

# Adaptive nature of chromosome variation in placental mammals and applicability to domestication and invasiveness

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## Abstract:

Research on chromosome evolution accumulated in the past three decades that seems to validate the hypothesis postulated that chromosome changes that increase or decrease of chromosome number are adaptive partly because they increase or decrease in variation via effects on recombination and segregation in meiosis. The paper reviews some of the new data relevant to this question and especially focus on studies on interspecific and intraspecific chromosome variation in placental mammals. We find data in support of that hypothesis coming from many areas and for the first time suggest applications in some domesticated and invasive species of mammals. This hypothesis does not explain all chromosome number variation in mammals but it does advance our understanding and opens future avenues of research into mammalian variation and adaptability.

**Keywords:** genetic variation, Chromosome number, meiosis.

**Received:** 2021-12-03

**Revised:** 2022-05-12

**Accepted:** 2022-06-28

**Final review:** 2022-03-18

## Short title

Adaptive nature of chromosome variation

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## Introduction

The range of chromosome numbers in mammals is between  $2n=6$  to 7 (Muntjac, Wurster and Benirschke 1970) to  $2n=102$  (a South American rodent though maybe polyploid, Gallardo et al. 1999). Chromosome evolution patterns and rates are variable with many lineage specific differences; some of it associated with higher speciation rates (Bush et al. 1977; Bengtsson 1980; Bourque et al. 2004; Romanenko et al. 2012; Castiglia 2014; Martinez et al. 2016). Older literature supposed fixation of even deleterious chromosome rearrangements because of genetic drift and population bottlenecks without chromosome rearrangements having adaptive value (Wilson et al. 1975; Bush et al. 1977; White 1978). The fact that this variation is not random and certainly not seen only in populations of vertebrates with possibilities of bottlenecks (Ruiz-Herrera et al. 2012), forced many authors to start thinking of alternatives and the field of examining adaptive nature of rearrangements has expanded significantly (see Dobigny et al. 2017 for a review). Thus, recent data challenged the model of bottlenecks or extended them . This was necessitated to cover areas including step-wise adaptation and the drive towards fixation even in situation of monobrachial homology (Bickham and Baker 1979; and see discussion and references below).

If one adopts the idea that chromosomal changes are adaptive and not merely because they allow reproductive isolation then it is possible to begin to understand patterns of chromosomal variation within a species and also between species and higher categories (see review in Qumsiyeh 1994). Some

authors postulated that Eukaryotic genome evolution proceeds directionally by fissions increasing chromosome numbers (Imai et al. 2002, Fontana and Rubini 1990, Todd 1975) while others postulate a “fusion” drive resulting in decrease in chromosome number (Fontana and Rubini 1990). But there is now a significant body of evidence accumulated and a consensus that different lineages may acquire fusions or fissions and thus some lineages increase chromosome number and some decrease it (King 1982; McClintock 1993; Qumsiyeh 1994; Phillips and Rab 2001; Ferguson-Smith and Trifonov 2007). There is also evidence that higher categories of classification that are clearly monophyletic (e.g. a monophyletic family like Rhinolophidae) have chromosome constitution that may not change much after the formation of the taxon (this is termed the canalization model of chromosomal change Bickham and Baker 1979). The latter authors did not deal with mechanism of adaptability via chromosomal changes though they did mention the various possibilities without discussing them (position effects, supergenes, linkage groups, centromere position, and regulatory functions). For Robertsonian translocations (ROBs) and whole arm translocations that increase or decrease chromosome number without causing hardly any regulatory or position effect, the explanation has been more difficult. This is also compounded by the fact that ROBs are the most common rearrangements in mammals including for intraspecific variation (see below). Yet, there is some evidence that such translocations may indeed alter the nuclear architecture and thus have consequences beyond their effect in meiosis (Qumsiyeh, 1995; Garagna et al. 2001)

A model that attempted to explain the widespread presence of fissions and fusions in mammals was proposed more than 20 years ago (Qumsiyeh 1994) that challenges the earlier notions of deme size models and fixation of random events. The model is based on the simple idea that increase in chromosome number in itself allow more variation in progeny due to two factors: a) random segregation in meiosis where number of possible outcomes is  $2^n$ , and b) due to the fact that higher chromosome numbers are also associated with increased chiasma frequency. The model thus argues that the drive to increase or decrease chromosome numbers in different lineages creates more or less variation that is then advantageous depending on the environmental situation. According to this model, there could be selection for increased chromosome numbers in lineages which increase variation in progeny thus allowing response to stressed or heterogeneous environments. The reverse is true with species subjected to stable environments undergoing reduction in chromosome numbers once they reached the optimum karyotype. This is not a challenge to the canalization model (Bickham and Baker 1979) but an explanation of it.

Since that notion of linkage of segregation and recombination with variation was developed in 1994 as an explanation of possible adaptive nature of the karyotype after fissions/fusions (though obviously not the only effect of such rearrangements), many authors published data on chromosome number in heterogeneous or stressed environments that fit well within this model and the authors commented on its applicability. This paper reviews accumulated data

and explain potential applicability of the hypothesis to recent on issues ranging from interspecific variation in wild species to invasive and domestic species to mammalian intraspecific variation. The paper reviews accumulated data, both for interspecific variation and intraspecific variation with special emphasis on decrease and increase in chromosome number by fusion and fission (and not other chromosome rearrangements) in association with organisms' adaptability. In the case of inversions, the effect on recombination is found in the selection for suppression of recombination both within the inversion loop in heterozygotes and elsewhere in the genome (Trickett and Butlin 1994; Hoffmann and Rieseberg 2008).

### **Recombination and Genetic Variation**

The hypothesis of Qumsiyeh (1994) basically can be summarized as stating that these effects on recombination provide a "drive" towards higher chromosome number (via fissions) in unstable heterogenous environments and towards lower chromosome numbers (via fusion) in stable environments when the species is highly adapted to that environment. This is due to both impact in increase on probabilities of gametes by random segregation of chromosomes (probabilities  $2^n$  where n is haploid chromosome number) AND on recombination rates. Qumsiyeh (1994) provided numerous examples of how this can increase variation (genetic and hence also phenotypic) and discussed the issue of recombination relating to increase and decrease in chromosome number and

effect on recombination. More recent data on recombination confirms these trends.

Chromosome numbers and FN (number of autosomal arms) are directly proportional to recombination which also impacts variation (Qumsiyeh 1994). This requires some more research but note for example the correlation between the sex averaged genetic map in mammals and number of chromosomal arms (Coop and Przeworski 2007). There are data that show positive relationship of FN to recombination in rodents, marsupials and primates (Pardo-Manuel de Villena and Sapienza 2001a and references there-in). The chromosome size in and of itself (outside the issue of random segregation) affects recombination (Gazave et al. 2003; Kaback and Guacci 1992; Kaback 1996; Qumsiyeh 1994; Kong et al. 2002). Further, patterns of recombination are affected not just by length of chromosome but also by interference and centromere and telomere effects (Borodin et al. 2008).

If the environment is constantly shifting, one would expect natural selection to favor increased variation in progeny (Burt and Bell 1987). Increased recombination can also drive genome size reduction in mammals leading to stabilization (Nam and Ellegren 2012). There are still many questions about genetic controls of recombination but there is no question now about evolutionary significance associated with variation in chromosome number and structure (see reviews in Coop and Przeworski 2007; Paigen and Petkov 2010; Baudat et al. 2013). New mechanisms for regulation of recombination hotspots

are also being discovered and related to potential selective forces operating at the molecular level which could explain meiotic drive (e.g. Odenthal-Hesse et al. 2014). Recombination rate and hotspots of recombination are controlled by few genes such as PRDM9 (Paigen and Petkov 2018; Ubeda et al. 2019) and these can be subject to environmental selection that suits ecological and habitat needs (see Burt 2000; Stapley et al. 2017 and references therein). The relationship of recombination to chromosome number is reviewed by Stapley et al. (2017) shows a clear relationship between chromosome number and recombination in fungi, plants, and animals though for animals the relationship was quadratic. Certainly, more work is needed in this area. Indeed recombination changes due to FN changes or other mutations that increase recombination can help explain issue of phenotypic variation not related to chromosome number. The cat with  $2n=38$  has a very high recombination rate (4370 cM, Menotti-Raymond et al. 2009) while the dog  $2n=78$  is lower (1978 cM Campbell et al. 2016). It would be difficult to say that dogs have either higher or lower variation than cats based on these data.

### **Intraspecific Variation**

Intraspecific variations/chromosome polymorphisms are common in mammals including marsupials, insectivora, primates, carnivores, perissodactyla, and rodents (Qumsiyeh 1994; Dobigny et al. 2017). It is also not surprising then that there are many species with intraspecific variation of chromosome numbers especially in small mammals because of the ease of getting karyotypes on good sample sizes (Dobigny et al. 2017). In the mole-rats of the genus *Spalax* there is

strong evidence that the chromosomal species with the highest chromosome number occur in the most stressed habitats (Nevo 1991, 1998; Nevo *et al.* 1994).

One of the most polymorphic species studied intensively is *Blarina carolinensis* and the data is suggestive of rapid polymorphism via fissions that lead to increase in chromosome number, which is correlated to the tectonic instability of the area (Qumsiyeh *et al.* 1999; Qumsiyeh *et al.* 1997). The fact that some species with highly polymorphic chromosomes in Robertsonian translocations seem to fit the Hardy-Weinberg expectations indicate that there is little strong negative consequences for heterozygotes (Nachman and Myers 1989; Qumsiyeh *et al.* 1997). ROBs could have impact on volume or positions of chromosomes in interphase nucleus which is critical in gene expression (Qumsiyeh 1995; Qumsiyeh 1999; Garagna *et al.* 2001) but in some cases they do impact structure of the nucleus (Acloque *et al.* 2013). While some authors postulated that we would see more centric fusions than centric fission in ROBs, clearly this view is an oversimplification and there are many mammalian lineages with centric fissions (Perry *et al.* 2004).

The house mouse is a good model of significant variation in chromosome number due to Robertsonian translocations with  $2n$  ranging from 22 to 40 occurring relatively recently and associated with little genic variation (Britton-Davidian *et al.* 1989). While controversial, there are data that suggest habitat segregation for mice with low and high chromosome number (Chatti *et al.* 1999;

Castiglia and Caporioni 2005). Mice with Robertsonian translocation were found to have a decrease and a re-patterning in chiasma frequency (Dumas and Britton-Davidian 2002) which substantiates the hypothesis of link between recombination and chromosome speciation (see discussion in Giménez et al. 2016). Further there is an apparent non-randomness in terms of chromosomes involved in fusion suggesting selective forces operate in the mouse model (Gazave et al. 2003) different than the human model (Pardo-Manuel de Villena and Sapienza 2001b). In such cases and in the case of human carriers of balanced translocations, the gametes produced are not random in terms of segregation but there appears to be a drive in female meiosis towards increased gametes with either higher number of centromeres or lower number of centromeres in other words non-random preferential segregation in female meiosis (de Villena and Sapienza 2001a). This may actually explain mechanistically the way the drive is selected for to increase or decrease chromosome numbers via female meiosis (i.e. drive to fix after starting via heterozygous condition, see Chmátal et al. 2014). =The West African *Gerbillus nigeriae* also shows significant variation with Robertsonian translocation and excess heterozygosity which suggested that this helps the species in its rather unstable environment (Hima et al. 2011).

### **Interspecific variation**

There has been an accumulation of data since the initial publication in 1994 that show that interspecific chromosome variation in wild mammals is associated with degree of environmental heterogeneity (i.e. unstable environments have taxa with higher chromosome numbers). A quick scan of the literature reveals

that the hypothesis relating to independent assortment, recombination, and variation is not only applied to taxa listed above but include other mammals ((Peppers 1998, Ropiquet et al. 2008; Nash et al. 1999) and is even noted in fish (Symonová et al. 2013; Nirchio and Oliveira 2006; Phillips and Rab 2001; Danzmann et al. 2005; Azevedo et al. 2007), reptiles (Olmo et al. 2002), beetles (Proença et al. 2002), scorpions (Qumsiyeh et al. 2014), lice (Shao et al. 2009), ants and wasps (Imai et al. 2001), and cereal plants (Devos and Gale 2000). By contrast, few authors questioned whether the models fit their group of interest such as data on deer chromosomes (e.g. Slate et al. 2002).

Literature does not include a discussion of why some mammal species were prone to domestication and invasion in relation to genetic variation due to higher chromosome numbers as would be predicted by the model. Natural selection leading to invasiveness would be expected in species with higher chromosome numbers/higher FN/higher recombination which would allow them to adapt to various conditions in different invaded habitats (different than the one they evolved in). Domestication is in essence similar to invasiveness but in a selective breeding program by human mediated artificial selection rather than natural selection. In other words, species with high variation would be easier to domesticate than species with lower variation (easy to find enough variation in each generation). Domesticated animals today would be expected to have on average higher chromosome number than wild undomesticated and related species. The consensus is that the ancestral chromosome number in placental mammals ranges from 44 to 50 with the most likely being 46 which

happens to also be around the mean number (Ferguson-Smith and Trifonov 2007; Ruiz-Herrera et al. 2012).

In a quick examination of chromosome numbers of invasive, domestic and some commensal mammalian species were noted to have high chromosome numbers but that there are exceptions. Examples of high chromosome numbers include dogs ( $2n=78$ ), reindeer ( $2n=70$ ), donkeys ( $2n=62$ ), horses ( $2n=64$ ), goats ( $2n=60$ ), yak ( $2n=60$ ), guinea pig ( $2n=64$ ), common cattle/cow ( $2n=60$ ), Cambodian cattle ( $2n=56$ ), Asian Elephant ( $2n=56$ ), llama ( $2n=74$ ), and camels ( $2n=74$ ). But there are some species that have intermediate range chromosome numbers: mink ( $2n=30$ ), fox ( $2n=34$ ), pig ( $2n=36$ ), cat ( $2n=38$ ), black rat ( $2n=38$ ), ferret ( $2n=40$ ), coypu ( $2n=42$ ), Norwegian rat ( $2n=42$ ), the pig ( $2n=38$ ), nutria ( $2n=42$ ), hamster ( $2n=44$ ), and rabbit ( $2n=44$ ), domesticated hedgehog ( $2n=48$ ). The reasons might be lineage specific meiotic drive (see discussion below). But let us take all these 25 species and compare their average and standard deviation to those of mammals with known chromosome numbers compiled by O'Brien et al. (2006). The data for 854 mammals (all orders) have a mean diploid number of 42.671 (standard Deviation 14.6882, maximum 102, minimum 7). The data for the 25 species listed above have a mean diploid number of 51.76 (standard Deviation 14.17, maximum 78, minimum 30). The 25 species have diploid numbers with the mean number of chromosomes (51.76) significantly higher than the population mean of 42.671 (2-tailed T-test,  $p=0.004$ ).

Yet, even though they are significantly higher in mean  $2n$ , invasive and domesticated species fall in two categories one with diploid numbers of 60 to 78 and one group with 38-44. The latter though have higher FN (more arms and hence more recombination) than similar species with similar numbers that are not domesticated or invasive. The discussion in Driscoll et al. (2009) about the modes of domestication of cat ( $2n=38$ ) versus dog ( $2n=78$ ) suggest the latter was under more artificial human selection than the self-selection of the former. The human karyotype ( $2n=46$ ) actually fits as a species that has self-selected as in Driscoll et al.'s (2009) cats! But this subject needs further research.

Nine inversions and one fusion distinguish humans from their closest evolutionary relatives, the chimpanzee (Szamalek et al. 2006). The average chiasmata in human and chimp are respectively 51 and 44 (Datta 1972, Falek and Chiarelli 1968). The difference in chiasmata would not be strictly attributable to increase in diploidy by one pair in human but by unique heterochromatin blocks in Chimpanzees that lowered recombination rate – or alternatively humans as having more recombination resulted in molecular plasticity (Ventura et al. 2012; Rogers and Gibbs 2014; ). Evolutionary rearranged human chromosomes (compared to Chimpanzee) are reported to have higher variability in nucleotide sequences than those that are co-linear (un-rearranged) (Navarro and Barton 2003). The evolution of the recombination map of human compared to chimpanzee has been indeed very rapid (Munch et al. 2014) and perhaps explains the phenotypic plasticity of humans due to a rich recombination around hotspots in both humans and chimpanzees (Auton et al.

2012; Stevison et al. 2016). Taken together, these data point to the need for understanding why the rearrangement in higher primates happened the way they did and their consequences for increased genomic variation and spread of human populations as well as recombination landscape (see Stapley et al. 2017) as a driver of phenotypic variation and ultimately selection and evolution.

There is strong evidence that invasive species are invasive because they were able to use molecular mechanisms such as genome reshuffling and polyploidy in plants to increase variation (Prentis et al. 2008). The increased number of progeny and higher variation due to increased chromosome number in invasive mammal species, might compensate for the bottleneck effect of initial invasion (Excoffier et al. 2009). Further studies especially on invasive mammal species are needed.

### **Discussion**

The data cited above from many authors over the past few decades about intraspecific and interspecific variation of chromosome rearrangement rates validated the adaptive (non-random) advantage of changes in diploid numbers and karyotypic structure including those caused by ROBs. The model of effect on recombination and segregation (Qumsiyeh 1994) received significant support subsequently from cytogenetic studies of many groups of animals with variation in numbers correlated with habitats and adaptation (see numerous citations in the introduction for different groups of animals studied). Yet, there

was little discussion in the literature on relevance of the model to intraspecific variation and other issues like domestication, and invasive species).

Some models of karyotypic evolution are based on fixation of chromosome rearrangements in parapatric population which then result in negative heterosis of progeny for example if the rearrangements are inversions in different chromosomes (Kirkpatrick and Barton 2006). Many of the existing models for ROBs suffer from the same shortcoming mentioned for inversions both in explaining existing empirical data and in lacking molecular cytogenetic explanations (Faria and Navarro 2010).

The developments of the fields of molecular biology in combination with cytogenetic studies allowed for a reexamination of the classical notions of mutations via step-wise events (classical Darwinian) with constraints and selection pressures acting to subdue potential dramatic evolutionary changes. One of the earliest of such data came from the drastic reorganization of the maize genome noted by Barbara McClintock (McClintock 1993). Subsequent reevaluation of chromosome changes validated the importance of structural chromosome issues in chromosomal orthoselection and punctuated evolution (von Sternberg 1996; Qumsiyeh 1994; Qumsiyeh 1995; Qumsiyeh 1999; King 1982; Parsons 1987; Bickham and Baker 1979).

For intraspecific variation, the model of ROBs impact on variation and adaptability appears to fit. This would explain the relatively recent

“Robertsonian fans” in animals like *Mus*, *Blarina*, and *Spalax* in unstable environments such as areas of volcanic activities (Capanna and Castiglia 2004; Qumsiyeh et al. 1999; Qumsiyeh et al. 1997). After all, what other explanation for the intraspecific variation by Robertsonian translocation in such habitats exist when populations of the same species occur elsewhere in the range without chromosome variation?

One of the questions mechanistically that had to be dealt with for fixation of chromosomal rearrangements via ROBs is the effect in producing unbalanced offspring (negative heterosis). The effects are not uniform for different species. Non-disjunction rates in simple ROB heterozygotes of *Sorex araneus* were 1.2 to 7.4% depending on ROB involved (Fedyk and Chętnicki 2007) while in house mice germ cell death can be produced from single ROBs from 19.5% to 30.2% due to unbalanced progeny (Sans-Fuentes et al. 2010). Humans fall in between but in all cases there seems to be deviation from expected frequencies based on random segregation with a preponderance of balanced progeny for ROBs (e.g. Honda et al. 2000; Ogur et al. 2006; de Villena and Sapienza 2001).

What cytogenetic and molecular mechanisms explain selection forces leading to both increase or decrease in chromosome number in different lineages and selection for non-random segregation in heterozygous ROB carriers? One hint comes from comparing human and mouse genomes. Humans have a drive towards metacentric chromosomes (fusions) and mice towards acrocentrics (fissions). It turns out that heterozygous carriers of Robertsonian translocation

differ in human vs mouse female meiosis in that the eggs preferentially get the acrocentric chromosomes in mice while they preferentially get the metacentric chromosome in humans (de Villena and Sapienza 2001b). The latter paper cited references for human and mouse segregation distortion (noted in females but not males) and suggested there is (yet to be discovered) mechanism that involves meiotic spindle preference for acrocentrics (in mouse) or metacentrics (in human) meiosis. However it turns out that female meiotic drive has been well studied in numerous papers dealing with maize and is due to proteins associated with centromeres (Malik and Henikoff 2002; Chmátal et al. 2014) and references therein). Further there are mechanisms that can explain the non-random segregation in carriers of Robs (avoiding negative heterosis) such as asymmetry in meiosis and functional heterozygosity at a locus that mediates spindle attachment (de Villena and Sapienza 2001b).

Other taxa cited above in the introduction as having decrease and increase in chromosome number might also be shown with additional studies to have a non-random distribution of chromosomes in heterozygous carriers between the egg and the polar body in female meiosis (see Chmátal et al. 2014). For example, female *Blarina carolinensis* carriers of Robertsonian translocations would be predicted to preferentially produce eggs carrying the acrocentric chromosomes. One caution to make is that independent acquisition of fissions might be missed in some lineages much more than independent acquisition of fusions (Qumsiyeh 1989) and this could lead to bias in favor of documenting fusions via retrospectively examining current living individuals.

Recent molecular tools such as chromosome painting have allowed for better reconstruction of ancestral mammalian karyotypes confirming many elements of the adaptive nature of the changes during evolution (Ferguson-Smith and Trifonov 2007).

It does not escape our attention that the variation in chromosome number seen in population of the same species and potentially partly explainable by recombination and variation would be a prelude for understanding variation between species (i.e. chromosome evolution and speciation). The difference between the karyotype of the Indian and Chinese muntjacs are very good examples of two closely related species with different specializations/niches that is associated with different chromosome numbers ( $2n=6/7$  and  $2n=46$ ) (Qumsiyeh 1994). Another example of this might be the variation seen in the genus *Acomys* whereby there are two groups of extant species with high and low chromosome numbers (Denys et al. 1994). Yet a third example is the genus *Gerbillurus* from South Africa (Qumsiyeh et al. 1991). In the latter cases, there are indeed habitat differences. For example, the *Acomys* species with high diploid numbers are the diurnal ones while the lower diploid numbers are found to be nocturnal (hence more protected from predation) (Qumsiyeh 1996).

Nothing in what was said implies that chromosome number variation is the sole explanation or even the main one in population variation but that it is a contributing factor and may help shed some light on some biological

phenomena. Having said that, this field can use many more studies especially focusing on meiotic drive, asymmetrical spindles, and segregation controlling genes. Many of the examples cited above for intraspecific variation could act as tests of the model by examining meiotic behavior and level of genic variation in populations with different karyotypes as was partially done for *Mus* and *Spalax*. It is now also possible to test our hypothesis using chromosome painting FISH techniques, it is now possible to perform analysis determining phylogenomic changes (Murphy *et al.* 2005, Graphodatsky *et al.* 2011). Another area of exciting research that could add data to support (or reject) the hypothesis relating to adaptive role of chromosome rearrangements in evolution is to apply molecular studies of recombination such as those now available in yeast and human (e.g. see Baudat *et al.* 2013; Odenthal-Hesse *et al.* 2014 ) to interspecific and intraspecific variations noted in the model organisms above. Yet another idea is to collect data on recombination in domestic animals that are self-domesticated (e.g. cat with  $2n=38$ ) and intentionally domesticated (dog with  $2n=78$ ) (see discussion of mode of domestication in Driscoll *et al.* 2009).

### **Acknowledgements**

We thank two anonymous reviewers who helped edit and made suggestions to this manuscript.

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