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The primate X and Y chromosomes are believed to have diverged from a set of ancestral autosomes that over time accumulated enough genetic differences to make them mostly non-homologous. More specifically, since its appearance approximately 166 million years ago the Y-chromosomes has been plagued by a series of mutational deletions that has shortened its length dramatically (Warren et al., 2008). The evolution of the Y-chromosome and its degradation therefore has radically changed the active genes that were once present in common ancestors from those living today (Charlesworth, 2000). However, its massive erosion over time has become somewhat of a concern, as it leads to questions of whether or not the Y-chromosome is on the path to extinction. To answer this question, a detailed analysis on the historical divergence of the Y-chromosome, as well as an investigation on the evolutionary mechanisms molding the Y-chromosome is needed to determine whether or not the male sex is on the brink of extinction.

The Structure of the Primate Y-chromosome

A brief overview of the makeup of the Y-chromosome in primates will give insight into why it shrinks so readily. Today, the human Y-chromosome contains approximately 50,000 base pairs that have been mapped to correlate 86 functional genes on the Y-chromosome (Payer et al. 2008). Geneticists have partitioned the Y-chromosome into two main regions (Figure 1): the pseudoautosomal region (PAR), and the male specific region (MYS). The PAR is the terminal homologous regions (chimps and macaques only have one PAR; humans have two) that are

capable of undergoing meiotic recombination with its paired X-chromosome, making it the only region on the Y-chromosome that is capable of any recombination (Rappold, 1993). The remainder of the chromosome is defined as the MYS region, which codes for all the male sex differentiating material that distinguishes itself from the X-chromosome (Hughes et. al 2012). Scientist have further broken down the MYS region into five more distinct zones. The heterochromatic portion of the Y-chromosome is the area in which DNA is tightly packed together to give greater control over gene expression. Researchers currently have the least amount of data on these sections, however they seem to vary in length across primate species. Next, the X-transposed region refers to the area of the Y-chromosome which is believed to have been transferred from an ancestral X-chromosome somewhere around three to four million years ago. Similarly, the X-degenerate region on the Y-chromosome shows a relation to an ancestral X-chromosome, except in that it was not transposed, but rather is an ancestral remnant of the autosome that the X and Y chromosome came from sometime before its diversification. As its name would suggest, this region of the Y-chromosome has severely deteriorated over time since its divergence (Bachtrog 2013). Finally, and maybe most importantly, there are several ampliconic regions of the Y-chromosome**.** These regions are characterized by repetitive palindromic sequences of DNA that house different highly copied genes that express traits for male gonad differentiation in development. Important genes that are found in this region include the SYR gene (aids in testes development), and the DAZ gene (promotes healthy spermagenesis) (Yueh-Hsiang et al. 2008). The length of these ampliconic regions vary greatly by primates species, as chimpanzees and humans have the longest regions being 14.7Mb and 10.2Mb respectively, while macaques have a significantly shorter sequence that is only about .5Mb (Bachtrog 2013). As stated earlier the MYS cannot undergo recombination with the X-chromosome. This allows mutations to accumulate in the MYS during DNA replication

that will, consequently, be identically passed down father to son because its lack of recombination prevents variation on this region. Therefore, without variation natural selection cannot act upon the chromosome because there is no force that can remove the deleterious mutations out of the population. This highlights the importance of the ampliconic region as it acts as a homologous region for itself and therefore can protect important genes (most vital sex determining genes are in the ampliconic region) by recombining with itself just as regular autosomal recombination would do. This also essentially allows the chromosomes to undergo purifying selection by itself, and remove large portions of DNA that may have accumulated deleterious mutations (Griffen, 2012). Hence, the repetitive nature of this region makes the Y-chromosome easily susceptible to mutational deletion, and is most likely the source of why it is so dynamic in length over time (Hughes et al., 2012).

Phylogenetic Analysis of Y-chromosome Evolution

The origin of the Y-chromosome predates the primate order, and is believed to have emerged somewhere early in the evolutionary history of mammals. Its genesis was caused by a major mutation that rearranged the proto Y-chromosome significantly enough that it could no longer recombine with its autosomal twin. It is suggested, however, that the Y-chromosome did not bear its sex determining function till the addition of genes like SRY that aid in testicle development (Graves, 1995). The disrupt in homology between the proto-X and proto-Y allowed for selection to act on the Y to promote further differentiate from the X-chromosome through time (Bachtrog, 2006).

The emergence of the mammalian Y-chromosome was a homoplasious event, as sex chromosomes are observed across many different classes (Graves, 2001). Evidence for homoplasy was determined through a comparison of the mammalian Y-chromosome with the sex determining

genes of birds and reptiles. In contrast to mammals, birds and reptiles have sex chromosomes dubbed ZZ and ZW, where birds in particular have heterogametic females and homogametic males (Raymond et al., 1999). Furthermore, a comparison of the SRY gene on the mammalian Y-chromosome with the analogous DMRT1 gene on the avian/reptilian Y shows no evolutionary relationship between the two. These findings led to the conclusion that the mammalian Y-chromosome had to independently appear sometime in the very early existence of the mammals, and most likely appeared in its most basal group the monotremes (Figure 2) (Veyrunes et al., 2008).

A closer investigation of the monotreme's sex chromosomes reveals a complicated evolutionary pathway of the XY chromosome structure of therian mammals. The platypus, a modern day monotreme, has five pairs of sex chromosomes that align in a chain like structure in which XX denotes a female and XY male (Grützner, 2006). A comparison of these X-chromosomes with other vertebrate sex chromosomes reveals that they share several regions of homology with avian sex chromosomes, but none with the therian sex chromosomes. Hence, further supporting the hypotheses that the therian Y-chromosome most likely diverged convergently from avian/monotreme sex chromosomes. Further comparisons of the platypus genome with therian sex chromosomes revealed an ancestral relationship between the autosomal chromosome 6 on the platypus indicating this may have been the autosome in which the therian Y and X chromosomes diverged from (Veyrunes et al. 2008). The divergence of autosome 6 into the Y-chromosome is hypothesized to occur through a transposition in which the autosome acquired the x-linked SOX3 gene which is expressed in both avian male and female sexual organs. Homology between the SOX3 and SYR gene indicate that the SOX3 might be a distant relative of the SYR (Figure 3). It is therefore most likely that this mutation triggered selection to act on the SOX3 gene to become a more male defining trait in which over time has further specialized it to

relate to sex determination (Graves, 2008). These findings effectively date the mammalian Y-chromosome to independently appear no earlier than 166 million years ago with the appearance of monotremes, and no later than 148 million year ago with the appearance of therians (Veyrunes et al. 2008).

Looking more specifically into the Y-chromosome of the primate order, it becomes apparent that it has endured a series of mutations that vary the Y-chromosome across primate species. The azoospermia factor (AZFc) is a multi-ampliconic region on the Y-chromosome that houses many of the important male-defining genes found in higher primate lineages; deletions or complex mutations within this area often result in infertility in males (Kuroda-Kawaguchi, 2001). Most of the amplicons found in the AZFc were transposed from ancestral autosomes into the Y-chromosome at various points in time during primate evolution. The major transposition events of the AZFc in primates is hypothesized to have occurred in three different waves. The first wave occurred just after the divergence of the new world monkeys approximately 35 million years ago, in which two major ampliconic regions, denoted green and red in the literature (Figure 4), were inserted into the primate Y-chromosome and subsequently duplicated into high copy numbers. The transposition of the red amplicon into the AZFc introduced the DAZ gene to the primate Y-chromosome, which is an important gene that aids in spermagenesis. The second wave of ampliconic transposition occurred around seven to eight million years ago after the diversification of gorilla lineages. This wave involved the transposition of the yellow amplicon from chromosome 15, which over time reproduced high copy numbers of itself on the Y-chromosome. The final wave of ampliconic insertion occurred two to three million years after the second wave in accordance with the divergence of human, bonobo and, chimpanzee lineages. At this time, the orange and grey

amplicons were transferred into these species of primates Y-chromosome (Yueh-Hsiang et al., 2008).

As mentioned earlier, the DAZ gene was inserted into the Y-chromosome during the first wave of ampliconic transpositions, and since then has become an important genetic marker for primate evolution due to its variation in copy number across primate species. Macaques have a single copy of the DAZ gene while higher taxa carry multiple copies. This indicates that somewhere after the divergence of old world monkeys the DAZ gene was amplified via inverted duplications to give a head to head orientation of the DAZ genes found in hominidae. This head to head oriented duplication underwent additional replication events to create the four extra DAZ copies found in modern orangutans, chimps, and humans. The timing of the duplication events are still unclear, as the absence of the four additional copies of DAZ genes in bonobos and gorillas (who only have two copies) complicates the timeline of inheritance (Yueh-Hsiang et al. 2008).

Another trait often used as a marker for the genetic evolution of the primate Y-chromosome is the RSP4 gene family. These genes have been highly preserved over the history of life on Earth, as evidence of its presence in ancient eukaryotic lineages (Alksne et al., 1993). However, the deviation of the more modern RSP4X and RSP4Y genes from RSP4 family have only been found within the primate order (Fisher et al., 1990). More specifically, through PCR and sequencing it has been detected that RSP4X and RSP4Y are present in macaques, the great apes, and gibbons. Ancestral mammalian populations carried a primitive version of RSP4X and RSP4Y, but all modern mammalian clades seemed to have lost the two genes somewhere along the line, leaving higher order primates as the only lineage carrying both traits (Bergen et al. 1998).

Mechanistic Basis of Y-chromosome Evolution

Evolutionary forces such as mutation, genetic drift, and natural selection all have played a heavy role in molding the primate Y-chromosome into its current form. The Y-chromosome's lack of homology allows the mechanisms of evolution to easily alter its genetic structure, thus posing a possible threat to the existence of the male chromosome.

Mutation

Mutation is one of the largest evolutionary forces acting upon the Y-chromosome due to its inability to weed out negative additions via recombination. As noted previously, the Y-chromosome has undergone a series of deletions since its divergence from its ancestral autosome. This is due to the pressures applied to the Y-chromosome after it had distinguished itself from the autosome through the addition of a sex defining genes. Specifically, the addition of these genes made it impossible for regions of the proto X and Y chromosomes to recombine, and therefore has prevented the Y-chromosome from fending off the fixation of deleterious mutations (Charlesworth, 1978). For example, because the homologous X-chromosomes in females are capable of recombining, their structures are able to combat the fixation of deleterious mutations; hence, X-chromosome structure has remained somewhat conserved over the span of its existence in primates (Graves, 2006). Conversely, because the MYS is incapable of recombining with the X-chromosome it can build up mutations relatively quickly. To compensate, the Y-chromosome has deleted large portions of its make up over time in the hopes of removing the bulk of these deleterious mutations (Griffen, 2012). For instance, the Y-chromosome appears to be more prone to the accumulation of human endogenous retroviruses (HERVs) DNA via transduction than any other autosomal parts of the primate genome because of its inability to quickly filter these genes out via recombination (Sin et al. 2010).

The addition of transposons from autosomes and bulk removal of deleterious mutations have attributed to the dynamic length of the Y-chromosome over its existence, thus, indicating the evolution of the Y-chromosome has occurred in multiple events making some parts more recent than others (Skaletsky et al., 2003). These more recent additions are at an earlier stage of degeneration than other parts of the chromosome in which less DNA has yet to be removed, which as a result, has created a mosaic of genes on the Y-chromosome that are at different stages of degeneration. This finding may imply that complete Y-chromosome degradation is unlikely, as over time it has introduced new material to prevent the Y-chromosome from completely eroding. The constant addition of transposons therefore keep the Y-chromosome from completely whittling down. However, these transpositions have to be large and frequent enough to combat current shrinking trends (Bachtrog, 2006).

Selection

The addition of sex determining genes to the Y-chromosome has made it an easy target for selection forces. It is most widely believed that the Y-chromosome deletes large portions of its genome to remove deleterious mutations as an act of purifying selection (Charlesworth, 2000). However, there has been compelling evidence in Drosophila miranda populations (which has a Y-chromosome that functions similar to primates) that positive selection may drive the accumulation of these deleterious mutation in the Y-chromosome (Bachtrog, 2004). This hypothesis suggests that selection acts on beneficial mutations in which deleterious mutations genetically hitchhike with them to fixation because of genetic linkage (Rice, 1987). The pure nature of sex inherited chromosomes allows for the possibility of sex linked adaptations to occur to promote further differentiation; this is specifically apparent in males, as only a father can pass on his Y-chromosome to a son. Hence, the Y-chromosome over time may develop traits that would

selectively favor being “more” male. However, this phenomena does not always turn out to be completely beneficial for males as the sex differentiating traits that are being targeted via selection may also fix deleterious mutations via linkage. Purifying selection therefore acts against positive selection to remove the deleterious mutations from the Y-chromosome (Bachtrog, 2004).

Sexual selection has also been an observable force on the Y-chromosome within bonobo and chimpanzee populations. In comparison, the two species exhibit different types of mating systems. Chimpanzees support a patriarchy, in which dominant males choose the most profitable females with whom to mate with. In addition, female chimpanzees show distinct physical signs of ovulation, thus indicating to males that they are of an appropriate and advantageous time to reproduce. The combination of these traits create intense competition amongst male chimpanzees to mate with the visually sexually ready females (Goodall, 1986). This competition in return puts selective pressure on the spermagenesis genes of the chimpanzee males (Schaller et al., 2010). Bonobos, on the other hand, align their social order in a matriarchy, and assign power roles to female bonobos rather than males. In addition, female bonobos show no phenotypic indication of when they are ovulating. The arrangement of nonvisual sexual readiness, as well as dominance of the female sex both significantly decrease the competition for males to mate with the female bonobos, thus, putting less selective pressure on the spermagenesis genes of the male bonobo (Marvan et al., 2005). Comparing the amount of DAZ copies in the Y-chromosomes of these two species specifies how the opposite mating systems can cause differing pressures on Y-chromosome variation between the two populations. Due to the lack of sexual pressure put on the bonobo males, the amount of DAZ copy numbers in their Y-chromosome do not vary much from individual to individual within populations. Conversely, chimpanzee males show a wide variety of DAZ copy numbers on their male chromosomes, which supports the idea that the male chimpanzees need to

make quick sexual adaptions to their spermagenisis genes in order to be fruitful in their reproductive efforts (Schaller et al., 2010). This phenomenon also has also been recorded in the more distantly related orangutans and gorillas. Orangutans hold similar hierarchal systems as bonobos indicating once again that because male to male competition is reduced in orangutan populations there is less selective pressure on genetic variation within the Y-chromosome. Gorillas additionally have been noted to sometimes mate in monogamous pairs, which reduces the competition to mate with multiple females, and therefore, decreases the amount of selection that needs to occur on the Y spermagenesis genes. (Dixson, 1998). These findings note a similarity to other studies in which it has been found that gorillas, orangutan, and bonobos have similar genetic regions on their Y-chromosomes comparably to that of chimpanzees and humans (Rasheed et al., 1991).

Genetic Drift

One of the unique characteristics of the Y-chromosome, as stated earlier, is that it can only be passed down from father to son, male to male. This does not occur in the X-chromosome, as the mother passes on one of her X-chromosomes to either a potential son or daughter. Therefore, all accumulated mutations, both bad and good, on the Y-chromosome are passed down to each generation making it incredibly vulnerable to genetic drift (Graves, 2006). Additionally, because not everyone carries a Y-chromosome its effective population size will be much smaller than that of other autosomes. This increases the strength of genetic drift on Y-chromosomes as drift fixes mutations faster when acting on smaller populations (Jobling et al., 2003). This can actually be a major problem for males, as genetic drift can cause a population of Y-chromosomes to remove all nonmutants. Therefore, a population loses any ability to reintroduce beneficial traits back into the population once a chromosome is lost (Graves, 2006).

The Fate of the Y-chromosome

Given the trends of Y-chromosome evolution, does its deterioration suggest eventually the Y-chromosome shall go extinct? Currently, there is conflicting evidence on this subject. It was found on the mouse Y-chromosome (who shares a common ancestor with primates) that only two genes were needed in order to allow for successful reproduction of viable offspring. Thus, demonstrates that the importance of the Y-chromosome may be less than we thought. Transgenic male mice had their Y-chromosomes shortened from approximately 78Mb to 2Mb, cutting out the Y-chromosome's long arm entirely. The only genes that were found to be needed in order to produce viable offspring were the SRY, and Eif2s3y gene. The Eif2s3y function was detected to aid the first meiotic division after spermagenesis, and therefore helps in supplying enough sperm for male fertility. Although these genes allowed for the production of viable pups, the transgenic fathers were incapable of delivering sperm to their female partners due to underdeveloped sex organs. As a result, in vitro insemination was utilized to aid the males in fertilizing the females (Yasuhiro et al., 2014). Nevertheless, with only needing two genes to reproduce viable offspring, this begs the question, "is the Y-chromosome useless?" The answer is most likely no, as there are genes on the Y-chromosome that do prove to be important for male fertility. The fact that the mice couldn't reproduce by themselves without the use of technology shows that the Y-chromosome is still needed in some capacity. However, this experiment does show the extraordinary shortening a Y-chromosome can undergo to still be deemed sexually fit. Hence, highlighting the fact that the Y-chromosome may not be as important for reproduction as previously thought.

There is also evidence that supports the potential for the Y-chromosome to go entirely extinct. It has been both calculated and observed that the Y-chromosome can eventually vanish given enough time for deleterious mutations to accumulate. Lab experiments that examined the Y-

chromosome's in populations of *Drosophila melanogaster* suggested that enough damaging mutations had occurred on the Y-chromosome over time it had become useless. Eventually Drosophila's Y-chromosome was either lost or rearranged within the fly genome, demonstrating that extinction may be possible. However, once it was lost, alternatives quickly popped up. One population singled out a section of heterochromatin on the Drosophila X-chromosome, and paired up homologous autosomes to transpose genes that could aid in sex differentiation. Thus, once again reestablishing another Y-chromosome. Another population had the X-chromosome morph with an autosome; effectively creating another Y-chromosome that has already showed signs of deterioration in the lab (Carvhalo and Clark, 2005). There also have been examples of species that have lost their Y-chromosomes completely, but have sequestered all the important male determining genes, such as SRY, onto autosomal different locations. This most likely would be an appealing safe alternative to sex chromosomes, as the autosome could potentially protect the SYR gene from being lost (Graves, 2006).

Applying these data to primates, can the order potentially live without a male Y-chromosome? Evidence supports that most likely, with male extinction comes primate extinction. This is because imperative maternal genes are sometimes activated through males on their Y-chromosomes (Graves, 2006). But there is still a possibility, as the loss of the Y-chromosome after relocation of the SRY gene might prove successful for humans, as it has in other mammal species like the mole vole and Japanese spinous country rat (Arakawa et al., 2002). The loss of the Y-chromosome seems daunting when analyzing how important it is to primate reproduction in the status quo, however evidence shows that when a Y-chromosome becomes functionless species are readily capable to adapt to male-less conditions (Graves, 2006).

Studies of the Y-chromosome have shown the importance of mapping out its evolutionary history in order to better understand why the Y-chromosome looks and functions the way it does presently. Its divergence outside of the monotremes showed that primates have ancestral Y-chromosome relationships with earlier therian mammals that independently evolved from other sex chromosome systems (Veyrunes et al. 2008). Similarly, the variation of male specific genes, such as DAZ, display how significant the modification of the Y-chromosome truly can be. Its susceptibility to evolutionary pressures such as mutation, drift, and natural selection also indicate why the Y-chromosome's potential for being conserved across lineages is relatively low. Thus, although total loss of the Y-chromosome in primates seems somewhat unlikely, it is undoubtable that it will undergo significant change for generations to come.

Appendix

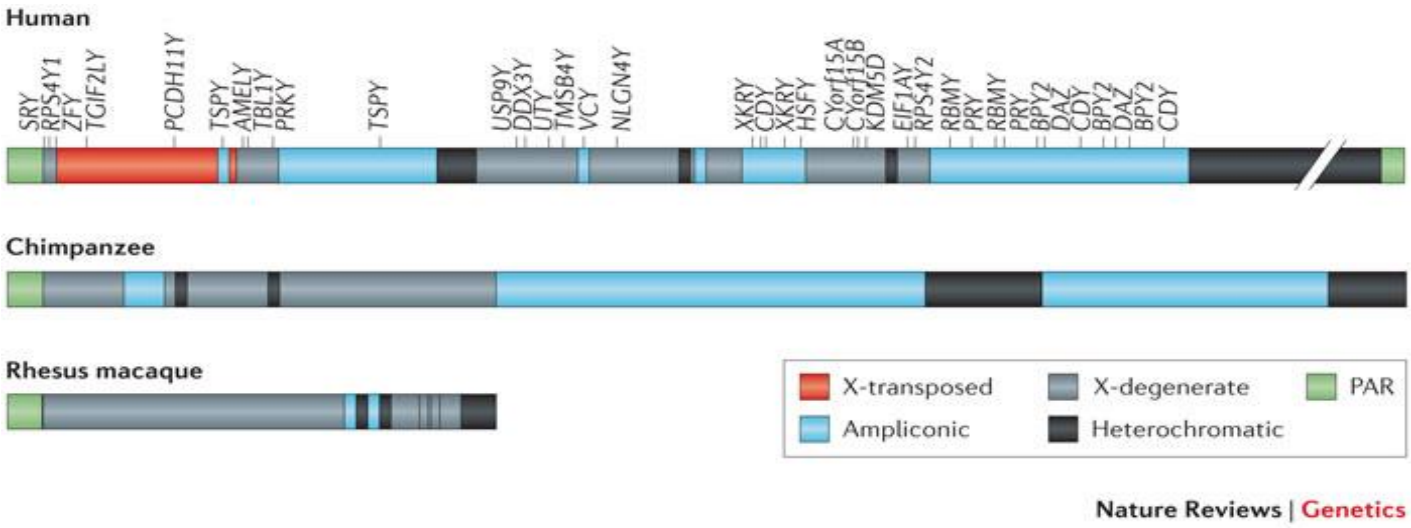

Figure 1. The arrangement of the PAR and MYS regions on the Y-chromosome of human, chimpanzee, and rhesus macaque males (Bachtrog, 2013).

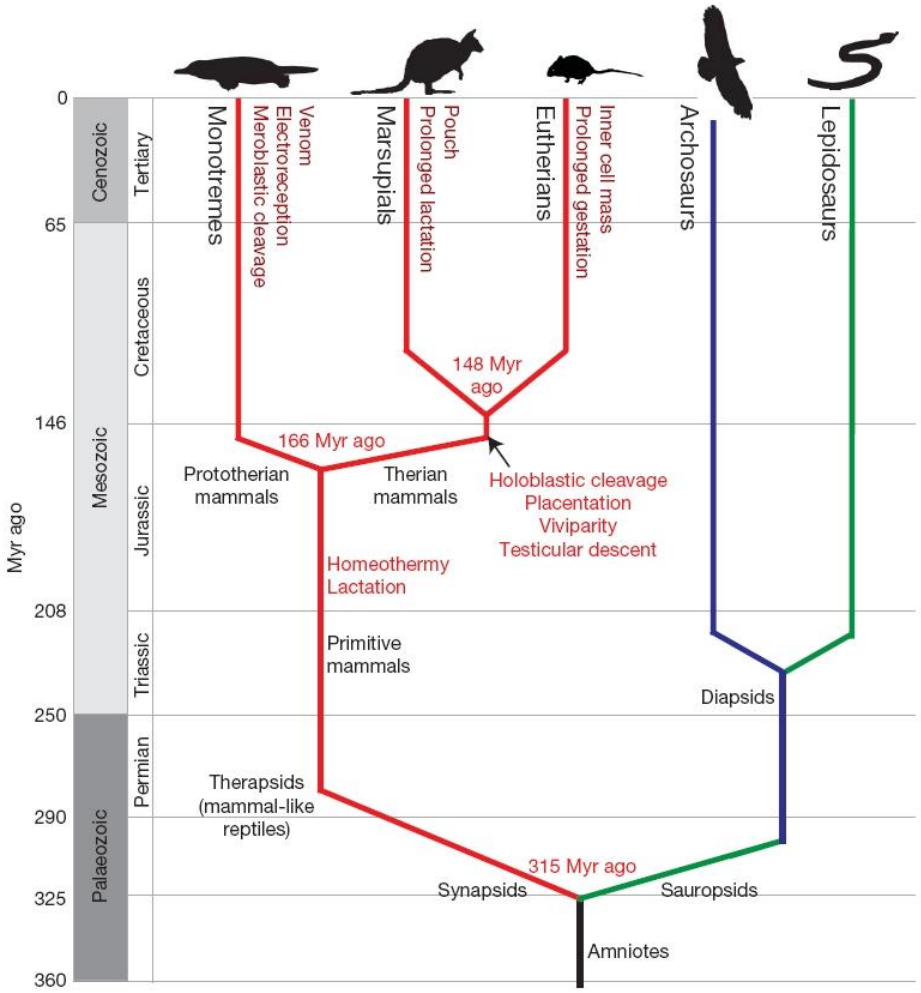

Figure 2. A phylogenetic tree that shows the relative times and relationships of divergence of the mammalian class (Warren et al. 2008)

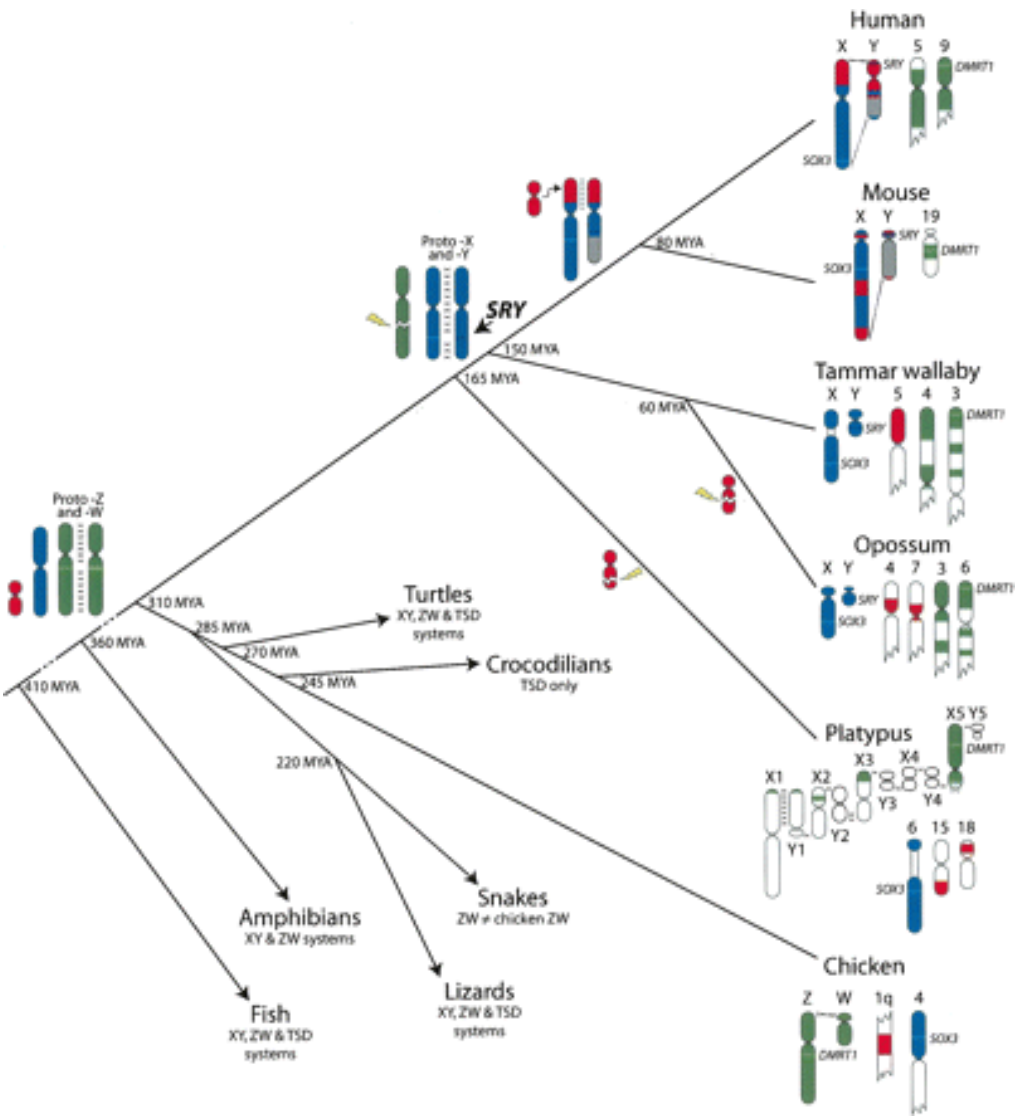

Figure 3. A phylogeny that maps the evolution of the Y-chromosome across avian, monotreme, and therian species (Veyrunes et al., 2008).

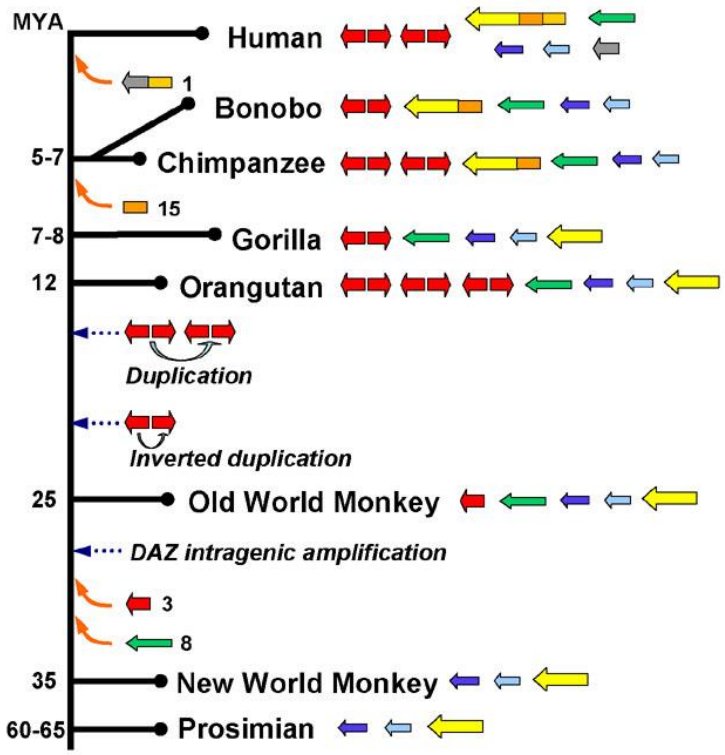

Figure 4. A timeline of the insertion and duplication of various amplicons, denoted by color, throughout the evolutionary history of the primate order. (Yueh-Hsiang, Yu, et al, 2008).

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