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HUMAN GENOME IS BILLIONS OF YEARS OLDER THAN MAN: A REEMPHASIS ON RANDOM DISTRIBUTION OF DNA SEQUENCES DURING EARLY PHASES OF EVOLUTION

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ABSTRACT

All whatever is happening in this kind of scientifically advancing technological race is gradually becoming unethically-scientific. Discoveries can not, but inventions (man made) can be patented!. The year 2005 was marked the 25th anniversary of the landmark court decision that opened a floodgate of patenting on both DNA and even whole organism. Ethical issues about patenting life have been taken seriously in several countries. After all how can you patent a gene in a chromosome which is not man made ? . A gene that has been cloned, is a “chemical photocopy”/ or a pirated copy of the original gene. So a gene in the test tube can be patented but the right for “owning the gene in form and function” of the original gene present inside the cell on account of patenting would be a totally unqualified claim or gross misinterpretation of the scientific discoveries. Patent for a gene can not amount to patent of that gene present in other organisms; this needs serious concern by all those who realize the marvelous mystry of Biological Evolution. As very well documented by now, copies of DNA stretches have been randomly distributed among variety of organisms during evolution and these can not be exclusive acquisitions of any one organism. Unity and Diversity are the inherent and vital parts of all organisms that exist or that had had existed in the distant past, and also, will exist on this planet in future.

Keywords : Evolutionary genetics; Human Genome, Comparative genomics; Random dispersal of genes in evolution; Bioinformatics

Despite world’s derision, unfortunately, many genes are being cloned for patenting and such an effort which amounts to copyright of human genes, their forms and functions is becoming a very sensitive issue of human and medical ethics. Many chromosomes have several patented loci and within a decade or so, we shall have entire chromosomes patented. Hereunder this is argued, that the genes “cloned” and patented, are not exclusively human; exact copies of these genes (DNA sequences) are also present in other organisms. This has been aptly demonstrated by now, that human X and Y chromosomes and other chromosomes too, have evolved by sharing and transferring DNA sequences at various stages of evolutionary steps from diversified groups of organisms. Patent for a gene can not amount to patent of that gene present in other organisms; this needs serious concern by all those who realize the marvelous mystry of Biological Evolution. Unity and Diversity are the inherent and vital parts of all organisms that exist or that existed and also will exist on this planet. Apart from this, the patented gene is a chemical copy/pirated gene of the original gene present in a chromosome. How can a copy of the gene (man made) in the laboratory lead to patenting of an original gene present in a chromosome ? This may be a violation of legal, scientific, as well as ethical values. Technically, the genes owned in test tubes can not hold patent for the genes / chromosome domains in situ because these are not exactly same.

Concept of patenting:

The concept of patenting, may hold good for a plant and or animal product whose sale or benefits of which are in public interest and the product to be marketed would need huge monetary investments by the inventor or any manufacturing unit. The product has to be utilized by people and in order to avoid unauthorized duplicacy, patenting of products obtains acceptable restrictions. In this process the inventor or a group of investigators are also recipients of benefits. In other words monetary profits could be distributed among many owners or shared by patent holder. Similarly, patenting gene products also appears justified because then only useful products, enzymes, medicines and many life saving drugs can be produced and sold in the world market by authorized companies. This has been argued that unless they have patent (s) in their favour it would be huge expense with a lot of risk involved to install a big manufacturing unit because others would copy down soon depriving the inventor and related benefit holders. Arguments are both in favour as well as against the patenting concept but the greatest worry faces all human beings world over is that we are stretching these approaches too far. In this context, American courts have given a dictum "Any thing man made can be patented" but we have started interpreting or claiming "patenting genes in chromosomes". Furthermore those who have obtained patents may claim that the candidate gene in the chromosome (gene locus)has also been patented. This brings unhappy situation for all human beings. For example, a gene that makes the protein that the hepatitis A virus uses to attach to cells, has been patented by US Department of health; similarly a gene that plays a key role in spinal cord development is owned by Harvard University group.

The ethics of the Judicial Judgment (order) was to enhance the ingenuity of human mind but not to claim the copy rights on different parts and functions of human body. Above all is the argument that the genes in the "test tube"(cloned chemical sequences) are not exactly the same as is being patented. Cloned genes are not exactly present on a chromosome. Furthermore, the" gene-environ" in a chromosome is different from the copy of the gene patented. This amounts to a serious legal blunder!. Not on ethical values, but on very sound judicial grounds a second thought be given and debated as to how can a cloned and patented gene in the laboratory own a copy right for the original gene in a chromosome(Goswami, 2006a) ?. Additionally, hereunder, we also examine that a cloned gene (specific DNA sequence) from human genome is also present in various other related and far more distinct organisms thereby offering non- ending complications of biological nature.

Distribution of DNA stretches has been random in evolution

A large number of DNA sequences are being reported to have been conserved in various divergent animal phyla, many of the genes retaining the same function in humans. The cat has a highly conserved karyotype, closely resembling the ancestral karyoptype of mammals while the dog has one of the most extensively rearranged mammalian karyotypes, investigated so far (Yang et al, 2000). With the help of reciprocal painting techniques on chromosomes, M.A.Ferguson Smith and his colleagues in Cambridge have produced extensive maps of many mammalian species with comparative data on evolutionary mechanics leading to speciation. Dog paints specific for the 38 autosomes and the X chromosomes delineated 68 conserved chromosomal segments in the cat, while reverse painting of cat probes onto red fox

and dog chromosomes revealed 65 conserved segments. Most conserved segments on cat chromosomes also show a high degree of conservation in G-banding patterns compared with their canine counterparts. At least 47 chromosomal fissions (breaks), 25 fusions and one inversion are needed to convert the cat karyoptype to that of the dog confirming rhat extensive chromosome rearrangements differentiate the karyotypes of the cat and the dog. Comparative analysis of the distribution patterns of conserved segments defined by dog paints on cat and human chromosomes has refined the human-cat comparative genome map and, most importantly, have revealed 15 cryptic inversions in seven large chromosomal regions of conserved synteny between human and cats

There are also a large number of DNA sequences known to have strict homology, but for quite different functions. For example in Drosophila melanogaster patched mutations are known to cause faulty winged veins and the human version of this PTC gene results in defective ribs as well as skin cancer. This gene is mapped on the long arm of human chromosome 9, very near the site where genetic linkage studies have shown the presence of gene for basal cell nevus syndrome.

Another such example where a normal gene in fruit fly causes cancer in other organisms is wntl gene which in fruit fly, functions as wingless gene, while it causes mammary tumour in human on becoming overactive. Also a human GLI gene which was discovered as an oncogene in a rare human brain tumour is now known to be the counterpart of the Cubitus interruptus gene of the fly . Lately, this is becoming very clear that humans other mammals and also other organism have their own versions of genes found in many organisms. For example, vertebrate homologues of hh and ptc have been identified in mice, chicken and Zebra fish. In humans these genes have important roles in organizing many tissues including neural tube, skeleton, limbs, cranofacial structures and skin. We have strong evidences to assume that conserved sequences can be found in diversified and apparently unrelated phyla but the functions performed in that organism by that very gene need not be the same.

Genes are not exclusive of the Organism:

The important point of argument is that a DNA stretch of a gene may be, very rarely though, found in a totally unrelated species without any evolutionary significance. Indisputably this is a truthful legacy of evolution with no obligation on lineages/ relationships. This can be emphasized here that higher percentage of concordance in the DNA sequences of a few genes among some plants and animals including man, may account for geological persistence of certain DNA stretches/versions of genes (? conserved through billions of years probably due to random distribution). These DNA sequences must have been lodged as integral part of subgene pools much before the divergence of plants and animals in the Pre-Cambrian to Cambrian (500 to 600 billion years ago) genomes are elastic from evolutionary point of view and have phylogenetically travelled through millions of years and spread over among diversified organisms world over at all times since the advent of life on the earth. Certainly therefore, a gene, present in one organism at one chromosome domain may be present for the different or related similar function at a different domain in another organism, and thus in no way is an exclusive, “bonafide resident” within/ of that organism. To be very precise and more pragmatic, even one or more human chromosomes, for instance,

human Y chromosome has been tailored in evolution from tit bits of several sequences and congregated in to one unit chromosome representing according to David Page and his colleagues a mosaic of DNA sequences bearing homology to many organisms. This also implies, as also very explicitly demonstrated by modern molecular biological techniques that a gene functions in one way in one organism and does have different function in another with differences in positions at different chromosomes Also, a single gene may have many functions , pleiotropic in nature. Indisputedly, neither a gene nor any gene function can be patented. Because, a human gene specifically is not "exclusive human" but belongs to many organisms, the multiple patenting is improbable and unscientific.

Same DNA sequences in plants:

On the basis of earlier and present experimental approaches by DNA finger printing, the emphasis is laid on resemblances of some genomic DNA sequences of *I pantii* to a few human Y chromosomal sequences. Brief comments on recent discoveries of human Y chromosome MSY region DNA sequences by different authors in a bryophyte, *Marchantia polymopha* and in several other plants, have also been discussed particularly with the intention that our hypothesis advanced during 1990s that many plants must have some sequences from human genome or vice versa, appears to be valid. All these observations (Nagl, 1991; Goswami and Chandorkar, 1994; Okada et al, 2000, 2001; Tanurdzic and Banks, 2004, Goswami, 2011) also support our earlier hypothesis advanced on the basis of genomic studies as well as computer search (DNA blasting) of a part of *Isoetes genomic* DNA with the human genomic data, that the DNA sequences, must have ceaselessly replicated and randomly distributed among evolving cells before the bisecting of evolutionary lineage to plant and animal cells during very early phase of evolution and differentiation among cells.

Evolution of sex chromosome within the genome:

Sex determining systems have evolved independently in vertebrates. Placental mammals and marsupials have an XY system , birds have a ZW system. Reptiles and amphibians have different systems including temperature dependent sex determination and XY and ZW systems that differ in origin from birds and placental mammals.

Sex chromosomes are generally believed to have descended from a pair of homologous autosomes. Monotreme sex chromosomes are easiest to explain on the hypothesis that autosomes were added sequentially to the translocation chain, with the final additions after platypus and echidna divergence (Rens et al, 2007). Genome sequencing and contig anchoring show no homology yet between platypus and therian Xs, thus monotremes have a unique XY sex chromosome system that shares some homology with the avian Z chromosome. As has been established, the male platypus has five X and five Y chromosomes, no SRY and DMRTI on any X chromosome. Chromosome paintings generated by Ferguson-Smith and his group have revealed (Grutzner, et al 2004; Rens et al, 2007) that the meiotic chain of nine sex chromosomes in the male echidna are according to a specific order. Two chromosomes differ from those in the platypus, three of the platypus sex chromosomes differ from those of the echidna and the order of several chromosomes is rearranged. Results obtained on comparative gene mapping shows that in addition to bird autosome regions, regions of bird Z chromosomes are homologous to regions in

four platypus X chromosomes, that is X1, X2, X3, X5, and in chromosome Y1. Evolution of human sex chromosomes has been still fascinating story among chromosome evolutions. Because of its distinctive role in sex determination, particularly the Y chromosome has long attracted special attention from geneticists, evolutionary biologists and even the lay public. It is known to consist of regions of DNA that show quite distinctive genetic behaviour and genomic characteristics. The two human sex chromosomes, X and Y, originated a few hundred million years ago from the same ancestral autosome , a non-sex chromosome , during the evolution of sex determination. These chromosomes then diverged in sequence over the succeeding aeons. Nowadays, there are relatively short regions at either end of the Y chromosome that are still identical to the corresponding regions of the X chromosome, reflecting the frequent exchange of DNA between these regions ('recombination') that occurs during sperm production. But more than 95% of the modern-day Y chromosome is male-specific, consisting of some 23 million base pairs (Mb) of euchromatin the part of our genome containing most of the genes with a variable amount of heterochromatin, consisting of highly repetitive DNA and often dismissed as non-functional or redundant. Skaletsky *et al*.(2003) report the complete sequence of the 23-Mb euchromatic segment, which they designate the MSY, for 'male-specific region of the Y'. Coauthors of this team of David Page designate MSY region as mosaic of discrete classes.

The worry is for tomorrow; someone having patented, say " gene A" present in *Drosophila* or an aquatic weed, is also present in humans and performs function of producing a remedial protein, would claim "property rights on three different products" because he or she has cloned and patented " man made" chemical copy of the gene present in chromosomes of three different organisms.

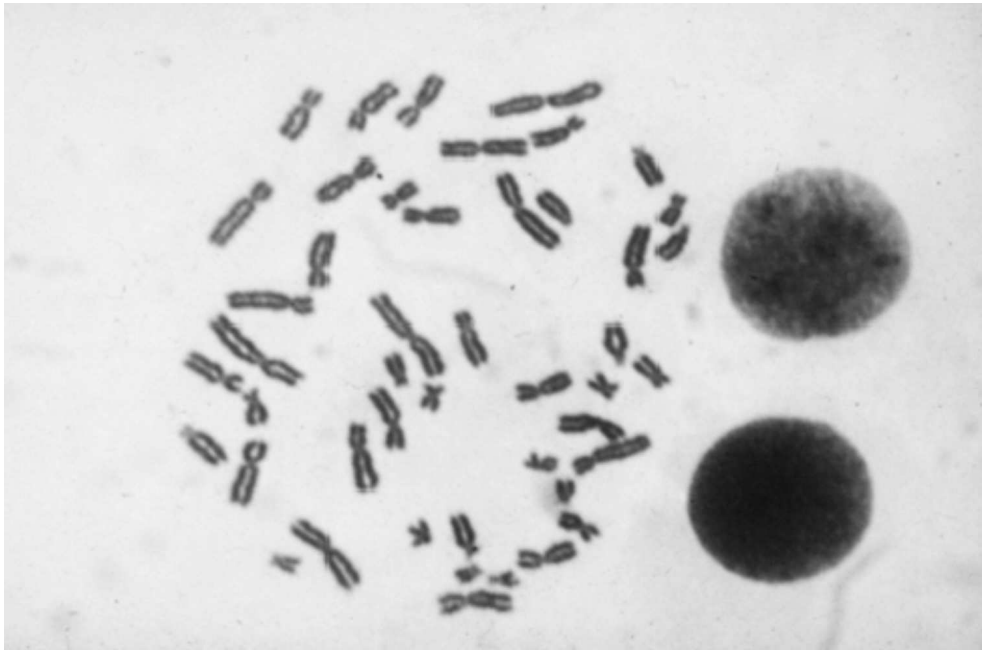

Fig.1– Human Chromosomes (Lymphocyte culture stained with Giemsa) at metaphase (male 2n=46)

Fig.2 – Translocations and breaks are not rare features
(Levaninan translocation; transfer of a chromosome on a chromatid end : After Goswami).

Fig.3. "I have donated DNA stretches to humans" A symbolic figure depicting chromosome and gene transfer during evolution of human genome.

Therefore, cloned genes patented in the test tube do not account for genes *in situ*. Practically, no gene or its function and or any chromosomal domain can be patented; only the product of a gene at a specific point of origin and locus can be and should be patented subject to "use in public interest". Biologists, ethicists and judges have very rightly formed a common platform to discuss on the speedy wave of patenting human genes because the US Patent and Trademark Office had issued patents to corporations, universities, government agencies and nonprofit groups for nearly 20% human genome. About 50% of the cancer genes have been patented and to emphasize on facts nearly 15% genes stored in the National Center for Biotechnology Information 's database are tagged with at least one patent.

Our Conclusions

Following basic points have already been emphasized (Bajpai and Goswami, 2002;

Goswami, 2009) which offer support to the hypothesis that in the early phases of cellular evolution, the DNA sequences must have been tirelessly multiplying and continued to multiply thereby enormous amount of DNA stretches must have been randomly distributed before the diversion of plant and animal cells. There can be no other reason for the commonness of quite many DNA stretches among all organisms as well as with so much of specific variability. New chromosomes originate from within the genomes and natural hybridizations have offered supplementary material for reconstruction and rearrangement with the help of aberrations like deletions, translocations, inversions and duplications (Goswami,1993, 2005, 2011; Figs 1-3)

1. DNA sequences for basic functions are uniformly similar in all organisms the best example comes for respiratory functions;

2. DNA sequences for fundamental structural organizations of chromosomes in eukaryotes are the same (ucleosomes etc). The genes controlling mitotic and meiotic cell divisions are essentially same in eukaryotes (Critchlow, Payne and Griffin, 2004; Lima de Faria, 1975,1980; Goswami, 1993). There is now a wealth of evidence that SMC proteins play an important role in responses to DNA damage. All eukaryotes examined atleast have six SMC proteins (Lehmann, 2005).This is also important to recall in prokaryotes that chromatin ends are attached to plasma membrane and most remarkably this is repeated by eukaryotic chromosome as an “evolutionary tribute” that in the interphase of mitosis in eukaryotes, chromosomes attach to the nuclear membrane. Eukaryotic chromosome have this inherent potentiality for such an attachment was once demonstrated when the magnetic field exposure resulted in totally uncoiled chromosomes, removal of nuclear membrane, and chromosome ends were seen pierced in the plasma membrane (Goswami, 1977). This is evolutionary affiliation.

3. Sequences that are dispersed among prokaryotes and a large number of lower groups of plants and animals viz. retrosposons like PLTEs; (Arkhipova, 2006) but not in higher animals like mammals;

4. Sequences common to plants and animals alike suspected much earlier; (Lima de Faria, 1975, 1980a, b) recently being detected among plants and animals including man (telomeric, centromeric as well as some specific genes and parts thereof; (Nagl,1991, Goswami and Chandorkar, 1994; Bajpai and Goswami, 2002; Bajpai, Goswami and Goswami, 2004; Goswami et al 2006 ; Mikolos, 1985).

5. Certain deeply conserved DNA sequences rarely express among genomes with very special or relic characters; unless provoked by genomic reshuffling triggered by any molecular mechanism and or natural hybridization (Silence genes; Bajpai, Goswami and Goswami, 2004; Goswami, 2009)

6. Specialized sequences evolved and remained unaltered after selection for specific functions among all organisms as per their evolutionary status and particulate biological demand of the organism. Prevalence of the same DNA sequences among sex chromosomes of some plants and their higher concordance with the MSY region of human Y chromosome are exemplary

demonstrations that DNA sequences/ genes are not exclusive or confined to one or the other organism but have been randomly distributed irrespective of their evolutionary position. This could have been possible only when "unity-diversity concept in DNA distribution must have been initiated in early phases of evolution.

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