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Review Article

Down's Syndrome - Etiology and Mechanism Revisited

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ABSTRACT

Down's syndrome is one of the commonest chromosomal disorders seen in human being. The most common cause of Down's syndrome is the presence of an extra copy of chromosome 21. Non-disjunction is the most common mechanism for trisomy 21 and it occurs due to error in recombination during meiosis I and meiosis II stages. Although less common mechanism, the robertsonian translocation, isochromosome, mosaicism and partial translocation are also important contributors in the occurrence of down's syndrome.

Keywords: Down's syndrome, non-disjunction, robertsonian translocation, isochromosome, mosaicism.

INTRODUCTION

Down's syndrome (DS), the leading cause of congenital birth defects and mental retardation is the most common aneuploidy compatible with life, [1] occurring in about 1 out of 700 live births. [2] Although most common cause of DS is due to the presence of an extra copy of a complete chromosome 21 but over expression of few genes contained within 21q can also result in the same phenotype. [3]

Trisomy 21 has a significant impact on the development of many tissues, most notably the heart and the brain. It is associated with a small number of conserved features, occurring in all individuals, including mild-to-moderate learning disability, craniofacial abnormalities and hypotonia in early infancy. The degree to which an individual is affected varies. Additionally, trisomy 21 is also associated with variant phenotypes that only affect some people with DS, such as atrioventricular septal defects (AVSDs) in the heart, acute mega-karyoblastic leukaemia (AMKL) and a decrease in the incidence of some solid tumours. [3,4]

HUMAN CHROMOSOME 21: A BRIEF INTRODUCTION

Human chromosome 21 is the smallest human auto some. The length of 21q is 38 Mb and approximately 3% of its sequence encodes for proteins. Chromosome 21 contains 225 genes and 59 pseudo genes. [5] Almost half of the chromosome 21 is a dark band when stained by Giemsa and such genes are known to be gene poor. The gene catalogue of chromosome 21 contains at least ten kinases, five genes involved in ubiquitination pathways, five for cell adhesion molecules, a number of transcription factors and seven ion channels. Exact gene responsible for the phenotype in DS has not yet been identified. [5] The complex phenotype that constitutes DS may in large part simply result from the over dosage of only one or a few genes within

the DCR (DS critical region) and/or region D21S55-MX1. DS critical region is a region of ~ 5.4Mb on chromosome 21q22 which harbours genes which are sufficient to produce many DS phenotypes. [6] This concept has been refuted by Olson *et al.*, (2004). [7]

The genes sequences present on the short arm of acrocentric chromosome are region wise described as in Table 1.

Table I: Genes sequences present on the short arm of Chromosome 21

Region	Genes present
p11 region	satellite DNAs I, II, III, IV
p12 region	multiple copies of the genes coding for the 18S and 28S ribosomal RNA (nucleolar organizer region); (NOR)
p13 region	β-satellite DNA and telomeric sequences

(Reviewed by Page *et al.*, 1996; Bandyopadhyay *et al.*, 2002)

In this brief review we summarize the causes and mechanisms behind the occurrence of trisomy in DS.

ETIOLOGY OF DOWNS SYNDROME

DS can be caused by three types of chromosomal abnormalities: 1) free trisomy 21 (non-disjunction), 2) translocation, or 3) mosaicism. [8] In a study of 238,942 consecutive births, free trisomy 21 was the commonest cause constituting 92-95% of cases and translocation and mosaicism constituting 3.6% and 2.3% respectively. [9]

3.1 FREE TRISOMY 21

Free trisomy 21 is characterized by the presence of three complete copies of chromosome 21. Free trisomy 21 arises by the mechanism of non-disjunction during oogenesis, or by selection of trisomic oocyte and spermatocyte due to parental mosaicism and gonadal mosaicism.

A. Non disjunction in trisomy 21

Origin of non-disjunction in about 93-95% of free trisomy 21 is maternal, 5% are paternal [10] and 2% are of mitotic origin. [11] Most of the aneuploidy including trisomy 21 arises due to non disjunction during oogenesis. Three general rules of human non- disjunction are 1) most trisomies originate during oogenesis 2) maternal meiosis I (MI) errors are more common than maternal meiosis II (M II) errors 3) the proportion of cases of maternal origin increases with maternal age. Maternal MI errors predominate in trisomy 21. [12] Hall (2007) [13] summarised the origin of human trisomy 21 (Table 2).

Table II: Origin of Free Trisomy 21

Origin of Trisomy 21				
Maternal		Paternal		PZM (%)
MI(%)	MII(%)	MI(%)	MII(%)	
69.6	23.6	1.7	2.3	2.7

Hall, (2007) (PZM -post zygotic mitosis)

Two risk factors for maternal non-disjunction of chromosome 21 are increased maternal age and altered recombination. [14]

Role of Recombination in non-disjunction

Other than increasing maternal age, altered recombination is the most important known etiological factor associated with human trisomy 21. [11] Process of recombination has an important role in ensuring proper segregation of chromosomes during meiosis.

The frequency and location of recombination has been shown to be aberrant in most human trisomies. [15] Recombination too near the centromere or too far from the centromere imparts an increased risk for non-disjunction. [16] The presence of a single meiotic exchange helps to facilitate proper alignment of homologous chromosomes on the meiotic spindle during cell division. In absence of meiotic exchange the homologous chromosomes are at an increased risk for mal-segregation during MI. In cases of maternal MI-derived trisomy 21, the majority of recombination events occurred was either absence of recombination or recombination at the telomere of 21q irrespective of maternal age, whereas exchanges occurring among meiotic II (MII) cases of trisomy 21 clustered at the peri-centromeric region. [14,11]

In maternally derived trisomy 21, the association between recombination and non-disjunction is complex and changes with age of the mother. In these cases, age wise association observed between recombination and non-disjunction are 1) telomeric exchanges are an important contributor among younger women, 2) pericentric exchanges in MII trisomies is more common in older women and 3)

failure to crossover (achiasmatic homologue) accounts for ~50% of maternal MI errors in both the young and oldest maternal age group. [12] In young women the meiotic machinery (Spindles, sister chromatid adhesive proteins, microtubule motor proteins etc) work optimally and correctly segregates chromosomes in all except in those with susceptible exchange pattern in oocyte (achiasmate bivalents and exchanges close to either the centromere or the telomere). In older women meiotic machinery becomes less efficient and/or more prone for error, so both correctly placed bivalents and suboptimal exchange bivalents become susceptible to non-disjunction. [17]

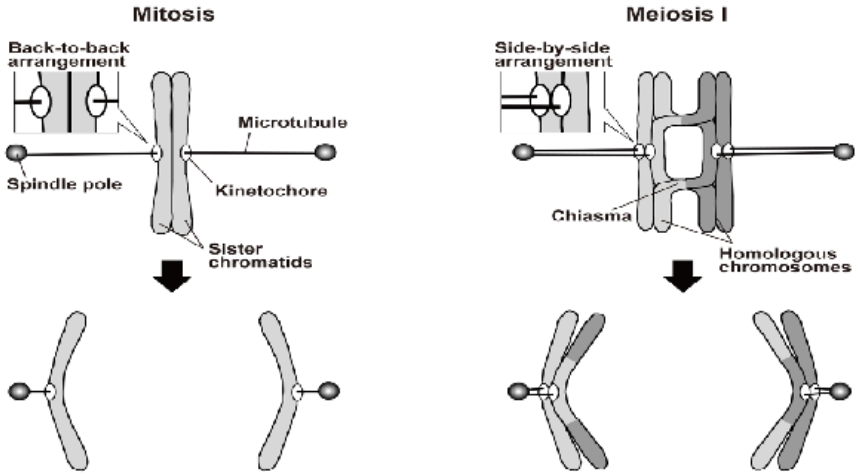

Figure 1: Spindle attachment of chromosomes and their segregation during mitosis and meiosis I. (**Hirose *et al.*, 2011**) d oi:10.1371/journal.pgen.1001329.g001

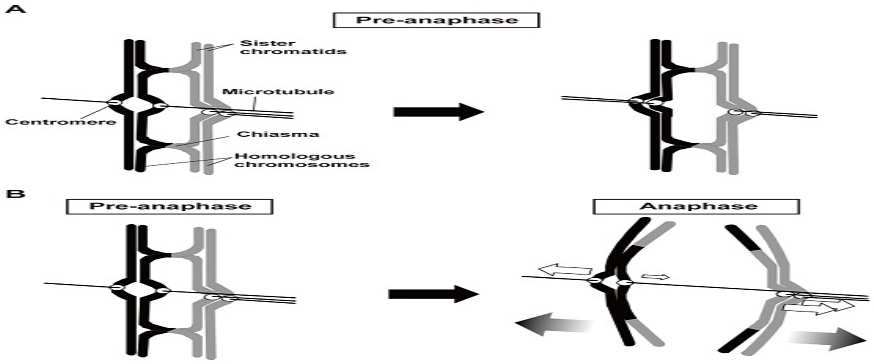

Figure 2 :Two major roles of chiasmata during meiosis I. (A) Chiasmata eliminate the bipolar attachment of sister centromeres (centromeres on left sister chromatids) during the pre-anaphase stage of meiosis I. (B) When the bipolar attachment remains during anaphase, chiasmata generate bias in the pole ward pulling forces to cause proper chromosome segregation. White arrows indicate the pulling forces exerted on chromosomes during anaphase I. A smaller arrow indicates a weaker or less continuously exerted force. For simplicity, only a single microtubule is shown to illustrate the spindle attachment of each (**Hirose *et al.*, 2011**) kinetochore doi:10.1371/journal.pgen.1001329.g008

During meiosis I the segregation of homologous chromosomes occur to the opposite poles. The chromosome segregation depends on attachment of chromosomes to the spindle via chromosomal sites called kinetochores and presence of chiasmata between the homologous chromosomes. Chiasmata are physical connections between homologous chromosomes at the site of recombination and they function to stabilize the paired homologues or tetrad at MI along with sister

chromatids and centromere cohesion. Chiasmata regulates segregation of homologous chromosomes through two mechanism 1) Chiasmata eliminate the bipolar attachment of sister centromeres during the pre-anaphase stage of meiosis I and 2) if there exist the bipolar attachment during anaphase, then chiasmata generate bias in the pole ward pulling forces to cause migration of homologous chromosome to opposite pole. It aids in proper chromosome orientation on the meiotic spindle and ensure their proper segregation to opposite poles [18] (Figure 1) (Figure 2). Absence of chiasma formation leaves the homologous pair free to drift randomly towards any poles and if they move together to same pole, it results in aneuploidy. As far as chromosome 21 non-disjunction is concerned, achiasmate meiosis is the major cause of reduction in recombination frequency. [16,17]

B. Parental mosaicism

Priest *et al.,* (1973) [19] suggested that 19% (11% of mothers and 8% of fathers) of trisomy 21 infants could be due to parental mosaicism.

Role of ovarian mosaicism in mothers of DS patient

The Oocyte Mosaicism Selection model was proposed by Hulten *et al.,* (2010). [20] The model was based on the observation that in 8 cell stage of embryo, chromosome mal-segregation of one or a few chromosomes is common, leading to embryonic mosaicism including a cell line with an aberrant chromosome number. The oocyte mosaicism selection model suggests that mitotic errors occur before entry into meiosis, leading to aneuploid oocytes in primordial follicles that are preferentially recruited with increased maternal age. According to this model the oocyte in fetal ovary shows mosaicism having normal and trisomic cells. In case of Trisomic 21 foetal oocyte, there is a substantial delay in foetal oocyte maturation in comparison to that seen in cases with a normal karyotype. The Trisomic 21 foetal oocytes may lag behind the normal oocyte during foetal development, [21] Trisomy 21 oocytes, lagging behind those that are disomic, may escape the timed pruning of the seven million of oocyte in foetal life to the 300-400 finally selected for ovulation in adult. The net effect of this preferential elimination results in accumulation of trisomy 21 oocytes in the ovarian reserve of older women. [20]

Hulten *et al.,* (2014) [22] have shown that an accumulation of Trisomy 21 cells occur from the first to the second trimester of pregnancy in a sample of ovaries from foetuses with a normal karyotype. They also suggested that the increased recurrence risk in younger women is likely to be caused by a higher incidence of fetal oogonial/oocyte T21 mosaicism. Thus these authors suggested that trisomy 21 occur due to recruitment of trisomic 21 oocyte for fertilization, resulting in trisomic zygote formation. Rowsey *et al.,* (2013) [23] in their study found no evidence of trisomy mosaicism for any chromosome in the oocyte. They concluded that errors in pre-meiotic germ cells are not a major contributor to human aneuploidy and do not provide an explanation for the age-related increase in trisomic conceptions.

3.2 TRANSLOCATION

In a study carried out at Ohio between 1970-1981, 5.2% of the total cases were diagnosed to be due to translocation. [24] In DS cases due to translocation of chromosome 21, extra chromosome 21 is joined or translocated in any other acrocentric or non-acrocentric chromosomes. [25] Robertsonian translocation was the most common type of translocation observed among them. [26] Robertsonian translocations (ROBs) in humans are whole-arm rearrangements between the acrocentric Chromosomes 13-15, 21, and 22. [27] In a large population study for DS, translocations observed were, 24.4% maternal, 2.2% paternal and 73.3% *de novo*, in origin. Translocation subtypes in the study were 14/21(45.7%), 15/21 (2.9%), 21/21 (40.0%), 21/22 (2.9%), and other (8.5%). Dividing the different subtypes into

their proportions from each source of origin, D/G translocations were 61.1% de novo and 38.9% maternal; G/G translocations were 85.0% de novo, 10.0% maternal, and 5.0% paternal; 14/21 were 66.7% de novo and 33.3% maternal; and 21/21 were 100.0% de novo [24] Commonest type of robertsonian translocation observed was t (14q;21q). [28] Kolgeci *et al.,* (2013) [26] reported t (21q; 21q) as the most common type.

Mechanism of de novo formation of ROBS

ROBs in humans are rarely formed by breakage within the centromere, the majority of breakpoints are located in the proximal short arms of the chromosomes involved, resulting in structurally dicentric translocations. [29]

The chromosomal rearrangements leading to Robertsonian translocations occur preferentially in satellite III DNA distal to centromeric alpha-repeat DNA and proximal to beta-satellite DNA on the short arm of the acrocentric chromosomes. It is hypothesized that guanine-rich satellite III repeats may promote chromosomal recombination by formation of tetraplex structures. [30]

The rate of de novo formation of ROBs is estimated to be ~$3.9X10^4$ mutations per gamete per generation. The non-random distribution of ROBs in the population suggests that there is a specific mechanism or underlying genomic architectures or sequences that promotes the exchange between certain acrocentric chromosomes. [31] ROB formation most likely occurs during meiosis I of oogenesis. The translocation event occurs during the time between pre-meiotic replication and the completion of meiosis I (segregation of the homologues). Translocation formations occur between single sisters chromatids of the replicated chromosomes. [27]

Most ROBs arise through adjacent chromatid exchanges corresponding to mitotic chiasmata, in the pericentric regions of the acrocentrics. [32] The mechanism driving Robertsonian translocation formation is thought to depend on genomic organization of acrocentric chromosomes. All 10 acrocentric short arms share several highly similar or identical blocks of repetitive DNA, including satellite III (sat III) and beta satellite. In addition, approximately 400 copies of the 43 kb ribosomal DNA (rDNA) cassette are distributed among the acrocentric short arms, existing as clusters called nucleolus organizing regions (NORs). After exit from mitosis, numerous mini-nucleoli are formed around actively transcribing NORs. The mini-nucleoli fuse to form larger nucleoli thereby bringing the NORs of multiple acrocentrics into close proximity. Acrocentric fusions are proposed to occur via incomplete homologous or non-homologous recombination between short arm repeats or through repair of short arm DNA damage that is corrected using a similar short arm DNA sequence on a nearby non-homologous acrocentric. [33] It is hypothesized that gene sequences are shared on the short arms of chromosomes 14, and 21 that participate in homologous recombination to form ROBs. Sequence is postulated to be in opposite orientation on chromosome 14, in comparison to chromosomes 13 and 21, which facilitates the formation of rob(14q21q), but impedes the formation of rob(13q21q). [32,34]

Role of robertsonian translocation in non-disjunction of chromosome 21

The breakpoints of rob (14q21q)s occur in the short arms of the participating chromosomes, leading to dicentric rearrangements due to a break proximal to rDNA. [29] Because of the location of the rRNA genes on all acrocentric short arms, non-homologous acrocentric chromosomes are brought into close proximity during the early stages of meiosis I to form the nucleolus and remain in this association throughout meiosis I and this close association during meiosis may facilitate the exchange in the short arm responsible for ROB formation. Berend *et al.,* (2003) [27] postulated that obligate short-arm event leading to the formation of the ROB may influence the segregation of the homologues or sister chromatids. One such mechanism

could be the alteration of the recombination pattern along the long arm of chromosome 21, which may increase the risk for mal-segregation of the ROB from the free-lying homologous chromosomes or sister chromatids, leading to non-disjunction (NDJ). (Figure 3)

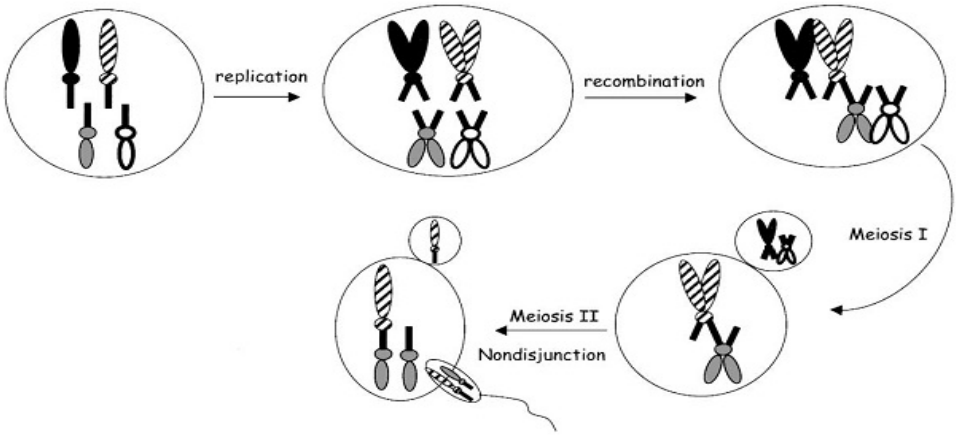

Figure 3: Proposed model for de novo ROB formation and non-disjunction of chromosome 21 in oogenesis. Chromosomes 14 (solid black or hatched) and 21 (gray or white) are shown. Replication duplicates the chromosome into two sister chromatids. During recombination of the homologous chromosomes, single chromatids from chromosomes 14 and 21 become translocated at the short arms, producing a dicentric ROB. Reciprocal acentric short-arm product is not shown. At meiosis I, homologous chromosomes separate into the secondary oocyte and one polar body. Non-disjunction at meiosis II results in a mature ovum containing the ROB and an extra chromosome 21. The extra chromosome 21 is the same chromosome as that translocated within the ROB. Shown is the second polar body containing only a chromosome 14 and nullisomy for chromosome 21. Fertilization results in a zygote that is disomic for chromosome 14 but trisomic for chromosome 21 (**Berend, *et al.*, 2003**).

Familial transmission of ROBs

Cytogenetic analysis of the parents of children affected with translocation trisomy 21 revealed that 1.0% of translocation was inherited from one of carrier parent of that translocation. [26] In most organisms, dicentrics typically break during cell division; however, dicentric human chromosomes can be stable in mitosis and meiosis. This stability is reflected particularly in those chromosomes which are inherited. [34,35] The risk of transmission of ROBs from parents to the offspring is estimated in Table 3.

Table III: Chances of recurrence (%) in familial transmission of ROBs

ROBs	Father	Mother	Chance of recurrence %
D/G	N	C	10 %-15%
	C	N	5%
21/22	N	C	10 %-15%
	C	N	5%
21/21	C	N	100%
	N	C	100%

(Emery and Mueller, 1992)

3.2.1 Rare translocations in downs syndrome (Partial translocation)

Over expression of few genes of chromosome 21 are believed to be responsible for some of the phenotypes observed in patients with DS. Variation in phenotype of DS occurs due to translocation of these genes. [36] Nadal *et al.*, (1997) [37] reported that partial translocation of chromosome 21 in a patient resulted in DS phenotype. The breakpoint was located on band 21q22.1 and translocated on chromosome 15. The partial translocation was inherited from father, who was also a carrier of the balanced translocation. Although the Robs translocations are the commonest translocations observed in Down's syndrome, numbers of case reports with different types of translocation in patients with DS phenotype have also been reported. Most of the translocations are reciprocal translocation between chromosome 21 and other non acrocentric chromosomes. Some of the reported translocations are 2;21 translocation (47,XY,+21,t(2;21)(q21;q22.3) mat, [38]

reciprocal translocation t(4;21)(q27;p11), (Jenkins and Boyd, 1976) reciprocal t (10; 21) translocation, [39] translocation between chromosomes 3 and 21 [t(3;21) (q21; q22], [40] de novo (X;21) translocation [41] some of them were *de novo* in occurrences and some of them were inherited from carrier parents.

3.3 ISOCHROMOSOMES

Most of the ROBS translocation 21; 21 are thought to be *de novo* robertsonian translocation. [24] Antonarakis *et al.,* (1990) [42] proposed that most of the *de novo* ROBS 21; 21 are in fact isochromosomes. Isochromosomes are structurally abnormal chromosomes that result from a duplication of a single chromosome arm. Isochromosomes cannot be distinguished from ROBs based on their chromosome morphology and staining. Instead, a molecular method, such as DNA polymorphism analysis, is used to delineate the origin of homologous acrocentric rearrangements. Isochromosomes of chromosome 21 account for about 34% of the rearrangement seen in Down's syndrome. According to various authors, the majority of homologous acrocentric rearrangements (~90%) are isochromosomes and not ROBs. [34]

The distinction between a homologous robsertsonian translocation and an isochromosomes can be inferred from mosaic cases. If the translocation cell line has 46 chromosomes then it is probably an isochromosome. If the translocation cell line is balanced with 45 chromosomes then this is more likely to be a Robertsonian translocation. [43]

MOSAICISM

Mosaicism is a condition in which an individual has two or more genetically distinct cell lines that develop from a single zygote. [44] About 2.3% of DS cases are due to mosaicism of cell line with normal chromosomal count and cell line of trisomy chromosome 21. [9] In a case of mosaicism the phenotype of the individual with Down's syndrome depends upon the proportion of trisomic cells present in the tissues of different embryologic origin (e.g., blood and buccal mucosa). [45]

Munne *et al.,* (1994) [46] described three type of mosaicism in monospermic diploid embryo, they are a) Aneuploid mosaics (occurring due to non-disjunction, random division, by anaphase lag, or by unknown mechanism), b) 2N/4N mosaics, c) 2N/N mosaics. The most common time for appearance of the mosaicism in monospermic diploid embryo was at 2nd cleavage and in subsequent divisions. Two mechanisms were suggested for occurrence of mosaicism in Down's syndrome.

(I) mitotic loss of the supernumerary chromosome 21 from a trisomic zygote resulting from a meiotic NDJ (class I mechanism)and

(II) mitotic duplication of a chromosome 21, occurring either post zygotic(class IIA mechanism), or pre-meiosis (class IIB mechanism).

58.8% of the cases of mosaicism probably originated due to loss of chromosome 21 by class I mechanism, 41.2% of the mosaicism results from a gain of a chromosome 21 , by class IIA mechanism, in a previously euploid zygote or by a pre-meiotic duplication in the parental germ cell line, leading to a trisomic zygote and subsequent loss of the supernumerary chromosome 21 (class IIB mechanism); or of a meiosis II error without a crossover in meiosis I and with a mitotic loss after fertilization (class IIC mechanism). [47]

CONCLUSION

Down's syndrome is one of the commonest chromosomal disorders seen in human being. Most common cause of the disorder is presence of an extra copy of a chromosome 21 and the most common cause of the extra copy of chromosome 21 is non-disjunction. Error in recombination during meiosis I and meiosis II results in non-disjunction. Failure to form chiasma or telomeric exchanges are the commonest Meiosis I error whereas pericentric recombination is mostly seen in meiosis II

error. Sharing of repeat DNA segments on short arms of acrocentric chromosomes and their proximity in nucleolar organizing region (NOR) predispose to *de novo* formation of robertsonian translocation. ROBs can also be inherited in DS. Although less common, isochromosome, mosaicism and reciprocal translocation are also important contributor in occurrence of down's syndrome.

Chromosome 21 is a very small chromosome with small number of physiologically active genes. Identification of genes responsible for individual phenotypic character can help in understanding the pathology and in planning for management of Down's syndrome.

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