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Ontogenes and Chromosome Nondisjunction in the *D. melanogaster* Meiosis

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Abstract

A mutation in an ontogene acts as a conditional dominant lethal: it is lethal in a certain genotype but not lethal in another. In total, 30 mutations of this type residing in the *Drosophila melanogaster* X chromosome have been assayed for their ability to cause meiotic nondisjunction. The level of X nondisjunction in the females heterozygous for the mutation in ontogene appears to be very high. The share of matroclinous daughters reaches 24.7% of the overall offspring and of patroclinous males, 24.9%. Neither inversion in the opposite X chromosome nor additional Y chromosome has any effect on the X nondisjunction. The balance of the XX and X0 egg cells is disturbed: exceptional daughters are prevalent in the offspring of the females with a normal opposite X chromosome and exceptional sons, in the offspring of the females with an inverted X chromosome. In addition, 12% of the matroclinous daughters of the females with a normal opposite X chromosome are homozygous for the marker of one of the maternal X chromosomes ("equational" nondisjunction). A "fading" parental effect of the mutation in ontogene on the X chromosome nondisjunction is also observed. Under experimental conditions, the mutant ontogenes reside in meiotic densely compacted X chromosomes. We infer that the ontogenes are DNA regions with controlled compaction. It is postulated that the genetic activity of ontogenes is determined by this compaction and has a biophysical (electromagnetic) nature. In a meiotic cell, ontogenes induce physical fields providing the operation of meiotic proteins. The structure of these fields is distorted in the mutants for ontogenes, thereby decreasing the efficiency of proteins and, as a consequence, causing meiotic defects.

Keywords

Conditional Mutation, Ontogene, Chromosome Nondisjunction, Meiotic Division, Drosophila

1. Introduction

A constant species-specific appearance of a living organism (intraspecific similarity) is provided by the conserved part of the genome [1] [2]. In the interspecific hybrids, the conflict between the genomes at the level of soma leads to lethality and at the level of embryonic tissue, to sterility. A study of the so-called *conditional dominant lethals* of *Drosophila melanogaster* was the approach used to examine the conserved part of the genome [3] [4]. Under certain genetic conditions, such as genotype, sex of mutant, and direction of crossing, a mutation acts as a dominant lethal, and under other conditions, dominant lethality disappears [5] [6]. This inconstant lethality makes it possible to generate the mutations of this type, keep them as fly stocks, and study the numerous and most curious manifestations that accompany the mutation in heterozygous flies [7]. The genes carrying conditional mutations got the name ontogenes [8] [9].

Some manifestations of the mutations in ontogenes are most exotic, such as the development of monstrosities (morphoses) [10] [11] and changes in the standard metabolism [7]. Some manifestations of conditional mutations are rarely observable in the case of common mutations, namely, parental inheritance [12] [13] and instability [14]. Finally, some manifestations are quite familiar and have been comprehensively studied in Mendelian mutations. The last deserve a high priority study since they allow for a better insight into the link between the world of the well-known Mendelian genes and the world of "strange" ontogenes.

In this paper, we describe and discuss the effect of genes on meiotic chromosome nondisjunction. As has been observed when studying the mutations of drosophila ontogenes, the offspring of mutant females contains many males with a patroclinous X chromosome [3]. This would suggest that ontogenes are responsible for the chromosome segregation in meiosis, whereas their mutations lead to the nondisjunction of homologs. Nondisjunction is the meiotic event resulting in the gametes either with two chromosomes of a particular pair or in the absence of both chromosomes. This phenomenon was discovered by Bridges in drosophila [15] [16] and is famous as one of the first arguments favoring the chromosome theory of inheritance. As for classical genetics, the phenomenon of nondisjunction is at the center of the research into the *meiotic behavior of chromosomes*, which comprises their pairing, crossing over, and segregation [17] [18] [19].

Despite several outstanding studies on chromosome nondisjunction, the logic of chromosome behavior in meiosis is still vague. The homology relying on the nucleotide sequence could be regarded as the basis for the mechanism underlying the chromosome recognition [20] [21]; however, the facts contradict this hypothesis. In particular, a change in the nucleotide sequence of a homologous gene or the presence of a chromosome rearrangement, which seems to interfere with homologous pairing and lead to nondisjunction, does not disturb chromosome segregation.

The goal of this work was to study in detail the effect of the mutation in ontogene on the meiotic distribution of the X chromosomes in *D. melanogaster.* We

assumed that this work, on the one hand, could enhance the insight into the specific features of a new class of genes, ontogenes, and, on the other hand, could assist in the clarification of the patterns of chromosome behavior in meiosis. Here, we describe the first observations concerning the effect of mutations in ontogenes on the X chromosome nondisjunction and the results of the subsequent advanced study of nondisjunction in one of the mutants. The study has shown an unprecedentedly high level of meiotic abnormalities caused by mutations in ontogenes. This suggests that ontogenes represent a special class of hereditary units. According to the character of abnormalities, the effect of ontogenes in meiosis can be qualified as a *biophysical activity of compacted DNA regions*, which is rather unusual in terms of the current concept of gene activity. It is believed that this activity is of a chemical nature and takes place in the decompacted DNA regions.

2. Materials and Methods

1) Generation of conditional mutations in the X chromosome of *D. melanogaster*

In total, 30 conditional mutations in the X chromosome have been studied; 20 of them were generated earlier with the help of gamma-irradiation and a specially designed selection system. The characteristic of each mutation is that it failed to act as a lethal in males but turned into a dominant lethal in the daughters of a mutant male crossed with *yellow* females [5] [6]. The presence of an inversion in the X chromosome eliminated the lethal effect of the mutation in a female [3]. Before the experiment, the mutations were kept as laboratory stocks using two schemes: 1) ♀ *In*(1)*Muller*-5/*l* × ♂ *In*(1)*Muller*-5 and 2) ♀ *C*(1)*DX*/× ♂ *l*. The chromosome *In*(1)*Muller*-5 in these stocks carried the inversion $In(1)sc^{S1L}sc^{8R}$ + *S*, sc^{S1} sc^{8} w^{a} *B* with the mutations *scute* (*sc*), *white-apricot* (w^{a}), and *Bar* (*B*) [22]. Hereinafter (in both body text and tables), the inverted chromosome is designated as *In*(1)*Muller*-5, w^{a} *B* or shorter, as *In*(1)*Muller*-5 or *In*(1).

Ten conditional mutations were selected from the recessive lethals in the X chromosome obtained using the Muller-5 method. The characteristic of these mutations was that they ceased to manifest themselves as lethal if the *In*(1)*Muller*-5/*l* female carrying them was crossed with the male of some genotype other than an *In*(1)*Muller*-5 male (as is usually done) [23]. The mutations before the experiment were maintained as a ♀ *In*(1)*Muller*-5/*l* × ♂ *In*(1)*Muller*-5 stock.

2) Monitoring the X chromosome nondisjunction according to formation of exclusive males

The first three experiments were focused on monitoring the males with patroclinous X chromosome. In the first experiment, mutant *In*(1)*Muller*-5/*l* females were crossed with *yellow* males. In the second experiment, the mutant females carried a pair of different conditional mutations each in both X chromosomes. These females were also crossed with *yellow* males. In the third experi-

ment, *In*(1)*Muller*-5/*l* females were crossed with *yellow* and *forked* males. The patroclinous exclusive males had a *yellow* phenotype in the first two experiments and a *yellow* or a *forked* phenotype in the third experiment.

3) Nondisjunction of the X chromosomes in the females carrying conditional mutation *l*(1)

A high rate of patroclinous sons of the females in the first three experiments demonstrated serious meiotic abnormalities in the mutant mothers and, correspondingly, the need to deepen the study. We decided (i) to use not only exclusive males, but also exclusive females as an indicator of nondisjunction; (ii) to determine the type of nondisjunction (primary or secondary) by monitoring the presence of free Y chromosome in the analyzed female; and (iii) to assess the effects of the *In*(1)*Muller*-5 inversion in the X chromosome and the additional Y chromosome on the nondisjunction.

a) *Preparation of the initial l*(1) *strain without free Y chromosome*

One strain with the *l*(1) conditional mutation in the X chromosome was selected for further study of nondisjunction. The strain was cleaned from any possible presence of a free Y chromosome. For this purpose, the *XY, y B/YO* males of the laboratory strain *XX, w/YO & XY, y B/YO* were used. Initially, we tested this strain for the absence of a free Y chromosome. For this purpose, the *XY, y B/YO* males of this strain were crossed with *yellow* females. The sons of this cross appeared to be sterile. Then, the *XX, w/YO* females of this strain were crossed with *yellow* males. The sons of these cross were sterile too. This demonstrated that the *XX, w/YO & XY, y B/YO* met the claimed formula and did not carry a free Y chromosome; thus, it was appropriate to clean the initial *l*(1)*/In*(1)*Muller*-5, w^a *B* mutant strain.

The next stage in the cleaning procedure was the cross of *l*(1)*/In*(1)*Muller*-5, w^a *B* females (possibly carrying a Y chromosome) with the *XY, y B/YO* males tested for the absence of the Y chromosome. In the resulting offspring, the *l*(1)*/XY, y B* regular daughters and *l*(1)*/In*(1)*Muller*-5, w^a *B* exclusive daughters had a *B/*+ phenotype. Both did not have any additional Y chromosome received from a male. Individual crosses with brothers allowed us to obtain the *l*(1)*/In*(1)*/Y*0 stock with guaranteed absence of an additional Y chromosome, necessary for further experiments. These were the tubes containing the *l*(1)*/In*(1) (phenotype *B/*+) females, *In*(1)*/In*(1) (phenotype *B* w^a) females, and *In*(1) (phenotype *B* w^a) males.

b) *Generating the strains carrying the l*(1) *mutation*

The *B/*+ females from these tubes carried the first genotype planned for this experiment, *l*(1)*/In*(1) (**Table 1**, row 1). To study the nondisjunction, they were crossed with the *white* males. All classes of the offspring differed in their phenotype, allowing the rate of X chromosome nondisjunction to be determined according to both females and males.

The crosses with *white* males were also used to get the females of three additional genotypes planned for the study. The daughters with + phenotype in this

cross were assayed for the X chromosome nondisjunction in the *l*(1)*/w* females (the variant of mutation and structurally normal X chromosome; Table 1, row 3); the *B/+* daughters were assayed for the nondisjunction in the *l*(1)*/In*(1)*/Y* females (the variant of mutation, X inversion, and free Y chromosome; Table 1, row 2); and the w/w^a *B* daughters, for the nondisjunction in the control *w/In*(1) females, lacking the mutation (Table 1, row 4). The genotypes of the males used in the crosses are also listed in Table 1 (column 2).

The control *w/In*(1) females, lacking the lethal mutation, quite unexpectedly displayed a rather high level of the X chromosome nondisjunction. We could not exclude the maternal effect of the *l*(1) mutation of their *l*(1)*/In*(1) mothers. This suggested the need in another (external) control. In this control, the *w/In*(1) females were not the daughters of the females carrying the *l*(1) mutation. The females were produced by crossing the strains *w/w* with *In*(1)*Muller*-5, w^a *B* */In*(1)*Muller*-5, w^a *B.* The X chromosome distribution there was studied according to the offspring produced by the cross with *y/Y.sc*^{8} males (external control 1) and *y B/Y*0 males (external control 2). Table 1 shows the structure of all performed crosses with the genotypes of parents and all classes of the offspring as well as the phenotypes of the unexpected offspring.

c) *Analysis of exclusive w females for the presence of w l*(1) *crossover chromosome*

The class of *w* daughters unexpectedly emerged in the offspring of the *l*(1)*/w* females (Table 1 and Table 5, row 3). These females could appear as a result of the *w* X chromosome nondisjunction in the second meiotic division (equational nondisjunction) or the nondisjunction of exchange X chromosomes in the first

Table 1. Performed crosses and the genotypes of offspring.

Genotype of studied female	Cross	Regular offspring				Exceptional offspring		Other
		♀	♀	♂	♂	♀	♂	
l(1)*/In*(1)	♀ *l*(1)*/In*(1)*Muller*-5, w^a *B* × ♂ *w*	*l*(1)*/w*	w^a *B/w*	w^a *B*	*l*(1)†	*l*(1)$/w^a$ *B*	*w*	–
l(1)*/In*(1)*/Y*	♀ *l*(1)*/In*(1)*Muller*-5, w^a *B/Y* × ♂ *w*	*l*(1)*/w*	w^a *B/w*	w^a *B*	*l*(1)†	*l*(1)$/w^a$ *B*	*w*	♂ + Notch
l(1)*/w*	♀ *l*(1)*/w* × ♂ *In*(1)*Muller*-5, w^a *B*	*l*(1)$/w^a$ *B*	*w* $/w^a$ *B*	*w*	*l*(1)†	*l*(1)*/w*	w^a *B*	♀ *w/w* ♂ + Notch
w/In(1) (control)	♀ *w/In*(1)*Muller*-5, w^a *B* × ♂ *y/Y.sc*^{8}	*w/y*	w^a *B/y*	*w*	w^a *B*	*w*/w^a *B*	*y*	♂ w^a ♂ *w B*
w/In(1) External control 1	♀ *w/In*(1)*Muller*-5, w^a *B* × ♂ *y/Y.sc*^{8}	*w/y*	w^a *B/y*	*w*	w^a *B*	*w*/w^a *B*	*y*	♂ w^a ♂ *w B*
w/In(1) External control 2	♀ *w/In*(1)*Muller*-5, w^a *B* × ♂ *y B/Y*0	*w/y B*	w^a *B/y B*	*w*	w^a *B*	*w*/w^a *B*	*y B*	♂ w^a ♂ *w B*

meiotic division. In order to clarify the real cause why the *w* daughters were formed, we attempted to make sure that the nondisjoined X chromosomes had undergone exchange. See Results for the details of crosses and their results.

4) Statistical processing of results

The reliability of the difference in nondisjunction frequencies was assessed by the Student's t-criterion.

3. Results

High frequencies of exceptional offspring

The emergence of patroclinous sons in the offspring were for the first time observed for the *In*(1) *Muller*-5, w^a *B*/+ females, carrying the conditional mutation in the X chromosome (+) [3]. The number of patroclinous *yellow* males was close to the regular classes of the offspring (**Table 2**). The same effect was repeated in the mutant females carrying mutations in the ontogene in each X chromosome (**Table 3**) and lacking *In*(1) *Muller*-5, w^a *B.* Finally, a large number of the patroclinous sons were for the third time recorded in the offspring of the females with the conditional mutations generated according to the Muller-5 method [23] (**Table 4**). None of the experiments was aimed at the study of chromosome nondisjunction but the high rates of patroclinous males (**Tables 2-4**) suggested the ability of these new mutations to induce an upsurge of meiotic nondisjunction. In the norm, the frequencies of the primary X chromosome nondisjunction assessed according to the exceptional females and exceptional males amount to approximately 0.05% and the frequencies of the secondary nondisjunction, to approximately 4% [5]. The highest rates of the exceptional males (40% - 50%) are known for the XXY females heterozygous for the X chromosome inversion [24]. The rates of exceptional males in the performed experiments (**Tables 2-4**) were close to these values although the females in the second experiment (**Table 3**) had no inversion in the X chromosome and the additional Y chromosome in the females in each of the three experiments could appear only accidentally.

Nonetheless, we decided to assay the female for the presence of an additional Y chromosome using the test for sterility of patroclinous sons. However, this test failed to make the issue more clear. Part of the patroclinous sons was fertile, as is typical of the patroclinous sones of XXY females, and part was sterile, as in the case of the patroclinous sones of XX females. As it turned out later, the cause of the uncertainty consisted in that the mutant stocks were contaminated with the XXY females. The main result of the first observations is that *the meiotic abnormality consisting in nondisjunction is a rule for the mutations in ontogenes.* In total, a high yield of the exclusive males in the offspring of females has been observed for 56 stocks carrying different mutations in ontogenes. The females of 39 stocks carried the *In*(1)*Muller*-5, w^a *B* inversion (**Table 2** and **Table 4**) and the females of 17 stocks, a mutation in each X chromosome (**Table 3**). In total, 30 different mutations in the X chromosome were involved in the experiment;

some of them were present in several stocks (Table 2 and Table 3). The highest rates of exceptional males were observed for the mutations selected from the lethals of the Muller-5 test (Table 4). As is evident from Table 4, the frequencies of nondisjunction are well reproducible in the crosses with the males of most different genotypes.

The data of a special set of experiments (Table 5) confirm that the production of patroclinous males by the females carrying mutant ontogenes was accompanied by generation of matroclinous daughters. Both are formed at a very high rate: the share of exclusive daughters reached 24.7% and of exclusive sons, 24.9%. The high rates of the XXY matroclinous daughters explain the cause of uncontrollable presence of the XX females along with the common females in the stocks of ontogene mutations. At a high rate of the primary X chromosome

Table 2. The offspring of the *In*(1)*Muller*-5, w^a *B*/+ females carrying a conditional mutation in the X chromosome and crossed with *yellow* males.

Mutation no.	Females		Males			Total offspring (with correction)*	Share of exclusive *yellow* males in offspring
	+	*B*/+	+	w^a *B*	*y*		
2	14	26	18	16	2	78	5.1
3	19	23	14	14	4	78	10.3
4	6	18	3	11	8	54	29.6
5	10	21	6	19	5	66	15.2
7	41	53	34	31	10	179	11.2
8	20	25	18	17	4	88	9.1
9	6	7	1	5	9	37	48.6
10	50	38	42	25	1	157	1.3
11	12	25	8	12	3	63	9.5
29	39	37	19	38	15	163	18.4
30	24	50	14	23	5	121	8.3
31	20	53	2	24	4	107	7.5
32	14	45	10	40	1	111	1.8
33	27	40	25	34	9	144	12.5
34	11	12	11	9	1	45	4.4
35	17	35	22	33	34	175	38.9
36	23	28	20	14	5	95	10.5
38	24	25	30	29	5	118	8.5
41	38	54	37	33	16	194	16.5
Total	415	615	334	427	141	2073	13.6

*The number of patroclinous *yellow* males is doubled when counting the offspring.

Table 3. The offspring of the females carrying a conditional mutation in each X chromosome and crossed with *yellow* males.

Number of stock of female*	Females +	Males +	Males *y*	Total offspring (with correction)**	Share of exclusive *yellow* males in offspring
6/41	97	78	3	181	3.3
6/8	58	62	3	126	4.8
6/38	29	22	1	53	3.8
6/29	96	84	-	180	0
6/7	50	38	-	88	0
6/3	57	50	6	119	10.1
6/10	33	27	8	76	21.1
6/11	40	29	5	79	12.7
6/4	5	1	3	12	50
6/9	67	78	1	147	1.4
6/35	28	35	24	111	43.2
6/5	13	12	3	31	19.4
3/11	11	14	-	25	0
3/8	38	25	19	101	37.6
9/10	29	32	25	111	45
9/5	1	6	1	9	22.2
9/11	24	24	20	88	45.5
Total	676	617	122	1537	15.9

*The number of stocks is composed of the numbers of studied mutations. **The number of patroclinous *yellow* males is doubled when counting the offspring.

Table 4. The offspring of the *In*(1)*Muller*-5, w^a *B*/+ females carrying a conditional mutation in the X chromosome (+) and crossed with *yellow* and *forked* males.

Number of stock of *M*-5/*I*(1) female	Cross with *yellow* (*y*) male			Cross with *forked* (*f*) male		
	Total offspring	Exceptional *yellow* males	Share of X0 gametes* (%)	Total offspring	Exceptional *forked* males	Share of X0 gametes* (%)
2	143	16	20	447	63	24.7
14	616	90	25.5	534	74	24.3
18	723	117	27.9	626	102	28.0
41	618	133	35.4	557	126	36.9
46	380	69	30.7	505	94	31.4
48	493	91	31.2	576	117	33.8
70	654	104	27.4	665	99	25.9
92	316	67	35.0	580	103	30.2
97	97	25	41.0	358	90	40.2

*Calculated as the ratio of the doubled number of exclusive males to the total living offspring plus the number of exclusive males.

Table 5. The effect of mutation in ontogene on the X chromosome nondisjunction in drosophila female meiosis.

Genotype of studied female	Regular offspring		Exceptional offspring		Other	Total offspring		Rate of exceptional individuals (%)	
	♀	♂	♀	♂		Imago	With correction to lethality*	♀	♂
l(1)/*In*(1)	691	380	126	268	5 morphoses	1465	2239	11.3	23.9
l(1)/*In*(1)/*Y*	373	164	109	154	10 ♂ + Notch	810	1237	17.6	24.9
l(1)/*w*	1132	730	362	149	49 ♀ *w* 1 ♂ *Notch*	2423	2934	24.7	10.2
w/*In*(1) (control)	1038	821	10	46	13 ♂ w^a 7 ♂ *w B* 2 morphoses	1935	1991	1.0	4.6
w/*In*(1) (external control 1)	946	922	1	23	(8 ♂ w^a) 3 ♂ *w B* 1 morphosis	1902	1926	0.1	2.4
w/*In*(1) (external control 2)	842	749	0	20	22 ♂ w^a 5 ♂ *w B* 10 morphoses	1638	1658	0	2.4

*The number of living offspring is supplemented with the number of exclusive females, exclusive males, and dead *l*(1) males (females of genotypes 1-3).

nondisjunction, a stock of mutation is rapidly contaminated with the XXY females. Over a half of the daughters of these females are an XXY female.

The confirmed phenomenon of combined generation of exclusive males and females in the offspring allows the discovered abnormality in the X chromosome distribution in the individuals with mutant ontogenes to be considered in the context of the classical problem of chromosome nondisjunction in meiosis. On the other hand, the nondisjunction pattern in the mutants for ontogenes has certain features either absent or untypical of the "classical" nondisjunction.

Disparity of the XX and X0 egg cells

The absence of the co-orientation of X chromosomes in meiosis leads to an equiprobable formation of XX and X0 egg cells and, as a consequence, the equal numbers of matroclinous daughters and patroclinous sons. The offspring of the *l*(1)/*In*(1) and *l*(1)/*In*(1)/*Y* females (Table 5) contained more than a doubled number of patroclinous sons. The X0 egg cells can emerge not only as a result of lost co-orientation of the X chromosomes (the variant of independent X chromosome orientation), but also because of the "loss of chromosome". The below data demonstrate that the X chromosome that carries the mutant *l*(1) ontogene is usually (or more frequently) lost.

In the last experiment (Table 5), the regular females consist of two genotype classes: (i) the females with an *l*(1) chromosome and (ii) those without it. Table 5 lists the total number of regular females without partitioning them into these

classes, while Table 6 gives the numbers for each class. It is evident that the daughters that carry an *l*(1) chromosome are always in deficit. At an expectation of 0.5, their share in the offspring of mothers of three genotypes falls in the range of 0.40 - 0.45. The deficit in the daughters with an *l*(1) chromosome was also observed among the females of experiment 1 (Table 2). The total data on the composition of regular daughters of the females in this experiment are shown in row 4 of Table 6 (*l*(1)/*In*(1) females). In this experiment, the mutations in ontogene are not absolutely lethal and do not prevent the females to give birth to sons (designated as ♂ *l*(1)2 in Table 6). It is thus possible to compare the numbers of the regular sons carrying mutation and without it. As is evident from Table 6, the sons with mutation are in deficiency. Their share in the total number of regular males is 0.44 versus 0.5.

These data suggest that the *l*(1) univalent of the two is lost (or is more frequently lost) in the absence of pairing between the X chromosomes. The loss of univalent leads to X0 egg cells and, as a consequence, to two events, namely, (i) emergence of an exclusive male and (ii) deficit in regular *l*(1) offspring as compared with the offspring lacking *l*(1).

The *l*(1)/*w* females display an opposite disparity: the number of exclusive females was twice as high as the number of exclusive males (Table 5, row 3). A likely cause of this disparity is considered in the next section on the nondisjunction of exchange X chromosomes.

Exchange origin of nondisjunctional X chromosomes

The *l*(1)/*w* females carrying a structurally normal X chromosome as an opposite one gave the highest rate of matroclinous daughters (24.7%). Another unusual fact is that these females gave daughters of a *w* phenotype (in total, 49 individuals; Table 5, row 3). Of the 23 tubes used for mating, 11 ones contained the daughters with this phenotype. Thus, this excluded the possibility of a premeiotic origin of the *w* daughters.

The matroclinous daughters homozygous for the mutation of one of the maternal X chromosomes can be formed as a result of the nondisjunction in the

Table 6. Deficit in regular offspring carrying the *l*(1) or *l*(1)2 mutation in ontogene.

Genotype of female	Regular offspring (♀)				Regular offspring (♂)			
	Total number of females	♀ *l*(1)/+	♀ +/+	Share of ♀ *l*(1)/+	Total number of males	♂ *l*(1)2**	♂ +	Share of ♂ *l*(1)2
l(1)/*In*(1)	691	313	378	0.45	–	–	–	–
l(1)/*In*(1)/*Y*	373	157	216	0.42	–	–	–	–
l(1)/*w*	1132	454	678	0.40	–	–	–	–
l(1)2/*In*(1)*	1030	415	615	0.40	761	334	427	0.44

*According to the results of experiment 1 involving 19 mutations in ontogenes (Table 2). **The males with the conditional lethals of an *l*(1)2 type in experiment 1 are viable.

second (equational) meiotic division [1] or the nondisjunction of the X chromosome after crossing over [25]. According to the first hypothesis, the *w* females must carry two *w* chromosomes that have not undergone exchange. As for the second hypothesis, one of the *w* chromosomes must have undergone exchange, for example, must contain an *l*(1) marker in addition to a *w* one. This suggested us to test the *w* "equational nondisjoiners" for exchangeability.

Of the 49 recorded *w* females, 29 were tested for exchangeability. The male offspring of each of these 29 *w* females in the cross with the *In*(1)*Muller*-5, w^a *B* males consisted of the *w* sons. In 7 cases of the 29, the number of *w* sons in the offspring was twofold (and more) lower as compared with the number of their sisters. The last fact indirectly suggests the presence of an exchange X chromosome, carrying the *l*(1) gene in addition to the *w* gene, in 7 of the 29 "equational" females. The putative genotype of the females was *w*/*w l*(1). The male offspring of the females was halved and comprised only *w* sons because of the death of the *w l*(1) sons.

The presence of an exchange *w l*(1) chromosome in seven putative cases of exchange was determined more accurately by assaying the daughters of the mentioned cross ♀ *w* × ♂ *In*(1)*Muller*-5, w^a *B*. The daughters of the *w*/w^a *B* phenotype were crossed with the *In*(1)*Muller*-5, *w* brothers; in total, 61 *w*/w^a *B* daughters were tested. The *w*/w^a phenotype of a daughter indicated the presence of the *w* marker in the nondisjoined X chromosome. Thus, 13 daughters had the male offspring comprising exclusively the *In*(1)*Muller*-5, w^a *B* sons. The absence of *w* sons among the male offspring suggested that the maternal *w* chromosome carried an *l*(1) lethal, which got there via the crossing over between the *w* and *l*(1) chromosomes. This confirms the presence of exchange X chromosomes in the sample of 29 nondisjoined X chromosomes.

The fact that the nondisjoined X chromosomes had undergone exchange in the *l*(1)/*w* females, carrying a structurally normal X chromosome as an opposite mutant X chromosome, is combined with the highest rate (in the overall experiment) of matroclinous daughters (24.7%; **Table 5**, row 3) as well as with the prevalence of matroclinous daughters over patroclinous sons, untypical of the classical nondisjunction. See Discussion for the explanation why these three phenomena took place simultaneously.

Arrest of the distributive chromosome pairing

The so-called distributive pairing is characteristic of the drosophila females, implying the contact between the chromosomes that have not undergone exchange, be they homologs or nonhomologs [17]. In particular, a chromosome inversion in one of the X chromosomes does not increase the nondisjunction of a pair of X chromosomes [26], whereas a free Y chromosome in the female genome increases the nondisjunction by two orders of magnitude [15] [17]. In our experiment, the mutant females carrying the *In*(1)*Muller*-5, w^a *B* inversion in heterozygote have a very high level of X chromosome nondisjunction (**Table 5**, row 1), whereas addition of a free Y chromosome to the female genome does not noticeably change it (**Table 5**, row 2). Both facts suggest that the females carrying

mutant ontogenes lose their capability of distributive pairing. A high rate of nondisjunction observed in the females with mutant ontogenes in both X chromosomes (Table 3) also confirms that distributive pairing is blocked.

"Fading" parental effect of a mutation in ontogene on the X chromosome nondisjunction

The *w/In*(1) females of the internal control (Table 5, row 4) did not carry the ontogene mutation and were used as a control. It was assumed that nondisjunction in these females was at the level of spontaneous nondisjunction; however, the rate of the matroclinous daughters of these females emerged to be by over one order of magnitude higher as compared with the spontaneous level and the rate of patroclinous males, by two orders of magnitude higher. The latter were observed in 26 tubes of the 32 used for mating, which confirms a meiotic origin of the exclusive individuals. The *w/In*(1) females of the external control (Table 5, rows 5 and 6) had the same X chromosomes as the *w/In*(1) females of the internal control; however, their level of nondisjunction was close to a spontaneous value. Exceptional females were almost absent and the rate of exceptional males was lower as compared with the females of the internal control (Table 5, rows 5 and 6).

The *w/In*(1) females originating from the internal control (see Materials and methods) had got their *In*(1) X chromosome and a half of the remaining chromosome set from the mothers carrying *l*(1) mutation. Statistically, the level of X chromosome nondisjunction in the females of the internal control is higher as compared with the females of the external control. The corresponding rates of matroclinous females (1.0 and 0.1%, respectively) differ in a statistically significant manner ($P > 0.95$) ($t = 3.84$) as well as the rates of patroclinous males ($P > 0.95$) (4.6 and 2.4%, $t = 3.76$). Thus, we believe that it is the *l*(1) mutation in the genome of their mothers, *l*(1)*/In*(1) females, that determine an abnormally high nondisjunction rate of the *w/In*(1) females from the internal control.

The effect of a mutation in ontogene on chromosome nondisjunction looks as a parental effect; however, its specific feature is evident: the effect of *l*(1) mutation in an offspring is weaker as compared with the parent. That is why a distinctive definition, "fading", was attached to the parental effect. An important genetic event, which we consider in Discussion, can underlie the fading of the action.

Other offspring

In addition to the offspring regular and exceptional with respect to the X chromosome, considered above, we have obtained a few individuals with morphoses and + males from the *l*(1)*/In*(1)*/Y* females (Table 5, column "Other"). Development of morphoses is typical of the stocks with mutant ontogenes [10] [11] and the + males are the result of loss of lethality of the chromosome carrying the *l*(1) mutation [3]. The w^a and *w B* males formally looked as the products of crossing over between the *In*(1)*Muller*-5, w^a *B* and *w* chromosomes. It is unclear what allows such exchanges to occur and why they are so frequent.

4. Discussion

As the experiment shows, the mutations in ontogenes dramatically interfere with the meiotic process. First and foremost, this is suggested by the high rates of exceptional offspring. A heterozygous presence of the *I*(1) in a female increases the X chromosome nondisjunction frequency by three orders of magnitude: this frequency increases from a spontaneous level of 0.05% to 24.7% when calculated according to matroclinous daughters and to 24.9% for patroclinous sons. Taking into account that a loss of co-orientation of two homologs gives not only 50% of aneuploid gametes, but also 50% of euploid ones, 100% of all meiotic divisions are abnormal in a female with the *I*(1) mutation. According to the generation of patroclinous males, a high level of X chromosome nondisjunction is characteristic of almost all studied mutations (**Tables 2-4**). The classical genetic factors that disturb the drosophila meiosis fall into two groups: (i) the chromosome rearrangements and additional chromosomes [15] [17] [18] [24] [26] and (ii) meiotic mutations [27] [28]. The mutations of ontogenes in their effects on the genome are different from each of these two groups.

The effects of chromosome rearrangements and additional chromosomes in the drosophila genome have been described in numerous papers. As has been shown, the presence of chromosome rearrangements in two and more chromosome pairs increases the nondisjunction of chromosomes of these pairs [17] [26]. Additional chromosomes in the genome also contribute to the nondisjunction [15]. The rate of nondisjunction also increases when chromosome rearrangements are combined with the presence of additional chromosomes [17] [18] [24]. In our experiment, the effect of mutations in ontogenes is so strong that the presence of the classical nondisjunction "inducers"—the rearrangements as the *In*(1)*Muller*-5, w^a *B* and additional Y chromosome—add nothing to the observed X chromosome nondisjunction level (**Table 5**). It is clear that the role of ontogenes in accomplishment of meiosis is considerably more important as compared with rearrangements and additional chromosomes.

The mutations in ontogenes in their effect exceed any meiotic mutations. Our experiment demonstrates that the distortion of meiosis is characteristic of each ontogene or an overwhelming majority of them. In total, 27 mutations in ontogenes of the random set comprising 30 such mutations displayed a high level of X0 gametes (patroclinous sons). According to the published data, the number of detected mei-mutants (genes) in drosophila is several tens [27] [28]; however, this number is naught as compared with the number of Mendelian mutations studied by geneticists over the last century without noticing their effect on meiosis [29]. Moreover, one dose of the mutations in ontogenes is sufficient for their effect versus the mei-mutations, requiring two doses (a homozygote for mutation).

A high efficiency of the mutations in ontogenes in their impact on meiosis is explainable with a direct action of an ontogene as a DNA region. An analog of this "representational" way of action is a chromosome rearrangement. A low ef-

ficiency of the mutations in Mendelian genes in their impact on meiosis is explainable with that the Mendelian genes, meiotic mutations included, are inactive in meiosis. A meiotic mutation can influence meiosis only in an indirect way via producing a protein necessary for meiosis in the nurse and follicular cells. Since the share of mutants with affected meiotic proteins among all kinds of other mutants is a priori very small, the overwhelming majority of Mendelian mutations do not interfere with meiosis. As for the very rare Mendelian mutations that are mei mutations, they act as any Mendelian mutations should, that is, only in two doses (in homozygote).

The effect of a mutation in an ontogene in a heterozygous state brings to mind the pattern of abnormalities characteristic of distant (interspecific) hybridization. It is known that the surviving interspecific hybrids suffer with meiotic disturbances making them sterile [30]. Actually, the interspecific hybrids are "interspecific heterozygotes" and the effect of genes in their genomes should be regarded as dominant. Similar to the mutations in ontogenes, the penetrance of a dominant effect on meiosis in hybrids is close to 100%. The effect of the mutations in ontogenes is similar to the genetic pattern of distant hybridization not only with respect to meiosis. The fact of similarity is of a paramount importance for the insight into the specific features of ontogenes and will be considered in a separate paper.

The singularity of the action of the mutations in ontogenes on meiosis consists in the broadness of their effect. The absence of chromosome pairing is regarded as a common cause underlying meiotic nondisjunction [17]. The experiment with the *l*(1) mutation demonstrates that the meiotic abnormality caused by a mutation in ontogene affects many aspects of the meiotic process rather than only pairing of homologs. Strong prevalence of patroclinous sons over matroclinous daughters in the offspring of *l*(1)/*In*(1)/*Y* and *l*(1)/*In*(1) females suggests that the chromosome has lost its connection with the spindle and is thus unable to reach the pole. The loss of the connection with the spindle or the inability to make this connection is the second type of meiotic abnormality after the disturbed X chromosome pairing.

The third type of abnormality involves the chromosomes that have entered the stage of crossing over. The members of a bivalent fail to separate and both X chromosomes find themselves in a meiocyte. The presence of crossovers among the nondisjoined X chromosomes in the offspring of the *l*(1)/*w* females suggests this type of meiotic abnormality. Two more phenomena are characteristic of this type, namely, the highest in this experiment rate of matroclinous daughters (24.7% versus 17.6% and 11.3% in the offspring of the *l*(1)/*In*(1)/*Y* and *l*(1)/*In*(1) females, respectively; **Table 5**) and the prevalence of matroclinous daughters over patroclinous sons, unusual for nondisjunction. The former is explainable by addition of the events of nondisjunction of the X chromosomes that have undergone crossing over and the latter, by the ability of an unresolved chiasma to guide the chromosome set to the polar body.

The absence of distributive pairing in the females carrying the *I*(1) mutation is the next, fourth type of meiotic disturbance and induction of the X chromosome nondisjunction in the daughters lacking mutations in ontogene, is the fifth type of abnormality. The parental effect of a mutation in ontogene on the X chromosome nondisjunction, defined as *fading*, deserves a special attention. The parental effect in itself suggests that ontogenes are active as early as before the meiotic divisions [12]. Their activity alters the chromosomes of the overall diploid set [13]. These changes together with the gametes are handed down to the offsprings of mutants, where they cause the nondisjunction following a parental effect. The parental effect can fade only if these structural changes are again "edited" in the next cycle of gamete formation [2], this time in an offspring.

The diversity of meiotic abnormalities, considered above, suggests that the ontogenes are responsible not only for co-orientation of chromosomes, but also for the organization of meiotic division in general. An active role of the ontogenes in meiosis gives a new perspective to the studies of meiosis in genetic research. Until now, meiosis is considered as the process that distributes the genetic material in an inactive state between the gametes. However, the performed studies suggest that this inactivity refers to only Mendelian protein-coding genes. As for the ontogenes, they are active and meiosis is the field of their action. The research into the role of ontogenes in meiosis may become the first of the discovered approaches to study the functions of this new class of genetic elements.

The mechanism underlying the action of ontogenes in meiotically dividing cells. Our results allow us to formulate several points on the kinds of ontogene activities:

1) A drastic increase in the rate of X chromosome nondisjunction caused by almost any mutation in an ontogene on the background of the absence of any effect on meiosis of the overwhelming majority of mutations in Mendelian genes [29] suggests that meiotic process, starting from the recognition of homologs and their approaching, is controlled by ontogenes;

2) The effect of each mutation in an ontogene in a heterozygous state on the course of meiosis means that this effect is caused by the mutation that is contained in the chromosome set of a particular meiotic cell;

3) The chromosomes in a meiotically dividing cell are compacted; consequently, the meiotic activity of ontogenes is determined by compacted DNA. The activity of ontogenes in meiosis has a biophysical rather than a chemical nature. All earlier obtained data on the ontogenes [4] [7] [9] exclude their direct involvement in protein synthesis;

4) A maternal effect of the ontogenes on nondisjunction demonstrates that (i) the compaction of ontogenes is genetically controlled and (ii) it takes place in mitotically dividing germline cells before entering meiosis;

5) The ability of ontogenes to recognize spatially separated homologs and approach them means that compacted ontogenes form physical (electromagnetic)

fields that provide remote interaction; and

6) According to our results, *an ontogene is a discrete hereditary unit represented by a DNA nucleotide sequence*, *which has a strictly determined conformation and possesses an individual electromagnetic field.*

It is believed that compaction of the DNA of Mendelian protein-coding genes *prohibits them to be active* [31] [32]. According to the data of our experiment, compaction of the DNA of ontogenes *opens the possibility for ontogenes to be active.* The condensed (coiled) regions of ontogenes may be represented as induction coils generating magnetic field during the passage of electric current in a conductor. The hypothesis implying the generation of an electromagnetic field by ontogenes was already proposed when explaining the pairing of two homologs one of which carries an inversion [21].

The idea of electrostatic interaction during meiotic pairing of homologs has been earlier proposed [33] [34]. Our data on a multilateral effect of ontogenes on meiosis suggest a somewhat different explanation. The electromagnetic fields induced by ontogenes serve to attract and orient specialized proteins (for example, tubulins), which are able to perform manifold energy-consuming actions but only in the case of proper orientation in space. This orientation is provided by the fields induced by ontogenes. In this case, the failures in the pairing of homologs and in attachment of univalents and bivalents to the spindle as well as the block of distributive pairing in drosophila meiosis are explainable with a defect in the recruiting of contractile protein molecules.

5. Conclusions

At the dawn of genetics, the phenomenon of meiotic chromosome nondisjunction became the keystone of the emerging chromosome theory of inheritance and the platform for goal setting [18] [19]. The study of chromosome nondisjunction in the mutants for ontogenes leads to an important inference that ontogenes are responsible for the organization of meiotic division. It is logical to assume that ontogenes are also responsible for the organization of mitotic division. If so, they are the particular players responsible for the construction of the cell scaffold (framework) in ontogenesis and switch on Mendelian genes in the formed cells [35]. Both processes are the essence of ontogenesis.

The fact of a sharp increase in the X chromosome nondisjunction rate caused by a group of mutant ontogenes residing in this chromosome pair proves the existence of genetic activity exerted by coiled DNA regions. The hypothesis on a biophysical nature of ontogene activity [2] [21] [36] [this paper] demands direct physical confirmations; however, genetic arguments favoring this hypothesis are convincing. In view of this, further studies into the meiotic abnormalities in the mutants for ontogenes may assist in solving the mystery of how ontogenes succeed in the implementation of the individual development plan of an organism.

The effect of mutations in ontogenes on the course of meiosis demonstrates the way to genetically control a biological process, which may be regarded as a

"dual control". Mendelian genes exert a chemical control over the synthesis of the proteins necessary for a particular biological process. The presence of the genes of this kind follows from the fact of the existence of mutations (including meiotic ones) operating as Mendelian genes. Ontogenes organize the biological process in cells in a biophysical manner and, possibly, control the very event of cell division. The data we obtained in the experiment suggest the existence of such control. Presumably, dual control is a typical pattern for genetic control of biological processes.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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