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# Structural maintenance of chromosomes: *him-1* and loss of synaptonemal complex structure in *Caenorhabditis elegans*

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**Summary.** A mutation in the cohesion gene *him-1* in *C. elegans* resulted in significant changes in the pairing efficiency of bivalents and in the structure of the synaptonemal complex (SC) during pachytene. The *him-1* (e879) strain, which is recessive and maps in Linkage Group 1, encodes a homologue of the conserved eukaryotic protein, SMC1, a member of the SMC (structural maintenance of chromosomes) superfamily that affects chromosome structure and function during meiosis. In the present study, the structure of the SC was compromised for an average of 62.5% of the total length of the pachytene bivalent. In these regions, the lateral elements were discernible; however, the central element, which was twice as wide as normal, was disorganized. Thus, the effect of the mutation in the cohesion gene is not on the axial cores/lateral elements of the bivalent, but rather on the transverse fibres of the central element of the SC. The organization of the gonad was also disrupted. The central rachis was poorly formed, although the pachytene nuclei were still arranged around it in a modified peripheral pattern. This resulted in the disruption of the transition zones between zygotene/pachytene and pachytene/diplotene. The frequency of X-chromosome nondisjunction was increased with a corresponding decrease in the numbers of Disjunction Regulator Regions (DRR). There were zero DRRs compared with six in the wild-type. The number of males produced in *him-1* was 17.0%, while in wild-type it was 0.3%. Recombination nodules, univalents, and trivalents were not observed in any nuclei. The ultimate goal of these studies is to correlate the physical and genetic maps. The locus for *him-1* is on Linkage Group 1, which has been identified in the pachytene nucleus of the free-duplication mutant *sDp1* (Goldstein, 2008).

**Key words:** *Caenorhabditis elegans,* cohesion gene, mutants, synaptonemal complex.

The free-living nematode *Caenorhabditis elegans* reproduces primarily as a self-fertilizing hermaphrodite, but a small number of morphologically distinct males (0.3%) are also present in the population (Hodgkin *et al.*,1979). The adult hermaphrodite has a pair of ovaries, 810 nongonadal nuclei and five pairs of autosomes with two X chromosomes (2A:XX). The adult male has a single testis, 970 nongonadal nuclei, and five pairs of autosomes but only a single X chromosome (2A:XO) (Hodgkin, 1980). Males arise from gametes that have been produced after X-chromosome nondisjunction; thus, the two sexes experience an unequal number of X chromosomes. They must compensate for this state of aneuploidy and develop mechanisms for gene expression and dosage compensation (Goldstein, 1987).

Changes in the number of sex chromosomes in *C. elegans* are better tolerated than those in autosomes due to genic balance *via* dosage compensation and X-chromosome inactivation. In addition, there is selective inactivation of specific genes *via* meiotic silencing (Kelly and Aramayo, 2007). A consequence of meiotic silencing is an X chromosome that is essentially inactive in male meiosis (Kelly and Aramayo, 2007). In other nematodes, such as *Ascaris*, there are extra Y chromosomes (Goldstein & Moens, 1976), however, the impact is small due to the reduced number of genes on the Y chromosome (Ohno, 1967). There may be a greater effect on the viability and fecundity of the organism when the reduced sex chromosomes are absent from the system, for example, XO females in humans. The alternative heterogametic situation could give rise to a lethal OY zygote (Ohno, 1967).

The synaptonemal complex (SC) has been highly conserved throughout evolution and occurs in a

wide variety of organisms during the pachytene stage of prophase I of meiosis (von Wettstein et al., 1984). This tripartite, proteinaceous structure, is usually limited to those organisms that undergo meiosis, and its presumed role is twofold: *i*) maintenance of proximity of homologous chromosomal segments, whereby the axial cores of the homologues become the lateral elements of the SC (Moens, 1968); and *ii*) regulation of ordered meiotic disjunction in which case the SC is maintained at the chiasma (Maguire, 1982). Irregular nondisjunction of the chromosomes at anaphase I may be a reflection of the pairing pattern at pachytene such that multivalent associations, as in polysomies and duplications, yield complex configurations that inhibit segregation (Rasmussen and Holm, 1980; Rose et al., 1984). In systems in which normal bivalent formation has been altered by the presence of duplications or translocations, the resultant univalents do not show ordered segregation patterns, and the resultant gametes are aneuploid.

In *C. elegans*, there are six SCs per germline nucleus. The XX hermaphrodite has five SCs associated with the autosomal bivalents and one SC for the XX bivalent. The XO male has only five SCs since the univalent X chromosome remains heterochromatic during pachytene (Goldstein & Slaton, 1982; Goldstein, 1982). The tripartite SC consists of two lateral elements and a striated central element with a distance between axes of approximately 100 nm. One end of the SC is attached to the inner nuclear envelope while the other end remains free in the nucleoplasm (Goldstein, 1982). There is no evidence of the configuration known as the 'bouquet' which facilitates homologous pairing via restricted chromosome movement (Gerton & Hawley, 2005). In addition, there are no recombination nodules present in *C. elegans,* although they have been described in other organisms (Zickler & Kleckner, 1999). Linkage Group 1 has been described in the pachytene nuclei from the free-duplication mutant *sDp1* in *C. elegans* (Goldstein, 2008) and has been the subject of intense genetic analysis (McKim & Rose, 1990). The *sDp1* free duplication is located on Linkage Group 1 and comprises 30 map units, which is significant. Most *C. elegans* duplications on the left half of chromosome 1 are unstable and subject to shortening (McKim & Rose, 1990) and are not involved in recombination. *SDp1* is stable, recombines with its homologue and carries the homologue recognition site on the right half of chromosome 1 (McKim & Rose, 1990). In addition, the free-duplication partially pairs with its homologue during pachytene (Goldstein, 2008).

Recently, a number of meiosis-specific proteins have been associated with the SCs in *C. elegans* (Colaiacovo, 2006). These include: *i*) REC-8, a cohesion protein that plays a key role in connecting sister chromatids along their full lengths, consequently contributing to proper chromosome segregation (Marston & Amon, 2004; Craig & Choo, 2005); *ii*) HIM-3, a protein recently implicated in meiotic pairing, DNA repair and SC formation; it associates with chromosomes upon entrance into meiosis between paired and aligned homologues where it remains until the metaphase I to anaphase I transition (Zetka *et al.*,1999); *iii*) SYP-1 and SYP-2, proteins that comprise the central element of the SC and have an important role in SC assembly (Colaiacovo, 2006). In pachytene, they localize continuously at the interface between paired and aligned homologous chromosomes. They dissociate from the bivalents through diplotene and diakinesis. Regions along homologous chromosomes that are not fully synapsed lack SYP-1 or -2; *iv*) ZHP-3, a protein that is not required for homologous pairing but is required for crossover recombination and consequent chiasma formation (Jantsch *et al*, 2004); and *v*) HTP-1,2 and 3- proteins that co-localize with SYP-1 along the interface between paired and aligned homologues throughout pachytene (MacQueen *et al*, 2005). There is a single homologue recognition site localized at or near one end of each of the chromosomes (McKim & Rose, 1990), which is involved in initiation of homologue pairing, recombination, and proper disjunction.

Hermaphrodites of the High Incidence of Males strain *him-1* (e879) have a high rate of X-chromosome nondisjunction as 17-20% of their progeny are male (Herman *et al.*, 1976) compared with 0.3% in wild-type. The *him -1* mutation is recessive and maps in Linkage Group 1 and has the following characteristics that differentiate it from wild-type:*i*) embryonic lethality of 5.8%; *ii*) response to UV light was abnormal; *iii*) reduced brood size to 66% of wild-type; *iv*) reproductive system development abnormal; *v*) DNA recombination abnormal to 58% of wild-type; *vi*) male fertility reduced to 1.4% of wild-type; *vii*) High Incidence of Male (*him*) progeny of 20.6% compared with 0.3% in wild-type; *viii*) Triplo-X progeny of 5.6% compared with 0.04% in wild-type; and *ix*) *him-1* was hypersensitive to X-ray irradiation (Wormbase, 2008). The *him-1* stain encodes a homologue of the conserved eukaryotic protein, SMC1, a member of the SMC (structural maintenance of chromosomes) superfamily affects chromosome structure and function during meiosis. It may interact with SMC-3 and DPY-28

localisation to meiotic chromosomes and the chromatin of transition-zone nuclei.

Disjunction Regulator Regions (DRR) were first described in *C. elegans* (Goldstein, 1982; Goldstein & Slaton, 1982). Analysis of the pachytene karyotypes of 113 complete nuclei in 12 different forms of *C. elegans* reveals that the frequency of X- chromosome nondisjunction is inversely correlated with the presence of DRRs and normal disjunction of the X chromosome (Goldstein, 1985). Thus, when there are zero DRRs present, the rate of X-chromosome nondisjunction can be as high as 51%, whereas when six DRRs are present on the SCs, the frequency decreases to 0.3% (Table 2).

## MATERIAL AND METHODS

The *C. elegans* individuals studied were 4- to 5-day old *him-1* hermaphrodites. The worms were processed for electron microscopy as previously described (Goldstein and Slaton, 1982). The *him-1* hermaphrodites were also selected after a few generations of growth and analysed in the same fashion. The computer technique for the analysis of serial ultrathin sections has been previously described (Peeples & Goldstein, 1989).

The karyotypes of five early-mid pachytene nuclei from *him-1* were reconstructed in this study from electron micrographs of serial sections (Table 1). One pachytene nucleus from each of five different worms was reconstructed. In addition, six complete pachytene nuclei were inspected in the electron microscope in order to determine the number of Disjunction Regulator Regions (DRR) and the extent of synaptonemal complex formation between the paired homologues in *him-1*. There were no DRRs observed in any of the nuclei which is consistent with the frequency of X chromosome nondisjunction (Table 2).

## RESULTS

The *him-1* strain of *C. elegans* is one of the High Incidence of Males and is located on Linkage Group 1 (Fig. 5). There was an increased number of males in the hermaphrodite progeny (20.6%), 5.6% Triplo-X hermaphrodites, and 5.8% inviable zygotes (Hodgkin *et al.*, 1979). The structure of the gonad and the peripherally located nuclei were not normal. In a normal gonad, the nuclei were arranged around the central rachis (Fig 1), which creates a communication network. This resulted in the synchrony of development in that specific area of the telegonic gonad such that successive stages of meiosis are present from the distal end. However, in *him-1*, there was a loss of the numbers of nuclei (50%) arranged around the central rachis and the

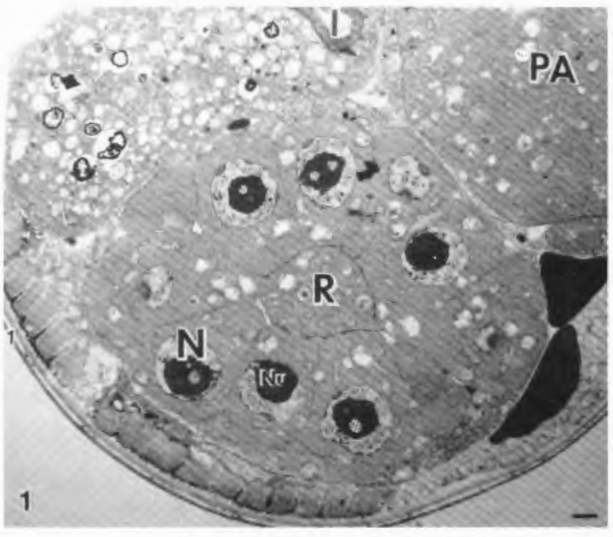


**Fig. 1.** The gonadal structure in wild-type *C. elegans* consisted of a central rachis (R) with the pachytene nuclei (N) arranged in a peripheral pattern. The pachytene stage was in the distal arm of the telogonic gonad. The synchronous development of the nuclei was the result of continuity between cells via the central rachis. Proximal Arm (PA) Nucleolus (Nu) Intestine (I) Bar equals 1 μm.

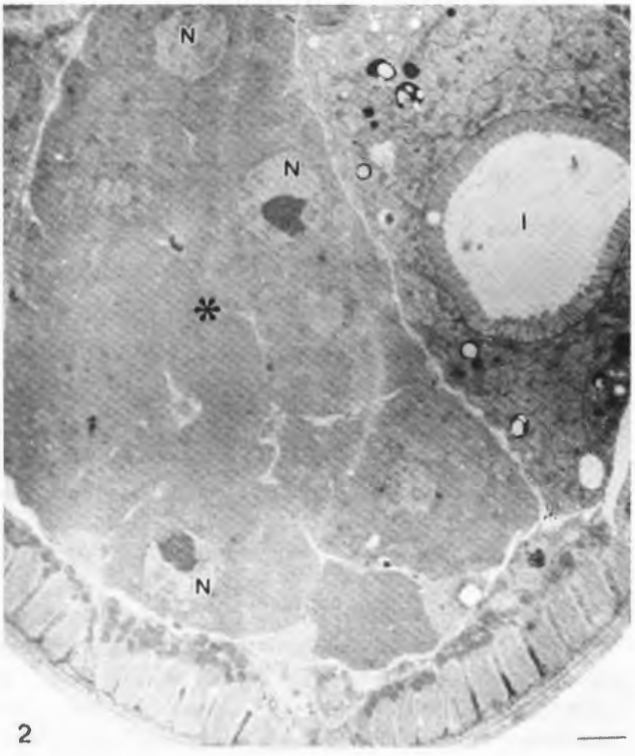


**Fig. 2.** The gonadal structure in *him-1* of *C. elegans* was compromised such that the central rachis (asterisk) was not well-formed and there was a loss of 50% of the pachytene nuclei (N). The peripheral pattern was aberrant. Intestine (I) Bar equals 1 μm.

**Table 1.** Pachytene chromosome lengths (μm) of *C. elegans him-1* (e879) hermaphrodites from three-dimensional reconstruction of serial sections of synaptonemal complexes and pachytene nuclei.

| SC # | Nucleus #1 | Nucleus #2 | Nucleus #3 | Nucleus #4 | Nucleus #5 |
|---|---|---|---|---|---|
| 1 | 2.5 | 2.3 | 2.6 | 2.5 | 2.7 |
| 2 | 9.7* | 9.6* | 7.6* | 8.4* | 7.5* |
| 3 | 7.8 | 7.1 | 6.8 | 6.3 | 7.5 |
| 4 | 8.2 | 7.1 | 6.5 | 6.3 | 7.8 |
| 5 | 7.1 | 6.9 | 8.7 | 5.3 | 7.3 |
| 6 | 4.8 | 5.7 | 5.3 | 4.8 | 8.1 |
| Total | 40.1 | 38.7 | 37.5 | 33.6 | 40.9 |
| Nuclear Volume $\mu m^3$ | 15.2 | 16.7 | 14.9 | 15.1 | 18.2 |
| Nucleolar Volume $\mu m^3$ | 2.8 | 2.7 | 2.5 | 6.8 | 5.3 |
| % Nu Vol. | 25.2 | 29.6 | 30.4 | 27.8 | 30.8 |
| # DRR | 0 | 0 | 0 | 0 | 0 |
| Position of NOR from Telomere | 10.3% | 17% | 29% | 15% | 47% |
| % Karyotype Complete SC | 21.2 | 46 | 39.2 | 42 | 39.4 |

* Nucleolar Organizer Region (NOR) found on this chromosome

**Table 2.** Comparison of occurrence of Disjunction Regulator Regions (DRR) and frequency of X-chromosome nondisjunction in various strains of *C. elegans*.

| Strain | # Nuclei Examined | Average Number DRR | % X-chromosome nondisjunction |
|---|---|---|---|
| Wild-Type (N2) | 10 | 6 | 0.3 |
| F4 | 13 | 5 | 0.3 |
| rad-4 | 6 | 7 | 0.03 |
| him-7 | 10 | 3 | 3.0 |
| him-8 | 9 | 0 | 37.0 |
| mnT6 (II:X) | 6 | 0 | 37.0 |
| Triplo-X | 8 | 0 | 51.0 |
| him-4 | 9 | 3 | 6.0 |
| mnDp1 | 10 | 3 | 1.0 |
| sDp1 | 11 | 3 | 2.0 |
| him-1 | 11 | 0 | 20.0 |
| him-5 | 10 | 2 | 16.0 |
| **Total** | **113** | | |

organization was disrupted (Fig. 2). The transition zones between zygotene/pachytene and pachytene/diplotene were disrupted. This is significant since it is the first time this has been observed in this author's work on 12 different forms of *C. elegans* (Table 2).

The structure of the SC is highly conserved along the phylogenetic evolutionary scale. In *him-1*, there were regions along the paired bivalents that had a normal SC, i.e., comprised of a central element and two lateral elements (Fig. 4). However, the structure was fully compromised for an average of 62.5% of the total length of the pachytene bivalent. In these regions, the lateral elements were visible. However, the central element was disorganized. In addition, the central element between the bivalent was twice as wide in those areas where the SC was not formed properly. In wild-type, there was a distance of 100 nm between the lateral elements of the SC (Goldstein, 1982); however, in the regions where an SC was not formed in *him-1*, the distance between the paired homologues was an average of 200 nm.

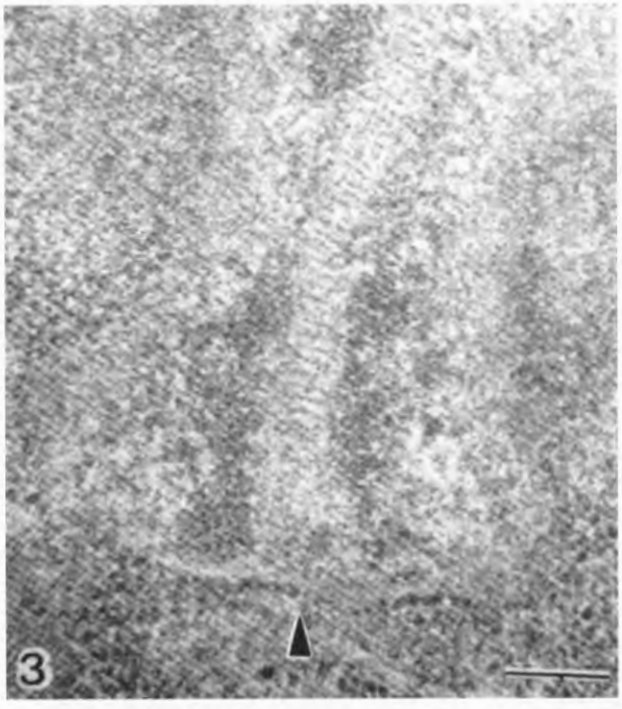


**Fig. 3.** Synaptonemal complexes in *C. elegans* were attached at only one telomeric end (arrowhead) to the inner nuclear envelope. The opposite end remained free in the nucleoplasm. Bar equals 0.1 μm.

Thus, the effect of *TIM-1*, the mutation of the SMC protein related to the *him-1* strain, is not on the axial cores/lateral elements of the bivalent, but rather on the transverse fibres of the central element of the SC.

Each pachytene nucleus of *him-1* had six tripartite SCs (n=6) that ranged in length from 2.3 to 9.7 μm. The average karyotype length of 38.2 μm was similar to that of the wild-type (37.5 μm). The shortest SC, which ranged from 2.3 to 2.7 μm long, was the XX bivalent and was located adjacent to the nucleus as in the wild-type. It was similar to every other strain of *C. elegans* previously studied (Goldstein, 1985). It is the only bivalent that was located directly adjacent to the nucleolus. Although Linkage Group 1 was identified in *sDp1* (Goldstein, 2008), due to switching of pairing partners with the free duplication, it was not morphologically distinct in the pachytene karyotype of *him-1*. Thus, the formation of the SC along Linkage Group 1 was disrupted for approximately 62% of its length. There were zero DRRs in each nucleus which is correlated with the frequency of X-chromosome nondisjunction.

Each SC was attached at only one end to the nuclear envelope with the opposite end being free in the nucleus (Fig. 3). Thus, there was no bouquet arrangement of the chromosomes at pachytene, although it is typical in other organisms. There were

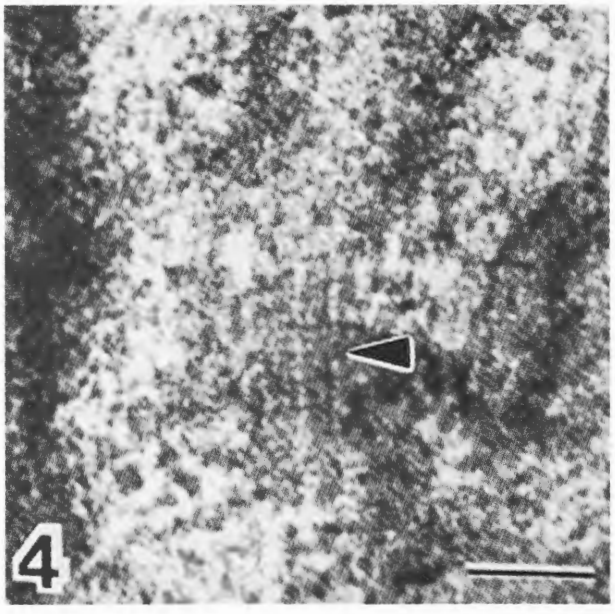


**Fig. 4.** Synaptonemal complex from *him-1* in *C. elegans*. The lateral elements (arrowhead) in this angled view appeared close together yet are actually 200 nm apart. The region directly above the lateral elements comprised the central element and transverse fibres that had not organized properly. The condensed chromatin of the bivalents formed the boundary. Bar equals 0.1 μm.

no univalents or trivalents present in the pachytene nuclei. In addition, there were no recombination nodules observed in any nuclei. That *C. elegans* has no recombination nodules, although recombination does occur, is similar to the situation in *Heterodera* (Goldstein and Triantaphyllou, 1979).

## DISCUSSION

Chromosome specific mutants, such as *him-1*, *him-5*, and *him-8* are unusual, having been reported in *Drosophila* and very few organisms. For example, *mei-1* (Valentin, 1973) is an autosomal recessive that affects only the X chromosome. In *C. elegans*, the synaptonemal complexes from pachytene nuclei have been described in *him-5* (Goldstein and Curis, 1987) and *him-8* (Goldstein and Huang, 1992). The structure of the SC can be used to determine stage-specific alterations (Goldstein, 1984). The mutant *him-1* is similar to the others in that a high number of males are produced due to X-chromosome nondisjunction, but different, since it is the only *him* strain studied thus far in which the structure of the SC is highly compromised.

The structural maintenance of chromosomes (SMC) during meiotic prophase is regulated by a class of proteins known as cohesions. The gene

*TIM-1* in *C. elegans* is associated with the cohesion complex and disruption of this complex resulted in decreased homologous chromosome pairing (Chan et al., 2003). Cohesion, consisting of two SMC subunits, SMC-1 and SMC-3, is loaded onto chromosomes during the S phase and establishes cohesion between the sister chromatids. The mutant *him-1* in *C. elegans* encodes SMC-1, which is required for functional activity of the complex.

Nuclei entering meiotic prophase go through a distinct morphological spatial reorganization from a honeycomb pattern into a highly structured region. At this time, the chromosomes within the nucleus become restricted to an area away from the nucleolus. Only the XX bivalent is associated with the nucleolus (Goldstein, 1982). It is within this transition zone for the leptotene/zygotene region, that homologues initiate pairing by a process that is independent of mature SC formation (MacQueen *et al.*, 2002). At pachytene, the nuclei are arranged peripherally around the central rachis and formation of the SCs along the length of the bivalents has been completed (Goldstein, 1982). After recombination, the bivalents undergo desynapsis following the disassembly of the SC, and are held together at the chiasma, which is the result of crossover recombination and chromosome cohesion distal to the crossover. There is another transition zone between pachytene/diplotene and diplotene/diakinesis which is morphologically distinct in the telogonic gonad.

The extended transition zone observed in *him-1* was the result of the disrupted SC assembly due to defective cohesion functions. This may also be the result of the effect of *TIM-1* on *SYP-1* location along the bivalents, such that it assembled in short-discontinuous patches along the bivalents rather than continuously, as was noted in wild-type (Chan et al., 2003). In the present study, ultrastructural analysis of the SCs revealed that the SC was in fact disrupted due to specific changes in the central element. Thus, the effect of *TIM-1* is not on the axial cores/lateral elements of the bivalent but rather on the transverse fibres of the central element of the SC.

Chromosome ends have been implicated in the meiotic processes of the nematode *C. elegans*. Cytological observations have shown that chromosome ends attach to the nuclear membrane and adopt kinetochore functions. In this organism, centromeric activity is highly regulated, switching from multiple spindle attachments all along the chromosome during mitotic division to a single attachment during meiosis. *Caenorhabditis elegans* chromosomes are functionally monocentric during meiosis. Earlier genetic studies demonstrated that the terminal regions of the chromosomes are not equivalent in their meiotic potentials. There are asymmetries in the abilities of the ends to recombine when duplicated or deleted. In addition, mutations in single genes have been identified that mimic the meiotic effects of a terminal truncation of the X chromosome (Wicky and Rose, 1996).

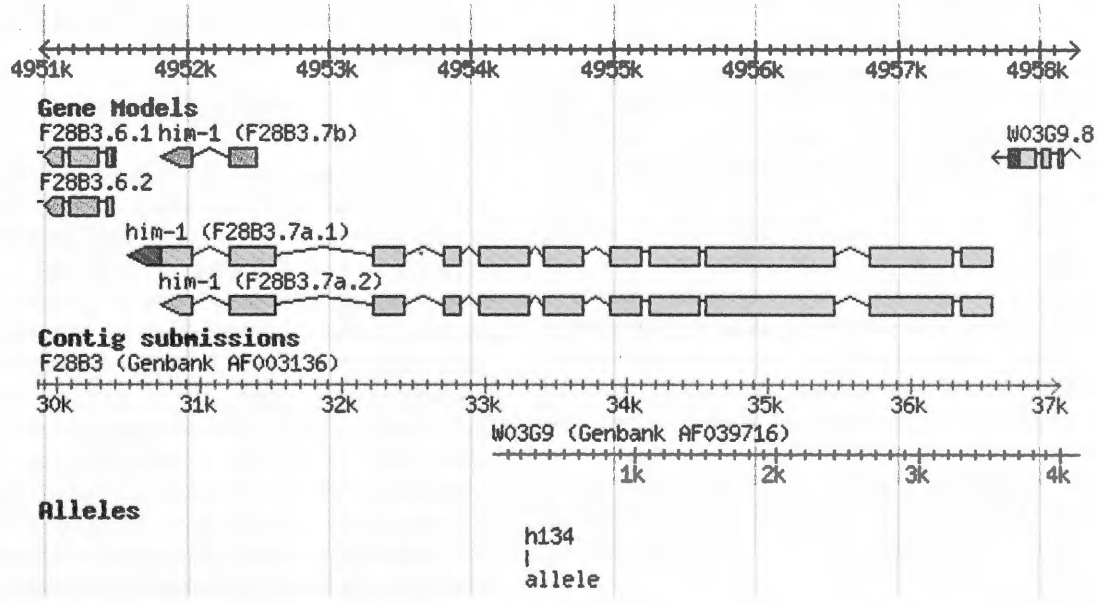


**Fig. 5.** Position of *him-1* on Linkage Group 1 (Wormbase, 2008).

**Genetic Position:** I:-0.45 +/- 0.007 cM [mapping data]

**Genomic Position:** I:4957670..4951575 bp

The frequency of self-progeny males decreased with age for *him-1* and *him-5*, however, in *him-5*, the structure of the SC was not altered in older specimens (Goldstein & Curis, 1987). Changes occured in the pachytene nuclei and gonadal organization in *him-5* during the aging process, some of which were similar to *him-1*. These included: *i*) loss of organization of the gonad; *ii*) differential condensation of chromatin with increased variance in length of the chromosomes; and *iii*) variation in nuclear and nucleolar volume along with increased density of the nucleoplasm (Goldstein & Curis, 1987).

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**Goldstein, P.** Поддержание структуры хромосом: мутация *him-1* и нарушения в структуре синаптонем у *Caenorhabditis elegans*.

**Резюме.** Мутация *him-1* в гене, отвечающем у *C. elegans* за объединение хромосом, приводит к существенным изменениям в эффективности образования пар бивалентов и к изменениям структуры синаптонемного комплекса на протяжении стадии пахитены. Штамм e879 несет рецессивную мутацию по гену *him-1*, входящему в состав группы сцепления 1 (Linkage Group 1) и кодирующему гомолог консервативного для эукариот белка SMC1. Этот белок относится к группе белков SMC (structural maintenance of chromosomes) обеспечивающих поддержание структуры и функции хромосом в процессе мейоза. Структура синаптонемного комплекса была нарушена у этих мутантов в среднем на протяжении 62.5% длины бивалента на стадии пахитены. В этих участках были различимы латеральные элементы, однако организация центрального элемента была нарушена, а его размеры вдвое превышали нормальные. Таким образом, было показано, что данная мутация по гену, обеспечивающему слипание хромосом, воздействует не на осевые структуры или латеральные элементы синаптонемного комплекса, а скорее на поперечные волокна центрального элемента. Были отмечены и нарушения в строении гонад. Так, оказывалось измененным строение рахиса, хотя пахитенные ядра все еще располагались на периферии рахиса. Эти изменения приводили в распаду четких зон перехода между зонами зиготены/пахитены и пахитены/диплотены. Частота нерасхождений Х-хромосомы нарастала с соответствующим уменьшением числа Участков Регуляции Расхождения Хромосом (Disjunction Regulator Regions или DRR). У мутантов не было обнаружено ни одного DRR, хотя у дикого штамма их число равно 6. Число самцов, образующихся у штамма *him-1* равно 17.0%, тогда как у дикого штамма - 0.3%. В ядрах не были отмечены рекомбинационные узелки, унивалентны и триваленты. Конечная цель этих исследований состоит в совмещении физической и генетической карт хромосом *C. elegans*. Локус *him-1* находится в группе сцепления 1 (Linkage Group 1), которая была выявлена в пахитенном ядре мутантов *sDp1* со свободной дупликацией (Goldstein, 2008).