achieved in *Sycp3*$^{-/-}$ oocytes, approximately two-thirds of these oocytes die soon after birth (170, 175). The perinatal oocyte death in *Sycp3*$^{-/-}$ mice is likely caused by inefficient repair of meiotic programmed DSBs and activation of a DNA damage checkpoint operating at this stage of oogenesis (34, 96, 170, 175). This phenotype potentially reflects a role for the lateral elements in promoting interhomolog and/or suppressing intersister repair of meiotic DSBs (96, 170). *Sycp3*$^{-/-}$ oocytes with low levels of DNA damage are able to progress through this checkpoint and form mature gametes (170, 175). However, crossover maturation of recombination events is delayed in *Sycp3*$^{-/-}$ oocytes, and approximately half these oocytes have univalent chromosomes that lack chiasmata at metaphase I, resulting in high rates of aneuploidy, and concomitantly high rates of embryonic lethality, being transmitted from *Sycp3*$^{-/-}$ mothers to the next generation (170, 175).

The *Sycp3* allele used in these mouse studies deletes the first three exons of the *Sycp3* open reading frame, including the start codon, and produces undetectable levels of *Sycp3* mRNA and protein, likely representing a null allele (176). The *Sycp2* mutant allele deletes an internal region of SYCP2 that includes the coiled-coil domain required for its interaction with SYCP3 (**Figure 2*c***). This truncated SYCP2 protein is expressed and localized to meiotic chromosomes (173). It is possible that mutations in specific domains of SYCP2 and SYCP3 might result in distinct molecular phenotypes from the alleles that have been characterized to date. However, these mouse genetic studies indicate that homozygous loss-of-function mutations in SC lateral element components would potentially cause distinct clinical phenotypes in males and females if present in human populations—specifically, azoospermia with meiotic arrest in males and either POF or recurrent pregnancy loss in females.

Loss-of-Function Mutations in Transverse Filament Components in Mice

The transverse filaments of the SC contain one known component, SYCP1 (35, 64, 110). Loss-of-function mutations in *Sycp1* cause infertility in both male and female mice (32). *Sycp1*$^{-/-}$ homozygous male mice exhibit azoospermia, with extensive cell death occurring in meiotic spermatocytes (32). The cohesin core and the axial element components SYCP2 and SYCP3 are all recruited to chromosomes in *Sycp1*$^{-/-}$ spermatocytes, but although homologous chromosomes often pair, they fail to synapse, and the paired axial elements detected by anti-SYCP3 staining remain separated by ~450 nm rather than by the ~200 nm detectable by super-resolution light microscopy in fully synapsed wild-type spermatocytes (27, 32). Some physical connections between these paired axial elements are visible by electron microscopy (32). The asynapsis in these mutant spermatocytes triggers the robust pachytene checkpoint and results in cell death at the pachytene stage (21). Interestingly, a small proportion of *Sycp1*$^{-/-}$ spermatocytes do progress through pachytene and even into metaphase I (32). However, recombination events do not mature into crossovers in the absence of SYCP1, and the resulting metaphase I spermatocytes have univalent chromosomes that lack chiasmata (32). The univalents in these metaphase I *Sycp1*$^{-/-}$ spermatocytes likely trigger the metaphase I checkpoint, inducing cell death (21).

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In contrast to *Sycp2*$^{-/-}$ and *Sycp3*$^{-/-}$ mutations, *Sycp1*$^{-/-}$ mutations cause infertility rather than subfertility in female mice (32). Adult *Sycp1*$^{-/-}$ ovaries are depleted of oocytes and follicles due to oocytes being lost during late fetal and/or early postnatal stages of development at a time when oocytes would be expected to be progressing through pachytene and into dictyate arrest (32, 81). The oocyte death in *Sycp1*$^{-/-}$ mice is likely caused by a combination of (*a*) asynapsis resulting in transcriptional silencing of asynapsed chromosomal regions and (*b*) persistent unrepaired meiotic programmed DSBs activating a DNA damage response (25, 34, 81). Interestingly, *Sycp3*$^{-/-}$ females have a less severe oocyte depletion phenotype than *Sycp1*$^{-/-}$ females, which may reflect a role of the SC lateral element in promoting interhomolog or suppressing intersister repair of programmed DSBs and a concomitant reduction in the amount of unrepaired DNA damage in *Sycp3*$^{-/-}$ oocytes (81, 96). Consistent with this hypothesis, *Sycp3*$^{-/-}$ *Sycp1*$^{-/-}$ double-mutant oocytes have a less severe phenotype and slower rate of oocyte loss than *Sycp1*$^{-/-}$ single-mutant oocytes (81).

The *Sycp1* allele used in these mouse studies deletes exons 2–8 (amino acids 1–197) of the *Sycp1* open reading frame, including the start codon; does not produce detectable *Sycp1* protein; and likely represents a null allele (32). The N-terminal, coiled-coil, and C-terminal regions of SYCP1 all have distinct roles in the structure of the SC, and therefore mutations in different domains of SYCP1 may result in distinct molecular phenotypes. Indeed, different mutations in the budding yeast transverse filament component Zip1p can separate the functions of this protein in SC assembly and crossover recombination (168, 169). Thus, although mutations in SYCP1 in humans might be expected to cause azoospermia in males and POF in females, it is possible that mutations or genetic variation in SYCP1 could also associate with gamete aneuploidy or recurrent pregnancy loss.

Loss-of-Function Mutations in Central Element Components in Mice

The central element of the SC contains five known components: SYCE3, SYCE1, SIX6OS1, SYCE2, and TEX12 (26, 56, 60, 150). Loss-of-function mutations in any of *Syce3*, *Syce1*, *Six6os1*, *Syce2*, or *Tex12* cause male and female infertility and/or failure to generate mature male and female gametes (15, 16, 56, 61, 150). Male mice carrying homozygous null alleles for any of these genes exhibit defects in chromosome synapsis, extensive spermatocyte death, and azoospermia (15, 16, 56, 61, 150). The cohesin core and lateral element components typically assemble relatively normally in these mutants (15, 16, 56, 61, 150). However, in *Syce2*$^{-/-}$ spermatocytes, the structure of the lateral elements is disrupted such that lateral elements are thicker and more irregular in this mutant (15). Homologous chromosomes often pair in spermatocytes carrying null mutations in central element components, but synapsis is discontinuous along the length of these chromosomes, and the tripartite structure of the SC is disrupted in the short stretches where the SC does assemble (15, 16, 56, 61, 150). Consistent with synapsis and the SC having a role in promoting recombination and repair of programmed DSBs in meiosis, these mutants typically have higher levels of unrepaired DNA damage and early recombination intermediates than wild-type spermatocytes (15, 16, 56, 61, 150). The asynapsis in these mutants will activate the spermatocyte pachytene checkpoint, leading to spermatocyte death and infertility (21).

Although null mutations in the central element components typically cause asynapsis and spermatocyte death, there are differences in their molecular consequences for SC assembly. In *Syce3*$^{-/-}$ spermatocytes, discontinuous fragmented stretches of SYCP1 assemble on both synapsed and asynapsed regions of chromosome axes but do not extend fully along the length of the chromosome (150). SYCE1 and SYCE2 are not recruited to *Syce3*$^{-/-}$ spermatocyte chromosomes, and central elements are not visible by electron microscopy even in regions where axial elements are paired (150). In *Syce1*$^{-/-}$ mutant spermatocytes, SYCP1 assembly is also disrupted and is detectable as

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discontinuous stretches on both synapsed and asynapsed regions of chromosome axes (16, 150). By contrast, SYCP1 assembly appears to be more limited in *Six6os1*$^{-/-}$ spermatocytes than in either *Syce3*$^{-/-}$ or *Syce1*$^{-/-}$ spermatocytes and is restricted to short assemblies in regions where chromosome axes are synapsed (16, 56, 150). Furthermore, *Syce1*$^{-/-}$ and *Six6os1*$^{-/-}$ mutations also have different effects on assembly of other central element proteins: No central element components are detected on *Six6os1*$^{-/-}$ spermatocyte chromosomes, but SYCE3, TEX12, and SYCE2 are all recruited to the discontinuous stretches of SYCP1 that assemble on *Syce1*$^{-/-}$ spermatocyte chromosomes (16, 56, 150). Lastly, *Syce2*$^{-/-}$ and *Tex12*$^{-/-}$ spermatocytes are also unable to fully synapse their chromosomes and exhibit discontinuous regions of synapsis between paired chromosomes (15, 61). SYCP1 assembly is largely restricted to these short stretches of synapsis (15, 61). The effects of these central element component mutations on SC assembly are consistent with the central element having a role in stabilizing the SYCP1-containing transverse filament bridges between homologous chromosomes at regions of synapsis and promoting subsequent extension of the nascent SC along the length of the chromosomes. However, the differential effects of these mutations on SYCP1 suggest that SYCP1 may be present in distinct structures in some of these mutants. It is possible that the SYCP1 associated with asynapsed axes in *Syce3*$^{-/-}$ and *Syce1*$^{-/-}$ spermatocytes reflects the disassembly of unstable SC in chromosomal regions where the SC had transiently assembled between homologs, whereas the SYCP1 restricted to synapsed regions in other central element mutants reflects nascent SC assembly between synapsed axes that cannot stably extend.

Oocytes in mice homozygous for null mutations in central element components similarly exhibit defects in chromosome synapsis, and ovaries from these mice are typically depleted of oocytes and follicles (15, 16, 56, 61, 150). The loss of oocytes in these mutants is likely related to both (*a*) asynapsis inducing transcriptional silencing of asynapsed chromosomal regions and (*b*) unrepaired DNA damage activating the Chk2-dependent DNA damage checkpoint (17, 21, 137). Interestingly, *Syce2*$^{-/-}$ mutations do show some sexually dimorphic effects on SC assembly, with *Syce2*$^{-/-}$ oocytes assembling SYCP1 and SYCE1 on asynapsed regions of the chromosome axes, though not necessarily colocalized in the same place. The less stringent pachytene checkpoint in female meiosis (21) allows the effects of central element component mutations on late recombination events to be more readily assessed in oocytes; although *Syce3*$^{-/-}$, *Six6os1*$^{-/-}$, and *Syce1*$^{-/-}$ oocytes all generate relatively normal or even elevated numbers of intermediate MSH4-containing recombination foci, very few of these foci progress to become MLH1-positive late recombination foci (16, 56, 150). The effects of these central element component mutations on late recombination foci are consistent with the SC having a role in protecting recombination intermediates from repairing through noncrossover pathways and/or promoting crossover recombination repair.

The SC central element mutations used in these studies typically do not generate detectable protein and likely represent null alleles. The *Syce3* and *Tex12* alleles replace the entire open reading frames, the *Syce1* allele replaces exons 2–11 (encoding amino acids 27–279) and likely also disrupts the protein sequence downstream of these exons, the *Six6os1* allele is a deletion that generates a frameshift and premature termination codon (PTC) at amino acid 10, and the *Syce2* allele is a gene trap integration that disrupts the open reading frame at amino acid 11 and likely also disturbs protein sequence downstream of this site (15, 16, 56, 61, 150). Notably, some genetic variants in human central element genes have been modeled in mice (43, 63, 143). These variants provide a useful comparison with their respective null alleles and are discussed in more detail in the next section of this review. In addition, roles for specific binding interfaces in SYCE3 and SIX6OS1 have been elucidated in vivo through the introduction of specific mutations in *Syce3* and *Six6os1* by gene editing in mice (28, 143). Mutations in SYCE3 that disrupt the SYCE3 self-assembly interface while leaving the SYCP1-binding interface intact (*Syce3*$^{WY/WY}$) result in different SC assembly

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defects than those seen in *Syce3*$^{-/-}$ null spermatocytes, as the SYCE3 WY protein retains the ability to disrupt SYCP1 tetramer lattices but is unable to drive assembly of integrated SYCE3-SYCP1 lattices (28) (**Figure 3*a***). Thus, *Syce3*$^{WY/WY}$ spermatocytes have more severe defects in SC assembly than *Syce3*$^{-/-}$ null spermatocytes in terms of the amount of synapsis and chromosomal recruitment of SYCP1, though both these *Syce3* mutations cause asynapsis and cell death during pachytene and azoospermia (28, 150). Mutations that disrupt the first of two SYCE1-binding sites in SIX6OS1 (*Six6os1*$^{\Delta 10-21/\Delta 10-21}$) result in a less severe spermatocyte asynapsis phenotype than *Six6os1*$^{-/-}$ null mutations, with reduced rather than undetectable amounts of SIX6OS1 and SYCE1 associating with chromosome axes in these mutants (56, 143) (**Figure 3*d***). SYCE2 and TEX12 were not detected on the chromosomes of *Six6os1*$^{\Delta 10-21/\Delta 10-21}$ spermatocytes, suggesting that multivalent interactions between SIX6OS1 and SYCE1 are required for recruitment of SYCE2-TEX12 and assembly of a stable SC extending along the length of the chromosomes (143). However, like *Six6os1*$^{-/-}$ null spermatocytes, *Six6os1*$^{\Delta 10-21/\Delta 10-21}$ spermatocytes also fail to progress through pachytene and undergo cell death, leading to azoospermia (56, 143).

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MUTATIONS IN SYNAPTONEMAL COMPLEX GENES AND INFERTILITY IN HUMANS

Human Infertility Genetics

Infertility is a common disease that affects approximately 7% of men and 10% of women of reproductive age (84, 174). Genetics is thought to play a significant role in both male and female infertility, and as the SC is a meiosis-specific structure that is essential for male and female fertility in mice (52, 178), mutations in SC genes might be expected to cause male and female infertility in humans. Although there are different types of male and female infertility, genetic variants that impair the ability of the SC to mediate synapsis would be expected to trigger pachytene checkpoints and cause meiotic cell death (21), which would manifest as quantitative defects in the number of sperm or oocytes in adults (84, 174). Moreover, genetic variants that primarily affect the ability of the SC to promote crossover recombination and hence accurate meiotic chromosome segregation would be expected to cause gamete aneuploidy and recurrent pregnancy loss (175). However, as gametogenesis involves multiple specialized differentiation events and epigenetic, chromosomal, and morphological changes, the pool of genes that could cause male and/or female fertility when they are mutated is relatively large, and variants in SC genes are unlikely to account for a large proportion of this genetically heterogeneous disease (78, 167).

In males, severe defects in spermatogenesis result in a complete absence of sperm (nonobstructive azoospermia), whereas weaker defects cause low (oligozoospermia) or very low (cryptozoospermia) sperm counts. Even nonobstructive azoospermia represents a spectrum of testis pathologies and spermatogenesis arrest points, presumably representing defects caused by variants in genes acting at different stages of spermatogenesis and involved in different spermatogenic processes (78, 84). Approximately 25% of nonobstructive azoospermia is caused by sex chromosome aneuploidy or microdeletions in the *AZF* (azoospermia factor) region of the Y chromosome. However, the genetic causes of most male infertility remain undetermined (70, 78, 84). In females, defects in oogenesis can result in reduced numbers of oocytes in the ovary and POF. In its severest form, this results in a streak ovary that lacks oocytes and follicles, causing amenorrhea and infertility. Less severe depletion of the ovarian reserve results in irregular menstruation and premature menopause (12, 174). Sex chromosome aneuploidies and fragile X syndrome together account for approximately 20% of POF, but a causative genetic variant is not identified in the majority of female infertility patients (12, 167, 174).

Whole-genome and whole-exome sequencing are being increasingly applied to infertility patients, and more and more infertility genes are being identified (70, 167). Because many infertility patients are sporadic cases that are typically diagnosed in adults, there can be challenges related to collecting parental samples to assess familial segregation of genetic variants identified in these patients (84, 123). This lack of familial segregation data increases the difficulty in identifying causal variants from the few hundred potential pathogenic variants typically identified in genome or exome sequencing data (55, 78). The contribution of de novo heterozygous variants operating through dominant-negative or haploinsufficient mechanisms (123), possibly along with the combinatorial effects of several heterozygous loss-of-function variants in functionally connected genes (107), can also complicate identification of causal variants in these sequencing data. Regardless, more than 175 human infertility genes have been identified, although disease variants for any one of these genes are typically found only in a small number of patients (70, 174).

Mutations in Lateral Element Components Associated with Human Infertility

The first mutation in an SC gene associated with human disease was identified from sequencing *SYCP3* as a candidate infertility gene in 19 infertile azoospermic men with meiotic arrest (111). This study identified a heterozygous single-nucleotide deletion (c.643delA) in two unrelated infertile men. *SYCP3* c.643delA is predicted to generate a PTC in the 236-amino-acid SYCP3 protein (p.I215Lfs*2) that removes its Ctip domain, which is implicated in self-assembly (**Figure 2*b***). This truncated protein interferes with the ability of ectopically expressed wild-type SYCP3 to self-assemble into filamentous structures in a dominant-negative manner (111). Thus, the underlying disease mechanism for this mutation likely reflects the PTC removing some, but not all, of the protein interaction interfaces in SYCP3 and the resulting truncated SYCP3 protein assembling into nonfunctional complexes with full-length SYCP3 protein expressed from the nonmutant allele. Dominant-negative mutations appear to be particularly relevant for structural proteins such as intermediate filaments and collagens that assemble into stable oligomers using α-helical coiled coils and triple helices, respectively, and can incorporate mutant protomers into higher-order structures (22, 50). Thus, α-helical-core-containing components of the SC such as SYCP3 (**Figures 2** and **3**) may similarly be susceptible to dominant-negative mutations.

The dominant-negative effect of the truncated protein encoded by *SYCP3* c.643delA on wild-type SYCP3 filament formation is consistent with heterozygosity for this allele associating with infertility in humans (111). However, dominant-negative effects on SYCP3 function in meiotic cells and the SC itself remain to be demonstrated. *SYCP3* c.643delA has not been directly modeled in mice, and the *Sycp3* null mouse allele expresses undetectable levels of SYCP3 protein; thus, the *Sycp3* null mouse mutation does not completely model the human mutation and, understandably, causes male infertility only when homozygous (176). Subsequent studies in different patient cohorts suggest that *SYCP3* c.643delA is not a common cause of male infertility (59, 108, 157). However, dominant-negative mutations that cause infertility in a heterozygous state are unlikely to reach high allele frequencies in the population, and any de novo *SYCP3* mutation that interferes only with the Ntip/Ctip self-assembly, or that retains a large enough portion of the α-helical-core coiled-coil domain to permit binding (**Figure 2*b***), could potentially cause sporadic infertility in a dominant-negative manner. Interestingly, a 4-nucleotide frameshift deletion in *SYCP3* (c.524_527delTTAA) has been identified as a candidate heterozygous mutation in a patient with severe oligozoospermia rather than the azoospermia present in *SYCP3* c.643delA patients and the null mouse model (122, 176). The abundance of the mutant SYCP3 protein and its affinity for wild-type SYCP3 likely influence the severity of any dominant-negative *SYCP3* allele and could result in different *SYCP3* alleles associating with different types of infertility. This

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c.524_527delTTAA mutation is predicted to generate a truncated SYCP3 protein (p.I175Nfs*8) that retains the Ntip and approximately two-thirds of the α-helical-core coiled-coil domain and could potentially bind weakly to the wild-type protein and act as a weak dominant-negative allele. Further genetic, biochemical, and in vivo data are needed to strengthen the potential association between *SYCP3* and male infertility in humans. However, *SYCP3* allele frequencies from more than 140,000 whole exomes and genomes (77) suggest that potential loss-of-function (pLOF) variants in *SYCP3* are not under strong constraint (observed/expected pLOF single-nucleotide variants = 0.65, 90% confidence interval = 0.33–0.95) (94). Thus, many PTC-containing alleles of *SYCP3* are likely not behaving as strong enough dominant-negative alleles to cause infertility.

Both *SYCP3* c.643delA and *SYCP3* c.524_527delTTAA mutations introduce PTCs in *SYCP3* mRNA and are proposed to cause disease via a dominant-negative mechanism in heterozygous patients (111, 122). Approximately one-third of human disease-causing mutations generate PTC-containing mRNAs that are targeted for degradation by the nonsense-mediated mRNA decay (NMD) pathway (73, 88). The NMD pathway targets two different types of mRNA for degradation. mRNAs that have a PTC upstream of the last exon will have exon junction complexes (EJCs) bound near the exon–exon junctions in the 3′ untranslated region of that mRNA (90, 100), a feature that can trigger EJC-dependent NMD. In addition, mRNAs that have long 3′ untranslated regions (typically >1 kb) can be degraded by EJC-independent NMD (20). Notably, PTCs that trigger NMD result in a reduced abundance of the PTC-containing mRNA and expression of low levels of the truncated protein and typically cause recessive diseases, whereas NMD-insensitive PTCs can result in a relatively normal abundance of the PTC-containing mRNA and expression of normal levels of the truncated protein, which can cause dominant-negative or recessive diseases depending on the truncated protein (88). Interestingly, meiotic spermatocytes downregulate EJC-dependent NMD, though possibly not EJC-independent NMD, such that many PTC-containing mRNAs are stable in these cells (6, 44, 76, 117, 153). Thus, meiotic spermatocytes may be particularly susceptible to mutations that generate PTC-containing mRNAs encoding truncated proteins that can interfere with normal cellular functions in a dominant-negative manner.

Heterozygosity for some *SYCP3* mutations has also been associated with recurrent miscarriage and recurrent pregnancy loss (19, 145, 158). Heterozygous mutations in *SYCP3* were first associated with female infertility through targeted sequencing of *SYCP3* in 26 women with a history of recurrent pregnancy loss. Two different *SYCP3* mutations were identified in two different women in this cohort but not in the control cohort of 150 fertile women (19). These *SYCP3* mutations are rare in the general population (c.553-16_19del is present in 1/247,294 *SYCP3* alleles, and c.657T>C is present in 14/24,875 *SYCP3* alleles) (77). Both of these mutations potentially affect splicing of the *SYCP3* transcript (19) and potentially generate truncated SYCP3 proteins that lack or reposition the Ctip involved in SYCP3 self-assembly (**Figure 2*b***). In support of these variants causing disease in a heterozygous state, the truncated SYCP3 proteins encoded by these alleles inhibit assembly of wild-type SYCP3 into filamentous structures when ectopically expressed in somatic cell lines (19). The association between these *SYCP3* mutations and recurrent pregnancy loss is consistent with the high rates of maternal aneuploidy and reduced litter sizes reported in *Sycp3*$^{-/-}$ null female mice (175). However, mutations in *SYCP3* are not a common cause of recurrent pregnancy loss (62, 140), and *SYCP3* c.657T>C is not consistently associated with recurrent pregnancy loss across multiple studies (19, 112, 145). Further research on how these *SYCP3* mutations affect SYCP3 structure and function and their in vivo consequences is probably needed to better understand the association between *SYCP3* and recurrent pregnancy loss.

Altered expression of *SYCP2* and heterozygous mutations in this axial element component have also been identified as candidate male infertility mutations (147). Three patients from a cohort of 625 infertile men were identified as having heterozygous mutations in *SYCP2* in a study that

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analyzed this candidate gene in exome sequencing data (147). These three *SYCP2* mutations were all 4- or 5-bp deletions that generate frameshifts predicted to generate PTCs. The predicted truncated SYCP2 proteins expressed from each of these alleles each retain the armadillo-repeat-like and Spt16M-like domains of SYCP2 but not the α-helical-core coiled-coil domain implicated in SYCP3 binding (**Figure 2*c***). The two shorter predicted SYCP2 truncated proteins (p.K674Nfs*8 and p.K932Sfs*3) were identified in patients presenting with cryptozoospermia, whereas the longest predicted SYCP2 truncated protein (p.K1023Lfs*2) was identified in a patient presenting with azoospermia and meiotic arrest (147). It is possible that the longest of these truncated SYCP2 proteins is more abundant or has a higher affinity for binding to other SC components or meiotic proteins. Furthermore, the *SYCP2* mutation encoding p.K932Sfs*3 was also identified in the mother of the male infertility patient with this mutation, suggesting that, as in mouse models, spermatogenesis is more sensitive than oogenesis to mutations in *SYCP2* (147, 173). Interestingly, pLOF variants in *SYCP2* are under strong constraint (observed/expected pLOF single-nucleotide variants = 0.1, 90% confidence interval = 0.06–0.18) (77, 94). This suggests that *SYCP2* pLOF alleles are selected against in human populations, consistent with heterozygosity for these alleles often affecting fertility. Further analysis of infertile cohorts for *SYCP2* heterozygosity may therefore identify additional *SYCP2* mutations associated with male infertility, and mechanistic analysis of the role of the armadillo-repeat-like and Spt16M-like domains of SYCP2 in SC structure and function is likely to shed more light on the consequences of *SYCP2* mutations for infertility.

In addition to mutations in SC genes themselves, some infertility genes likely cause disease by affecting, at least in part, the expression or function of lateral element components. Given the effects of mutations in meiotic cohesins on axial element assembly in mice (2, 98, 134), the homozygous and compound heterozygous loss-of-function mutations in *STAG3* and potentially also in *REC8* identified in POF and in nonobstructive azoospermia with meiotic arrest (23, 80, 85, 136, 164, 166), as well as the homozygous mutations in *RAD21L* identified in a nonobstructive azoospermia with meiotic arrest (85), all likely cause infertility at least in part due to the effects on axial elements and SC assembly. Furthermore, microdeletions in the *AZFc* region of the Y chromosome—one of the most common causes of male infertility, accounting for approximately 15% of azoospermic men (132)—are associated with defects in synapsis and fragmented SC assembly (53, 132). The reason why *AZFc* microdeletions cause defects in synapsis, defects in SC assembly, and azoospermia is not clear but is likely related to the fact that these microdeletions encompass the multicopy *DAZ* gene locus (132). *DAZ* is a member of a family of germline RNA-binding proteins (141) that bind to and stimulate translation of mRNAs encoding meiotic cohesins and SC components such as SYCP3 and SYCP1 (79, 135, 142).

Mutations in Transverse Filament Components Associated with Human Infertility

Mutations in the transverse filament component gene *SYCP1* have also been associated with male infertility, though at present only one *SYCP1* mutation has been identified (116). This mutation was identified in a consanguineous family in which three male siblings presented with oligozoospermia. This mutation deletes a single nucleotide in *SYCP1* (c.2892delA) and is predicted to cause a frameshift and a PTC that alters or truncates the C-terminal 10 amino acids of the protein (p.K967Nfs*2) (116). This mutation will disrupt the Ctip of SYCP1, which is conserved but is of unknown function, while leaving the entire structural core of the molecule intact (**Figure 2*a***). Homozygosity for *SYCP1* c.2892delA segregated with male infertility in this family, consistent with a recessive mode of inheritance (116). Notably, the human phenotype associated with homozygosity for this allele is less severe than the male phenotype described for homozygous *Sycp1*$^{-/-}$

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null mice, suggesting that the human *SYCP1* c.2892delA mutation may represent a hypomorphic or even a separation-of-function allele rather than a null allele (32, 116). Further biochemical and in vivo data would help provide more insight into why this mutation causes oligozoospermia and how the C-terminal 10 amino acids of SYCP1 contribute to SYCP1 function.

Notably, pLOF variants in *SYCP1*, like in *SYCP2*, are under strong constraint (observed/expected pLOF single-nucleotide variants = 0.12, 90% confidence interval = 0.07–0.22) (77, 94). The reduced representation of *SYCP1* pLOF variants in the general population suggests that heterozygosity for *SYCP1* pLOF alleles often results in severe genetic disease, death at an early age, or reduced fertility. Given that *Sycp1*$^{-/-}$ null mice are healthy but infertile (32), the constraint for *SYCP1* pLOF variants in humans likely also reflects effects on fertility. Furthermore, the homomeric self-assembly properties of SYCP1 would be compatible with dominant-negative mutations having phenotypic consequences in a heterozygous state (4). So why have heterozygous *SYCP1* mutations not been reported in infertility patients? This may, in part, be related to dominant-negative point mutations typically having milder effects on protein structure than loss-of-function mutations, and variant effect predictors typically underperform in calling dominant-negative point mutations as pathogenic (54). In addition, studies aiming to identify genetic causes of infertility often prioritize homozygous variants and recessive inheritance patterns, particularly those using whole-genome or whole-exome sequencing approaches. Notably, studies that associated heterozygosity for *SYCP3* or *SYCP2* mutations with infertility were searching for mutations in these specific candidate genes (19, 111, 147). Interestingly, a recent study using exome sequencing data from infertile male trios identified candidate de novo heterozygous mutations contributing to male infertility (123), and this approach could potentially prove fruitful in identifying infertility-associated mutations in *SYCP1*.

Mutations in Central Element Components Associated with Human Infertility

To date, mutations in two of the five central element components have also been associated with male infertility. Multiple mutations in *SYCE1*—including c.197-2A>G, c.271+2T>C, c.375-2A>G, and c.689_690del (46, 69, 105, 125, 143) (**Figure 3*c***); copy number variation (71, 72); and whole-gene deletions (3, 85)—have been identified in different male infertility cohorts. These *SYCE1* mutations all have recessive modes of inheritance, and male homozygotes generally present with nonobstructive azoospermia and meiotic arrest (3, 46, 69, 105). The deletion of *SYCE1* (3) likely resembles the *Syce1*$^{-/-}$ null mouse model and causes infertility due to defects in stabilizing the central region of the assembling SC that result in asynapsis (16). The c.197-2A>G splice-site mutation, which is predicted to cause intron retention and generate a PTC and a truncated SYCE1 protein (p.A66*), likely also causes infertility through a similar mechanism, as this truncation removes much of the α-helical-core coiled-coil domain that is central to SYCE1 structure, as well as the SIX6OS1-binding sites within SYCE1 (105, 143) (**Figure 3*c***). Two of the remaining known *SYCE1* mutations (c.271+2T>C and c.375-2A>G) are also located at splice sites and are predicted to cause exon skipping that would generate SYCE1 proteins containing internal in-frame deletions (p.A66_L91delinsV and p.K126_R155del, respectively) (69, 125). Each of these in-frame deletions disrupts one of the two SIX6OS1-binding sites in SYCE1 (143) (**Figure 3*c***), likely leading to infertility by preventing assembly of functional SYCE1-SIX6OS1 complexes and causing defects in stabilizing the central region of the assembling SC and synapsis, similarly to *Syce1*$^{-/-}$ null and *Six6os1*$^{-/-}$ null mouse models (16, 56, 143). The remaining *SYCE1* mutation associated with male infertility is a 2-bp deletion (c.689_690del) that generates a PTC and the predicted truncated protein (p.F230Sfs*21) (46). This mutation disrupts one of the two SIX6OS1-binding sites in SYCE1 (69) (**Figure 3*c***) and potentially also disrupts the ability of SYCE1 to interact

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with SYCE3 in a similar manner to the SYCE1 POF pQ241* protein truncation (143). Again, this mutation likely leads to infertility by preventing the assembly of functional SYCE1-SIX6OS1 complexes and causing defects in SC assembly and synapsis, similarly to the *Syce1*$^{-/-}$ null and *Syce1*$^{POF/POF}$ mouse models (16, 63, 143).

Consistent with the *Syce1*$^{-/-}$ null mouse phenotype (16), homozygous mutations in *Syce1* have also been identified in infertile women with POF (33, 69, 179). The ~4,000-bp homozygous deletion in *SYCE1* identified in two sisters with POF has not yet been completely defined at the DNA level but appears to delete a large part of the *SYCE1* open reading frame (179). More work is probably needed to determine how this deletion might affect SYCE1 structure and function. In addition, analyzing SC genes in whole-exome sequencing of idiopathic POF patients identified compound heterozygosity for *SYCE1* p.E159K and *SYCE1* p.F230Sfs*21 in one individual (69). Both of these alleles are proposed to affect SYCE1 stability and its ability to interact with SYCP1 in ectopic assays (69). However, the best-characterized *SYCE1* POF mutation, c.721C>T, generates a PTC that produces a truncated SYCE1 protein (p.Q241*). This mutation is also described as c.613C>T (p.Q201*) (33), reflecting its position in an alternative *SYCE1* transcript. This truncation disrupts one of the two SIX6OS1-binding sites in SYCE1 (**Figure 3*c***) and also disrupts the ability of SYCE1 to interact with SYCE3 (143). This mutation likely prevents assembly of functional SYCE1-SIX6OS1 complexes in the SC, causing defects in SC assembly and synapsis (143). The c.721C>T mutation may also affect *SYCE1* mRNA and protein abundance in spermatocytes (63, 143), though it is not clear whether this also occurs in oocytes. The *SYCE1* c.721C>T mutation has been modeled in mice, and the resulting homozygous females exhibit defects in SC assembly and synapsis during oogenesis, oocyte loss, and infertility (63, 143). The phenotype of these *SYCE1* c.721C>T mouse models is similar to the *Syce1*$^{-/-}$ null mouse phenotype (16).

Multiple mutations in a second central element gene, *SIX6OS1* (HGNC: *C14orf39*), have also been identified in male infertility patients presenting with azoospermia and meiotic arrest (43, 69, 80). These mutations are all predicted to generate PTCs and truncated SIX6OS1 proteins and represent 2-bp frameshift deletions or point mutations that introduce a PTC in the SIX6OS1 open reading frame (43, 69, 80) (**Figure 3*d***). The c.1180-3C>G intronic mutation affects the consensus 3′ splice-site motif of a GT-AG splice site (154) and generates a truncated SIX6OS1 protein (43), potentially through exon skipping and the introduction of a PTC downstream of Q393 (p.Q393…*). The more severe SIX6OS1 truncations (p.K45Nfs*5 and p.H68Qfs*2) will lack one of the two SYCE1-binding sites—the α-helical domain and the poorly characterized C-terminal domain of SIX6OS1 (**Figure 3*d***)—and will likely represent null alleles. Notably, some *SIX6OS1* male infertile patient material has been analyzed at the level of chromosome behavior in chromosome spreads and suggests that the disease mechanism in *SIX6OS1* c.204_205del patients is similar to that described in *Six6os1*$^{-/-}$ null mouse models; these mutations cause failure to recruit SYCE1 to meiotic chromosomes and fully assemble an SC, extensive chromosome asynapsis, defects in repair of meiotic DSBs and sex body formation, and defects in progression through pachytene (43, 56). Interestingly, patients with less severe SIX6OS1 protein truncations (p.E320* or p.Q393…*) that retain the SYCE1-binding sites and α-helical domain can still recruit the truncated SIX6OS1 protein to chromosomes and assemble short stretches of SYCP1 on their chromosomes, and they exhibit only partial rather than extensive asynapsis (43). The partial asynapsis in these patients is sufficient to cause defects in repair of meiotic DSBs, defects in sex body formation, and defects in progression through pachytene and therefore likely underlies the infertility in these patients. The effects of these shorter truncations on SIX6OS1 function have been modeled by making similar mutations in mice (*Six6os1*$^{\Delta C/\Delta C}$) (43).

Consistent with the *Six6os1*$^{-/-}$ null mouse phenotype (56), homozygous mutations in *SIX6OS1* have also been identified in female infertility patients presenting with POF (43, 69). Both of these

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mutations are predicted to generate PTCs that produce truncated SIX6OS1 proteins (p.H68Qfs*2 and p.R170*). The association between *SIX6OS1* p.H68Qfs*2 and POF represents the same family in which the association between *SIX6OS1* p.H68Qfs*2 and azoospermia was described (43). *SIX6OS1* p.H68Qfs*2 likely represents a null allele (**Figure 3*d***), and the consequences of this mutation for oogenesis are likely similar to those described for *Six6os1*$^{-/-}$ null female mice, i.e., defects in SC assembly and chromosome synapsis leading to delayed and impaired repair of meiotic DSBs, transcriptional silencing of asynapsed chromosomal regions, and oocyte death (56). Furthermore, mouse models of less severe SIX6OS1 truncations that lack only the uncharacterized C-terminal domain (*Six6os1*$^{\Delta C/\Delta C}$) suggest that *SIX6OS1* p.R170* (43) is also likely to cause female infertility by generating defects in SC assembly and synapsis that lead to increased levels of oocyte death during late fetal and perinatal stages of development, which in turn deplete the ovarian reserve.

Mutations in *SYCE3*, *SYCE2*, and *TEX12* central element genes have not yet been identified in male or female infertility patients. However, the phenotypes for null mutations in these mouse genes (15, 16, 150) make *SYCE3*, *SYCE2*, and *TEX12* good candidate human infertility genes. The relationship between SYCE3 and SYCE1-SIX6OS1 in the SC (28), along with the lack of recruitment of SYCE1-SIX6OS1 to meiotic chromosomes in *Syce3*$^{-/-}$ null mice (56, 150), suggests that *SYCE3* mutations might be identified in male azoospermia and female POF patients. SYCE3 is a relatively small protein (88 amino acids) encoded by a 3-exon, ~450-bp transcript. Therefore, it is entirely possible that mutations in *SYCE3* that cause infertility will be identified in the near future as the volume of sequencing data from infertility patients continues to increase.

The mouse genetic data suggest that mutations in *TEX12* might also be expected to cause azoospermia and/or POF in humans (61). TEX12 is a 123-amino-acid protein encoded by a 5-exon, ~1,150-bp transcript. pLOF variants in *TEX12* do not appear to be constrained (5.2 expected pLOF single-nucleotide variants, 5 observed, observed/expected = 0.96, 90% confidence interval = 0.49–1.78), and it is not entirely clear why candidate mutations in this gene have not yet been identified in infertility patients. It is possible that causal *TEX12* mutations will be identified as the number of sequenced infertility patients increases. TEX12 has been reported to localize to the centrosome independently of its interacting partner, SYCE2, in spermatocytes and in transformed cells (144). If TEX12 has centrosomal or other non-SC functions in somatic tissues or early embryos in humans that were not modeled in *Tex12*$^{-/-}$ null mice (61), this might preclude patients with mutations in this gene from presenting as infertile.

Given the *Syce2*$^{-/-}$ null mouse phenotype (15), *SYCE2* mutations might be expected to be identified in male azoospermia and female POF patients. SYCE2 is a 218-amino-acid protein encoded by a 6-exon, ~1,250-bp transcript. pLOF variants in SYCE2 are potentially under some constraint (12.3 expected pLOF single-nucleotide variants, 3 observed, observed/expected = 0.24, 90% confidence interval = 0.11–0.63), though the relatively small size of this gene limits the statistical power of these data. Notably, the three observed pLOF single-nucleotide variants for *SYCE2* (77) are all splice-site mutations located close to either the N-terminal or C-terminal end of the open reading frame and therefore likely represent recessive null or nondeleterious alleles. Given the underperformance of variant effect predictors in identifying dominant-negative mutations (54), it is possible that some *SYCE2* infertility mutations are being called as variants of uncertain significance and/or are causing disease in a heterozygous state and therefore are not being prioritized as candidate mutations. Therefore, increasing the number of infertility patients sequenced, and using pipelines to identify de novo heterozygous mutations in addition to homozygous recessive mutations in idiopathic infertility patients, could potentially identify mutations in this gene.

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SUMMARY POINTS

1. The mammalian synaptonemal complex (SC), which assembles between homologous chromosomes in meiosis, is composed of eight known proteins. Interaction interfaces, structures, and assembly properties of many SC components have been defined biochemically in vitro using purified proteins, and their roles in vivo have been assessed using genetically manipulated mouse models.
2. Mutations in SC genes cause male and female infertility, typically azoospermia and primary ovarian failure, in humans and mice due to the role of these genes in meiotic chromosome synapsis. Some SC gene mutations cause recurrent pregnancy loss in humans and mice that likely relates to defects in meiotic recombination and chromosome segregation.
3. Disease variants in SC proteins that do not appear to form core architectural structures of the SC and undergo multivalent interactions (SYCE1 and SIX6OS1) are typically recessive, consistent with loss-of-function disease mechanisms that weaken or ablate protein–protein interaction affinities.
4. Disease variants in SC proteins that provide core architectural assemblies within the SC (SYCP2 and SYCP3) are typically dominant-negative alleles that retain one protein interaction interface while disrupting a second, consistent with incorporation of these mutant proteins that poison the SC being part of the disease mechanism.
5. The phenotypic severity of SC gene variants depends on the extent to which these variants disrupt protein structure and different modular interaction interfaces and may not align directly with the phenotype of null alleles in mice. Heterozygous gain-of-function variants are most deleterious when they retain full binding affinity to a wild-type protein while poisoning a key function.
6. For some SC genes, few or no variants have been found to date that cause infertility in humans, even though potential loss-of-function mutations in these genes are under constraint in the population. Gene size, the underperformance of variant effect predictors in calling dominant-negative variants, and study designs that bias toward identification of homozygous null disease alleles are all likely influencing the identification of disease variants in SC genes.

FUTURE ISSUES

1. Improving our ability to link genotype to phenotype will continue to play an important role in determining causality for specific variants identified in exomic and genomic patient sequencing data. The genetic heterogeneity of infertility means that predicting phenotypic effects of specific missense, truncating, and noncoding variants in candidate infertility genes is becoming increasingly important. Given that the SC has multiple roles in meiotic chromosome biology, separation-of-function variants in SC genes could potentially cause distinct reproductive phenotypes.
2. A better understanding of the basic biology of the SC and how it fulfills its multiple roles in meiosis, in combination with quantitative approaches to modeling the biochemical, structural, and physiological effects of genetic variants, is likely to improve our ability

to predict the consequences of genetic variants in SC genes. Though there has been much progress in understanding how SC proteins interact to generate structural features and properties of the SC, our understanding of how the SC interacts with DNA and influences recombination remains poor.

3. The downregulation of nonsense-mediated mRNA decay in meiotic spermatocytes combined with the multimeric assembly properties of SC proteins during meiosis will make SC genes particularly sensitive to heterozygous dominant-negative variants containing premature termination codons. Gaining better insight into the extent that de novo heterozygous variants are contributing to infertility genetics and its heterogeneity will play an important role in interpreting the growing volume of sequencing data being generated from infertility patients.

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DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We thank the Wellcome Trust (Wellcome Senior Research Fellowship grant 219413/Z/19/Z to O.R.D.) and the Medical Research Council (Medical Research Council University Unit grant MC_UU_00007/6 to I.R.A.) for supporting the research in this area in our laboratories.

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