Karyotype, ploidy, and gene dosage*

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Abstract

The normal karyotype of *Caenorhabditis elegans,* with its five pairs of autosomes and single pair of X chromosomes, is described. General features of chromosomes and global differences between different chromosomal regions are discussed. Abnormal karyotypes, including duplications, deficiencies, inversions, translocations and chromosome fusions are reviewed. The effects of varying ploidy and of varying gene dosage are summarized. Dosage-sensitive genes seem to be rare in *C. elegans,* and the organism is able to tolerate substantial levels of aneuploidy. However, autosomal hemizygosity for more than about 3% of the total genome may be incompatible with viability.

1. Normal karyotype

In the earliest genetic investigations of *C. elegans*, Nigon (1949a) showed that hermaphrodites and males both had five pairs of autosomes, but differed in the presence of two X chromosomes in hermaphrodites (*2A;2X*) as opposed to one X chromosome in males (*2A;1X*). Cytologically, all chromosomes appear as short rods at mitosis or meiosis, with no obvious substructure.

The six chromosomes are roughly equal in size, both in terms of DNA content [ranging from 12.8 Mb (Linkage Group III, abbreviated LGIII) to 20.8 Mb (LGV)] and in terms of recombinational length, at about 50 centimorgans each. The 50 cM genetic map length reflects the fact that each chromosome usually experiences one and only one crossover at meiosis (see Meiosis).

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The mitochondrial genome is a small circular molecule of 13.8 kb, and is discussed at greater length elsewhere (see Mitochondrial genetics).

2. Overview of chromosome organization

Each of the five linkage groups corresponding to the five autosomes has a discernible organization, with a central region or cluster, containing a higher density of genes, flanked by arms with fewer genes. These clusters were apparent in the first genetic map of *C. elegans*, worked out by Brenner (Brenner,1974). With the availability of genomic information, it became clear that part of the clustering results from long-range variation in recombination rate, with a metric (ratio of physical distance to genetic distance) of 100 - 500 kb/cM on the arms, as compared to 1500 kb/cM in the cluster regions (Barnes et al., 1995). Various general sequence features also distinguish the arm regions from the clusters: the arm regions have, overall, a slightly lower gene density (5.12 kb per gene as compared to 4.56 kb per gene in the clusters) and a different distribution of repeat sequences (*C. elegans* Sequencing Consortium, 1998). Initial annotations also indicated that the cluster regions contain relatively more conserved and essential genes than do the arms (*C. elegans* Sequencing Consortium, 1998; Hutter et al., 2000). Large-scale functional analyses of the genome by RNAi have confirmed and extended these regional distinctions (Kamath et al. 2003; Miller et al., 2004).

The X chromosome exhibits much less dramatic variation in recombination across its length, so that there is no obvious gene cluster in the X linkage map, and it also has a significantly lower gene density (6.54 kb per gene) (*C. elegans* Sequencing Consortium, 1998). The X chromosome is also unusual from a functional point of view, in that essential genes are significantly under-represented on this chromosome as compared to the autosomes (Piano et al., 2000; Piano et al. 2002; Reinke et al., 2000; Kelly et al. 2002).

C. elegans chromosomes, like those of nematodes in general, do not have a single centromere. At mitosis, spindle microtubules attach at multiple points along the chromosome (Albertson and Thomson, 1982). It is not clear whether there are preferred points on the chromosomes for spindle attachment; if so, these chromosomes should be regarded as polycentric rather than holocentric. Heterologous DNA, introduced as a transgenic array, seems to be handled fairly adequately by the mitotic machinery (Stinchcomb et al., 1985), which suggests that there are no special sequence requirements for spindle attachment (see Cell division).

At meiosis, there is a necessary requirement for a single attachment site on each chromosome to allow resolution and segregation of recombined chromatids. It appears that either end of each chromosome can be used for this purpose (Albertson and Thomson, 1993). With respect to the initial pairing of chromosomes at meiosis, the ends do differ: there appears to be a preferred pairing site close to one end of each chromosome (see Meiosis; right end of LGI and LGV; left end of LGII, LGIII, LGIV, LGX).

The absence of a defined centromere means that the genetic maps for each chromosome were plotted around arbitrarily chosen zero points, in the approximate middle of each chromosome. Genes to the left of this point were given negative coordinates, and are drawn on the upper arm in vertical display; genes to the right were given positive coordinates, and are drawn on the lower arm in vertical display. With the advent of complete sequence information, it has become possible to correlate these genetic map coordinates with absolute sequence coordinates.

The telomeres of *C. elegans* conform to the usual eukaryotic pattern of a long series of hexanucleotide repeats, with a repeat sequence TTAGGC similar to the vertebrate repeat TTAGGG (Wicky et al., 1996). In contrast to some organisms, however, there are no obviously specialized sub-telomeric regions.

3. Abnormal karyotype

Many alterations to the normal karyotype have been generated and examined. In addition to changes in whole chromosome number, discussed in the following section, a variety of sub-chromosomal alterations are possible, including duplications, deficiencies, inversions, and translocations.

A special class of translocations is those involving the fusion of whole chromosomes. The first of these to be reported was *mnT12*, a fusion between the left end of LGIV and the right end of the X chromosome (Sigurdson et al., 1984). A stable and fairly healthy hermaphrodite line having only five pairs of chromosomes could be generated using *mnT12*. Males of constitution *IV/mnT12/0* are fertile, and can be regarded as having a neo-X (mnT12) neo-Y (LGIV) constitution.

Similar chromosomal fusions can now be readily generated by growing mutants with telomere maintenance defects (Ahmed and Hodgkin, 2000). After many generations, these mutants experience telomere erosion, which leads to promiscuous chromosome fusion. The resulting fusion chromosomes are propagated reasonably stably, because the holocentric nature of nematode chromosomes is permissive for such structures. A variety of different fusions have been generated so far, and it is not clear if there is any limit to the possible combinations that can be generated, or to the associated variant karyotypes. A fusion of three chromosomes has been used to examine control of crossover distribution (Hillers and Villeneuve, 2003).

An attached-X chromosome (two X chromosomes fused at their left ends, symbolized *X^X*) has also been obtained in a different kind of experiment; this can be propagated but tends to break down, reverting to a normal XX constitution (Hodgkin and Albertson, 1995). In comparison, attached X (and attached autosome) chromosomes that have been generated for *Drosophila melanogaster* are relatively stable.

4. Tetraploids, triploids and haploids

Nigon was also able to establish and examine tetraploid lines of the species, although these were subsequently lost (Nigon 1949b, 1951a, 1951b). He found two types of tetraploid hermaphrodite, both larger in size than normal diploids; the two types differed in progeny production, one producing <1% males and the other more than 40% males. He concluded that these were of constitution 4A;4X and 4A;3X respectively, and that the males were of karyotype 4A;2X. Madl and Herman confirmed and extended these conclusions (Madl and Herman, 1979). They reported that 4A;4X hermaphrodites were of lower fertility than diploids (average tetraploid brood 84 eggs as compared to about 300 for diploids). Tetraploid egg viability was lower, with 87% of eggs hatching compared to >99% for diploids.

Triploids were also generated and examined by these authors, by mating diploid males and tetraploid hermaphrodites and vice versa. 3A;3X animals were found to be hermaphrodite and 3A;2X animals were male. The 3A;3X hermaphrodites exhibited high levels of embryonic inviability in their broods, with only 15% of eggs hatching, which presumably results from the production of many aneuploid progeny.

The implications of these observations on the effect of X chromosome dosage and autosomal dosage on sexual phenotype are discussed more extensively in the chapters on Sex determination.

Haploids of *C. elegans*, generated by extrusion of the maternal pronucleus after fertilization, are unable to complete embryogenesis although they produce several hundred cells. (Schierenberg and Wood, 1985). It was suggested that a female pronucleus might be necessary for successful embryogenesis, despite the fact that no imprinting appears to occur in *C. elegans*, as discussed below. Chromosomal balance should be identical between a normal diploid (*2A;2X*) and a haploid (*1A;1X*). Another possible explanation for haploid inviability is that excess dosage compensation occurs, resulting in insufficient X chromosome expression and therefore lethality. A third possibility is that the nuclear volume of a haploid *C. elegans* cell is simply too small to sustain normal gene regulation and expression. Nuclear volume seems to be largely determined by DNA content, and the 50 megabase DNA content of a haploid *C. elegans* nucleus would be smaller than any known animal genome.

5. Aneuploids

In principle, there are six possible trisomies and six possible monosomies for the *C. elegans* diploid genome, of which one, monosomy X or XO, occurs naturally in the form of the male sex. XO individuals are entirely viable as a consequence of the X chromosome dosage compensation system (see X-chromosome dosage compensation), which equalizes gene expression between the XX sex (normally hermaphrodite) and the XO sex (normally male). Trisomy X is also viable but abnormal: *2A;3X* individuals, otherwise known as triplo-X animals, are hermaphrodites with a dumpy body morphology, slower growth rate and lower fertility than normal *2A;2X* hermaphrodites (Hodgkin et al., 1979). Since they are abnormal, it seems that the dosage compensation mechanism is not proportionately more active in a triplo-X animal than in a diplo-X animal. Triplo-X animals with partial defects in dosage compensation, such as *dpy-21* mutants (which are viable but dumpy as diplo-X individuals) are inviable (Hodgkin, 1983). Individuals of karyotype *2A;4X* appear to be inviable, as inferred from the proportion of dead eggs produced in the progeny of *2A;3X* hermaphrodites. In all these cases, the inviabilities presumably result from cumulative over-expression of sex-linked genes. It is unlikely that any single gene on the X chromosome contributes a major part of the lethality, because screens for suppressors of the lethality due to defective dosage compensation have not yielded any candidates. Reduction in X chromosome dose has also been examined: individuals of karyotype *3A;1X*

are viable males, but they are noticeably abnormal and unhealthy, suggesting that any further reduction would be lethal (Hodgkin, 1987).

Among autosomal aneuploids, one trisomy (for LGIV) is known to be viable. Trisomy IV was generated by means of the IV-X fusion chromosome, *mnT12*, and also by using a meiotic mutant, *him-6* (Sigurdson et al., 1984). The triplo-IV animals have surprisingly normal appearance and viability, although they produce 50% fewer progeny than normal hermaphrodites. The inviability of most of the other possible aneuploids was initially suggested by the very high level of embryonic lethality observed in some meiotic mutants, which have general defects in recombination and chromosome nondisjunction. Lethality is most probably due to extensive nondisjunction resulting in many nullisomic and disomic gametes and hence to aneuploid progeny. Consistent with this interpretation, males of such meiotic mutants sire many inviable progeny, when crossed with normal hermaphrodites (Hodgkin et al., 1979).

The general meiotic mutant *him-6* was explicitly tested for the production of nullisomic and disomic gametes for each chromosome in turn (Haack and Hodgkin, 1991). The results showed that all of these possible abnormal gamete types were being generated, at roughly equal frequencies. These experiments also tested for gross chromosomal imprinting effects, which appear to be absent, because it was possible to recover normal diploids that had received a pair of autosomes only from the maternal parent or only from the paternal parent.

The inviability of all autosomal monosomies can be inferred independently from the failure to recover them in any of the many screens for genetic deficiencies that have been carried out. Such screens have concentrated on specific regions on each chromosome, and as a result large partial deficiencies have been recovered for each of the five autosomes (these are discussed further below), but no cases of monosomy have been seen. The fact that large deficiencies are usually conspicuously unhealthy suggests that there is a limit to how much haploidy can be tolerated in the genome, and that a deficiency as large as a whole chromosome would be well above this limit. It follows that there is no general mechanism for autosomal dosage compensation.

Autosomal trisomies have not been recovered from screens for duplications, although trisomy for LGIV might have been obtained, and the large duplication *mnDp37* appears to duplicate almost all of LGIII (Table 1). Some of the other autosomal trisomies (for LGI, LGII and LGV) may possibly be viable, but no explicit crosses designed to generate them have yet been reported.

Table 1. Large free duplications. The table lists some of the larger free duplications that have been obtained so far, together with their approximate extent as inferred from genetic data, and minimum size in Mb, based on the physical distance between loci known to be duplicated. Exact endpoints are not known for most duplications. Some of the duplications may however contain internal gaps, and therefore be somewhat smaller than indicated.

Duplication name	Location	Approximate extent (centimorgans)	Minimum size (megabases)
sDp2	*I, L*	21.4	7.2
sDp1	*I, R*	31.7	10.6
mnDp34	*II, R*	21.3	3.8
sDp3	*III, L*	23.0	6.6
mnDp37	*III*	40.3	11.6
eDp6	*III, R*	15.7	2.8
mDp4	*IV, L*	31.7	9.1
yDp1	*IV, R+V, L*	26.0	7.0
yDp13	*X, L*	15.7	2.4
mnDp3	*X, R*	14.9	4.3

6. Chromosomal duplications

The holocentric nature of nematode chromosomes means that chromosomal fragments can be propagated readily through mitosis, as long as they retain a sufficient amount of centric material to capture spindle microtubules. As a result, chromosomal fragments have been generated and preserved for many parts of the *C. elegans* genome, as free duplications. Some of the larger free duplications are listed in Table 1. Additional duplications have also been recovered as stable translocations to other chromosomes.

The limits to generation of free chromosomal duplications are not known, but very small free duplications have never been reported. Extrachromosomal transgenic arrays which behave much like free duplications can be generated after microinjection; these arrays appear always to carry at least 40 copies of the injected sequences, probably adding up to a megabase or more in total length (Stinchcomb et al., 1985). Smaller arrays and small chromosomal fragments may therefore not be successfully handled by the mitotic machinery.

More than 80% the *C. elegans* genome has been duplicated by one means or another, implying that a 50% increase in gene dosage for any of the genes concerned has no seriously deleterious effect. Two large regions, on the left arm of LGII and the right arm of LGV, are not represented in the set of duplications, probably because no serious attempts have yet been made to generate duplications for these regions.

7. Chromosomal deficiencies

Numerous chromosomal deficiencies have been generated in the course of many different investigations, such that more than 75% of the genome is now covered by at least one deficiency. These deficiencies provide extremely useful tools for analysis of mutations, for manipulation of gene dosage and for mapping. The majority of deficiencies appear to be continuous, with breakpoints that can be exactly defined on both genetic and molecular maps. However, it should be noted that some deficiencies, like some duplications, appear to have more complex structures, with discontinuities or rearrangements within the overall span apparently deleted.

A few large segments of the genetic map are currently lacking in any deficiencies, notably on the right arm of LGII (17 centimorgans) and the left arm of LGIV (26 centimorgans). These absences may simply result from a lack of any systematic screens for deficiencies in the relevant segments, rather than from failure to recover them. However, in some small regions of the genome, deficiencies appear to be difficult or impossible to generate, presumably because one or more haplo-insufficient loci (discussed below) are present in the intervals concerned. A conspicuous example is provided by a region on LG II, genetic map interval 0.79 to 0.81. Numerous deficiencies extend leftward or rightward from this interval, but none crosses it (Sigurdson et al., 1984). One or more genes in this gap are likely to be haplo-insufficient, so that a deletion would have dominant lethal effects. The only gene in the gap that has been studied in any detail is *zyg-9*, which encodes a conserved spindle component, but mutations in this gene show no dominant effects (Matthews et al., 1998), so *zyg-9* does not appear to be needed in more than one copy. Some other possible haplo-insufficient regions can be tentatively identified on other chromosomes, but their existence is hard to prove, and the whole genome may contain fewer than ten.

The large-scale structure of chromosomes in *C. elegans* probably also contributes to the size and distribution of known deficiencies. As discussed above, the five autosomes all have a structure with a central cluster region, with slightly higher gene density, reduced recombination, and more conserved and essential genes, as compared to the flanking arm regions. Table 2 lists some of the largest deficiencies that have been obtained so far, together with estimates of their genetic length in centimorgans and minimum physical extent in Mb. All the largest deficiencies affect mainly arm regions, and none removes an entire cluster or more than about 4 Mb. Most or all of these deficiencies exhibit significantly reduced viability and fertility, as heterozygotes (*Df/+*). These deleterious effects probably result from the cumulative effect of reducing gene dosage. Consequently, it is expected that deficiencies larger than those generated so far would be dominantly lethal, although all of the genes affected may be individually haplo-sufficient. This effect will be greater for the cluster regions, because of the higher density of essential and non-redundant genes. One can predict that any deficiency, or combination of deficiencies, that removes more than about 3% of the total gene content of *C. elegans*, will be dominantly lethal. Tests of this prediction by combining smaller deficiencies on different chromosomes are feasible, but have not yet been carried out.

Table 2. Large deficiencies. The table lists a set of large deficiencies, two for each chromosome. Approximate genetic extents have been inferred from genetic data. Physical sizes are estimated from the distance between the last sequence-positioned genes that are known to be deleted, at either end of each deficiency. Therefore, these sizes may be underestimates. Exact endpoints are known for few deficiencies. Also, some deficiencies may be discontinuous, and therefore remove less of the genome than their predicted length suggests.

Deficiency name	Location	Approximate extent (centimorgans)	Minimum size (megabases)
hDf10	*I, L*	6.5	1.8
dxDf2	*I, R*	15.0	3.1
ccDf11	*II, L*	14.1	4.6
mnDf89	*II, RC*	3.7	2.5
nDf11	*III, LC*	5.1	1.1
eDf2	*III, R*	15.9	2.9
mDf9	*IV, LC*	2.6	1.1
nDf27	*IV, C*	5.3	2.1
sDf45	*V, L*	11.5	3.7
ozDf1	*V, R*	12.0	3.0
syDf1	*X, L*	4.6	2.0
mnDf1	*X, R*	8.0	3.4

8. Dosage sensitive genes

Most genes display no obvious phenotype when their dosage is reduced by 50%, in hemizygotes, or increased by 50%, in duplication-bearing animals. In general, it is likely that such alterations in dosage do have a small impact on viability, which is cumulatively deleterious in large deficiency heterozygotes, but the reduction in viability is not easily perceptible at the level of a single gene. Moreover, considerations from metabolic control theory indicate that genes encoding enzymes in metabolic pathways are expected in general to be insensitive to variations in dose (Kacser and Burns, 1981).

As noted above, the absence of hemizygously viable deficiencies for certain parts of the genome suggests that they may contain haplo-lethal genes, but no specific case of haplo-lethality has yet been demonstrated. A few genes do appear to be conspicuously haplo-insufficient, such that hemizygotes exhibit a recognizable phenotype. Most of these seem to be genes encoding structural proteins or regulatory molecules. An example of the former is the collagen gene *dpy-13* (von Mende et al., 1988). Examples of the latter are provided by the sex determination genes *tra-2* (Trent et al., 1983) and *fem-3* (Hodgkin, 1986). The expression of both of these genes is partly regulated by translational control, in order to achieve proper development of the hermaphrodite germ line (see Sex-determination in the germ line) so it may be that transcription levels for these genes are necessarily limiting, in order to facilitate the translational modulation. The paucity of haplo-insufficient genes in *C. elegans* is also evident from a general screen for dominant mutations in this organism (Park and Horvitz, 1986), which yielded many gain-of-function mutations but only one candidate for a gene with a dominant null phenotype, *unc-108*.

Haplo-insufficiency is rare when genes are considered alone and on a wildtype background, but it can become much more frequent on a sensitized background. Effects of this type are described and discussed further in the Chapters on Complementation and Genetic enhancers.

No examples of triplo-lethal genes have yet been reported in *C. elegans*. However, further increases in the dosage of many individual genes can be deleterious. Such increases are routinely achieved in the generation of multicopy extrachromosomal transgene arrays, which may have 50 or more copies of an individual gene. There has been no systematic study of copy number and corresponding expression levels for these arrays, and it is unlikely that these arrays express gene products as efficiently as the normal chromosomal copies do, but several-fold

over-expression seems probable. Creation of multi-copy arrays is difficult or impossible for some cosmid transgenes, probably as a result of such over-expression lethality. A few specific cases have been demonstrated, where multicopy transgene arrays of a particular gene have been impossible to generate, but integrated single-copy transgenes have proved viable and functional. One example is *rom-1*, encoding the rhomboid protease (Dutt et al., 2004); another is the collagen gene *dpy-17* (Jacopo Novelli and J. H., unpublished observations).

Genes encoding proteins that are needed in stoichiometric amounts, as part of a multi-protein complex, might be expected to show strong dosage effects, but these genes often exhibit a specific auto-regulatory mechanism, which ensures that protein levels do not go too high or too low. An example is provided by some of the ribosomal proteins, such as RPL-12, which appears able to inhibit productive splicing of its own pre-mRNA, as a negative feedback control (Mitrovich and Anderson, 2000).

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