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Commentary
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Can Alzheimer's Disease Shed Light on the DNA as ''Data'' versus DNA as a ''Program'' Paradigm?

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Commentary

For 100 years it was established that Alzheimer's disease can occur early (before 50) and late (after 65), but only in the 1970 the genetic makeup has been established for this disease [1]. Scientists pinpointed the cause of AD on two chromosomes, chromosome 21 and 14, finding that genes for APP and Presenilin are connected to how the amyloid was processed (the famous amyloid that Dr Alzheimer reported to be seen in the brain of the first patient, Auguste D). These findings and the notion that aneuploidy of chromosome 21 in Down syndrome leads to early AD suggested that etiological factor was found, even though that only 3% to 5% of all AD patients have mutations in these genes. AD cases of 95% are labeled as Sporadic AD (SAD) [1]. The genome project and later new technologies that utilize genetic screening and analysis opened a field of investigation to find the ''other'' risk genes that are in the base of SAD. This paradigm was and has been led by the viewpoint that DNA is a program. This view was established through the workings of Dr Ernst Mayer, 1961 [2] as still pursued today. On the other hand Henry Atlan, 2011 suggested that DNA is a data center and the program is utilized from what he called the ''complexity'' of a cell [3].

GWAS: The DNA Black Whole?

So, let's look at the question of GWAS studies in AD concerning the X chromosome and the gene PCDHX11. Using GWAS, researchers found that after analyzing more than 2000 subjects [4] five SNIPs emerged as risk factors for AD in women. The gene was PCDHX, protocadherin X, found on the X chromosome that regulates cadherin like neuronal receptors (these receptors are also related to presenilin dependent processes) in the brain of women and men [4,5]. Interestingly, subsequent studies haven't been able to confirm these results [6-8]. One reason maybe that the X chromosome is more prone to instability than other chromosomes, such X chromosome skewing [9], premature centromere instability or replicative asynchronization [10,11].

So, how can we explain these discrepancies in the results of different GWAS studies?

First of all, we must detour from the dogma that the genes, DNA and proteins are a GENETIC program, which then furnishes a non vitalist paradigm that DNA directs the development of an organisms [3]. To Mayer everything is organized mechanistically that is, everything is already determined and the ''purpose'' has only a form of ''appearance'' or the goal is not intentional, and by him everything is genetic. But, the genetic project of sequencing human DNA genome gave us insights in which we could not find a source code of genetic program [3]. This way we can see that some of our genetic ''delusions or dogmas'' that ''everything is genetic'' pervade in the mainstream thinking of genetic processes in science of today.

The first dogma: one gene is equivalent to one protein

The second dogma: that amino acid sequence determines the 3D form of a protein

The third dogma: there is confusion between coding and programming; this determines a unidirectional flow of information of DNA to RNA and proteins.

All these ''dogmas'' can be opposed by schematic representation of the epigenetic phenomena, i.e. there are loops, some proteins determine the state of activity of the DNA (not its structure) This means one should consider to include networks of proteins and not only one protein [3].

Moreover in the last analysis, pieces of DNA should not be called a gene. If one does so, then we are obliged to recognize that what we call genetics is not in the genes. Or inversely, one is obliged

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to consider a gene to be, at minimum, an ensemble of DNA together with proteins that are capable of performing certain activity. Richard Lewontin, 1992 [12] presented a notion that DNA is one of the most inert molecules one can imagine:

DNA by itself is a dead molecule, one of the most chemically inert molecules in the world. DNA has no power to reproduce itself. Rather it is produced out of elementary materials by a complex cell machinery of proteins. While it is said that DNA produces proteins, in fact proteins and enzymes produce DNA. The newly manufactured DNA is certainly a copy of the old…. But we do not describe the Kodak factory as a place of self-production of photographs. Not only DNA is incapable of making copies of itself, but it is incapable of making anything else [12]. Any activity demands the presence of active molecules, at minimum proteins, and RNA in conjunction with DNA.

To conclude: ''If DNA is a program: then the biochemical networks of cellular metabolism will interpret the program'' (an interpreter is always needed to read and execute a program). On the contrary if DNA is ''data'' then the cellular network machinery will play a role of a program, since the data must be treated by a program.

The cellular machinery ''as a distribute program'' or the cell is considered to be a ''state machine'' with has its principle properties:

1. The state of a cell is the set of concentration of its constituents inside its micro compartments

2. A network of biochemical reactions and transports moves the state of a cell from a state to another, over time

3. Protein activity –depend on the 3D structure –is at once a determinant and an effect of the state of the cell

4. Memory is coded not only in static structures, but in dynamic states, normal and pathological, which are transmitted in cell division

Also, between proteins and their functions one might have to include networks in which functions are not the result of a single protein but of interactions of multiple proteins [13].

Both of these processes, program *versus* data, show that, GWAS studies should be looked at a different angle, not related to the view of a ''program'' and to genes as risk factors, but look for genes to be more widely influenced by a number of networks that are ''programs'' that may now utilize these ''data'' centers (genes). An example is the calcineurin pathway, i.e. calcineurin connects A β and tau and using GWAS data sets should be probed for additional variants in the pathway [14].

This means that GWAS data should be re-analyzed for all variants of all known genes of given pathway, i.e. like the calcineurin pathway. Using the pathway or ''data'' approach which rests on the notion of interaction, researchers can come up with new contributions of genes in an additive manner that present risk to subjects for diseases, such as AD.

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