

Homework #2-Physics 498Bio-(Part B)

by Soon Yong, Chang – Oct/31/01

Are There Bugs in Our Genome?

This is a review of the articles “Microbial Genes in the Human Genome Lateral Transfer or Gene Loss?” by S. L. Salzberg *et al.* Science Vol. 292 June/8/2001 and “Are There Bugs in Our Genome?” by J. O. Andersson *et al.* 10.1126/science.1962241 May/17/2001.

INTRODUCTION & BACKGROUND

It is known that the phylogenetic reconstruction of the “tree of life” suffers from weaknesses, among them the possibility of lateral gene transfer. One of the hypotheses of the lateral gene transfer is that it was characteristic of organisms at early stage of evolution and complexity (prokaryotes and unicellular eukaryotes) and took place among species very close each other.

For some years there has been on-going research trying to identify the genes that are common to vertebrates (humans) as well as to bacteria and thus to show the possibility of gene transfer from bacteria to vertebrates. This type of gene transfer is not quite “lateral” as humans (vertebrates) and bacteria are far apart in the hierarchy of the tree of life. If it were possible to detect traces of such gene transfer, it would mean that the gene transfer is possible between organisms very distant in the tree of life and that such gene transfer might still be possible.

However, before jumping into such a wild speculation, it is necessary to analyze the methods and limitations of the study and look for different explanations other than direct gene transfer from bacteria to vertebrates. In fact, in order to confirm the bacteria to vertebrate (VTB) gene transfer hypothesis, the candidate genes must “survive” tests that attribute their existence in the vertebrate to alternative mechanisms.

In order to make sure that genes have been transferred directly from bacteria to vertebrate (including humans), the identification of the sequences in the genome that are common to the vertebrates and bacteria, however absent in other eukaryotic genomes is carried out. As it is claimed by Salzberg *et al.* , 113 to 223 vertebrate genes have significant similarity to those of bacteria but without similar counterparts in other eukaryote genomes. This number fluctuates somewhat, depending on the criteria and gene database used.

METHODS

First of all, the study of Salzberg *et al.* is backed up by the recognition of the importance of lateral gene transfer in the evolution. Lateral gene transfers among low-level eukaryotes have been well documented. The availability of the complete human genome makes it possible to embark on the current study. (The human genome sequences used in the study were those provided by Celera and Ensembl.)

A couple of basic assumptions are made to justify the existence of bacterial genes in the human genome: 1), the bacteria needs to manipulate human genome for its own benefit and 2), the foreign genes possess selective advantage that ensures their survival in the host.

One of the posed difficulties is that in order to determine the absence of certain gene in a species, the complete genome sequence is required. It might be possible to detect the presence of certain gene from an incomplete sequence but not the absence of it.

So, not only bacterial and vertebrate (human) genomes are needed but also a number of non-vertebrate genomes are required in order to confirm the absence of these genes in this stage of evolution. Well known invertebrate genomes have been used for this purpose: fruit fly, nematode worm, eukaryotic parasites, etc. However, the lack of more available genomes (complete), hinders the research efforts as explained in the following:

Many “candidate genes” have been screened out because they were detected in non-vertebrates. If any “robust” bacteria to vertebrate (human) gene is to exist, the number of invertebrate genomes against which it is samples should not have any impact. However, as the number of non-vertebrate genomes increases the number of candidate bacteria to vertebrate transfer genes seems to decrease.

This could lead to the conclusion that bacteria to vertebrate (BTV) lateral gene transfer is nothing but an illusion and as more and more complete invertebrate genomes become available we would ultimately be able to rule out the BTV gene transfer theory.

Moreover, an explanation that accounts for the apparent gene transfer from prokaryote (bacteria) to vertebrates without passing thorough other non-vertebrate eukaryotes proposes that the difference in the evolutionary rate (faster) and the accidental loss of the genes of the non-vertebrate genome can create the illusion of direct BTV gene transfer.

Does this mean the end of BTV lateral gene transfer theory? At this point, it might be premature to conclude decisively as even the total number of genes in the human genome is not exactly known; somewhere around 30 thousands. To make matters worse, the BTV candidates sorted out from Celera data do not match to those from Ensembl data. In the end, both data sets coincide in leaving with 40+ genes that “survive” the scrutiny. Certainly less than the initial estimate of 100 ~200 but still a significant number. Now, the attention of the present review is turned to the article by Andersson *et al.* for the final discussion.

DISCUSSION

In order to determine that some of the candidate BTV genes are really BTV genes, a test consisting in the construction of the molecular phylogenetic tree is proposed. If a vertebrate gene is nested within a “robust” cluster of bacterial genes, then the former can be traced back to several bacterial genes in the molecular phylogenetic tree and the conclusion is that the vertebrate gene is of bacterial origin.

As reported by Andersson *et al.* one convincing case was found by the above described method: the gene encoding N-acetylneuraminase lyase.

However, it is necessary to expand technologically the search method (BLAST-based analysis) to a large-scale phylogenetic analysis. Additional challenge is imposed as multiplicity of bacterial participation in the gene transfer can be supposed. As the genome sequencing of a broad range of eukaryotes is under way, we can hope some breakthrough in the near future.

One thing that we can be sure about is that, since the eukaryotes have evolved into multicellular organisms, the events of gene transfer have become rare exceptions.