J Hum Growth Dev. 2016; 26(1): 28-32
ORIGINAL RESEARCH

The evolution of genetics to genomics

Alan T. Branco[1]

DOI: http://dx.doi.org/10.7322/jhgd.113710

Abstract

Development of civilizations and the technology of Development improvement of crop and animals have been under human control for more than 10.000 years. Despite the term Genetics started being employed a few centuries ago, its practice is ancient and responsible for thriving of the human society to the point we see now. The recent advances in this field started with the theories of evolution, mathematical models to predict traits, and studies at cellular level. The explosion of knowledge on the last few decades associated with the advancing of internet and computers led to advent of a new discipline in genetics: genomics. Here is discussed the transition from genetics to genomics and some of the main factors that were responsible for this progress. Nowadays genomics is part of most of life science studies and the outcomes are leading to outstanding discoveries on how the genome is precisely concerted; the findings have been crucial to understand human illness and for development of personalized and more precise medical treatment.

Keywords: development. mathematical models, Genetics, Genomics.

INTRODUCTION

If we look into ourselves and pay close attention to the microscopic details of the blocks that make a living body, we will soon realize how magic life is. A great example of this magic, or miracle, is conception and development of a zygote to a baby. It begins with 2 cells that fuse to become the primordial unit. This new cell, which is microscopic, will multiply and organize perfectly all distinct tissues to generate a full grown individual with organs and systems as complex as brain and immune system. This one will soon be able to make movements more and more precise, learn and accumulate information, and, having that, generate more advanced knowledge and goods to empower the advance of the civilization as we see.

On the other hand, when we look at the laws of the universe we will see that all organisms, even the simplest one, have a high level of organization and, according to the 2nd law of thermodynamic, everything in the universe tends towards simplicity and even simple molecules are fated to become simpler until they reach stability. But living organisms oppose to what is dictated by the universe; it starts with autotrophic organisms building long-chain carbon molecules from CO_2, which will be the energetic source for animals and other organisms to make other kinds of matters, such bones and muscles. However, if we take "life" away from those, they will follow the laws that concert the universe, decay and disappear in dust. Therefore, the citation in the bible says "then the dust will return to the earth as it was" (Ecclesiastes 12:7) is a maxima in life, on which life is cycled: autotrophs use simple molecules from soil and air to build more complex and nutritive structures, other organisms use that to grow and reproduce, and after death, following the thermodynamic law, they will be reduced to the simplest molecule, which, again, will be the source for a new life cycle.

All these phenomena have been matter of wonder since the beginning of civilizations. The question "who are we?", "where do we come from?" have been asked for millenniums in different population that evolved independently around the globe. It is interesting that even lack of contact among civilizations led to similar ways to see life after death and worship gods. Furthermore, the eager for these answers is so relevant for human self-awareness that recent research has suggested that ceremonial temples came before formation of societies and, indeed, were determinants for establishment of civilizations Inomata *et al.*[1]. Even now origin of life is still a matter of questioning and an extremely complex subject to discuss in a few pages; however, the mechanisms that control all the processes that involve evolution of species, genetic heritage, and the molecular mechanisms that control these phenomena are con-

1 Harvard T. H. Chan School of Public Health. Department of Environmental Health Molecular and Integrative Physiology Program.
Corresponding author: Alan T. Branco - Email: alantb_cederj@hotmail.com
Suggested citation: Branco AT. The evolution of genetics to genomics. *J Hum Growth Dev. 26(1): 28-32. Doi: http://dx.doi.org/10.7322/jhgd.113710*
Manuscript submitted: Oct 30 2015, accepted for publication Feb 18 2016.

siderably well understood, and this will be the subject of this discussion.

Evolution comes from the Latin word *evolutio*, which means unrolling, and this word has been widely used to describe distinct human activities. In biology, the first time the word evolution was used to define development traces back to 1774, when the botanist and physiologist Albrecht von Haller mentioned the growth of a child within uterus. The use of this term to express development was further solidified by Charles Bonnet, which reinforced the idea that all organisms are preformed within eggs, and they distend until reach the form of an adult. The meaning of evolution as individual growth prevailed until the publication of the Charles Darwin's book "On the Origin of Species" on which, for the first time, he used evolution to describe the transformation of features in a global aspect of species: "*There is grandeur in this view of life, with its several powers, having been originally breathed into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being,* ***evolved***" Darwin[2].

Even though the theory of genetics was obscure at that time, in fact it had been applied in the field for millenniums and this practice was the foundation of civilizations. Accordingly, for more than 10 thousand years farmers have bred crops and animals with good traits aiming increasing in quality and productivity Hillman *et al*.[3]. As we can see, this was the beginning of genetics, and the methods developed for genetic improvement of crops was so successful that guaranteed thriving of civilizations in distinct parts of the planet Allard[4]. For instance, cassava and maize domestication was crucial for development of communities in the American Continent[5]. However, only a few centuries ago this scenario started being a matter of investigation. Initially Darwin suggested that organisms gradually develop new traits and start to diverge from a common ancestor to form species. His theory was compelling, but there was a gap when the fact was the transmission of these new individualities to next generation. This investigation started only on the second half of 19th century with Gregory Mendel. In his studies he evaluated several features observed in pea plants, such as color, size, and shape, and described how the inheritance of these characteristics follow mathematical models; therefore, the features in the progeny could be predicted based on the type of parental used to breed. Furthermore, Mendel observed that, following the same mathematical model, some traits not expressed by the parents could be expected in the progeny. At that time, he did not know what was responsible for that and called this factor "elementen"[6]. Based on these studies he formulated 3 laws: First, the elementens segregate during gamete formation and only one is carried by each gamete; Second, the segregation of different traits is independent; Third, some features are dominant, and, even when combined with a non-dominant trait, the individual will show the dominant feature. These 3 laws are the foundation of genetics and taught in every genetic class.

Despite the great findings, Mendel's work remained neglected for more than 20 years. By the rediscovery of his work, in 1901, the chromosome organization within the nucleus was knowledge; Theodor Boveri, leading scientist in this field, showed that the proper number of chromosomes was crucial for a proper embryonic development, and he was the first one to suggest that cancer is associated with chromosomal anomalies. These results were first associated with Mendel's discoveries by Walter Sutton in 1902. In his investigation on grasshoppers Sutton observed that chromosomes are individual entities that inside the cell form pairs. However, during meiosis these molecules segregate and, to reestablish the paired condition in a regular cell, it would be necessary the transmission of one molecule from father and another from mother. He concluded his work suggesting that this mechanism may be the nature of the Mendelian law of heredity[7].

Many persuasive evidences were on the table, but there is no concrete prove that connects heredity to a specific molecule in the cell. The answer came a few decades later with more refined biochemical studies conducted by the bacteriologist Frederick Griffith and, later on, by the medical researcher Oswald Avery. Griffith showed that incubation of a colony of bacteria with a bacterial extract from another strain, which is a mixture of DNA, RNA, and proteins, was able to change traits in the live ones. This phenomenon was called transformation[8]. However, it was left to Avery, 1944, to finally prove that the DNA was the molecule responsible to transfer the hereditary traits. Avery used the same approach developed by Griffith, but, instead of using a full bacterial extract, he used specific enzymes to degrade protein, DNA, or RNA. Using these treated extracts to transform live bacteria he observed that when bacterial lysates were depleted of DNA it became ineffective. This discovery was further confirmed by Alfred Hershey and Martha Chase when they showed that bacteriophages inject their DNA into host cells, and from the intracellular DNA new bacteriophages were formed[9]. After these elegant experiments the DNA was finally settle as the molecule of heredity. Of course, nowadays we know there are other ways to transfer genetic information, but certainly it was a breakthrough in genetics. In 1953 Watson and Crick uncover the double-helix DNA structure[10], and their model was compatible with the mechanism of DNA replication proposed by Matthew Meselson and Franklin Stahl[11].

In the following decades the scenario of genetics at molecular level advanced rapidly. This was mostly due to studies with virus and bacteria. As examples, 1969 the team led by the microbiologist and geneticist Jonathan Beckwith isolated a gene for the first time[12]; new enzymes isolated from bacteria allowed to manipulate chromosome structures to build chimeric DNA molecules; an enzyme from virus able to convert RNA to DNA was isolated proving that RNA can also transfer information through generations[14-15]; and advances on the knowledge of the DNA polymerase led to development of techniques to replicate *in vitro* segments of chromosomes[16-18]. With this new wave of knowledge and the diversity of enzymes to use as tools to manipulate DNA the method to sequence DNA was developed. Frederick Sanger and colleagues made use of the ability of the DNA polymerases to extend DNA strands to create an approach in which the enzyme stops randomly along the DNA molecule, and, thus, the sequence of the DNA could be "read" by the researcher[19]. As proof of concept, his team sequenced the genome of a bacteriophage Sanger *et al*.[20]. It was a very

small genome, but it was a milestone for the Genomics, a very recent field in Genetics that studies the genome as a whole in the deepest level of details.

The steadily advance of more sophisticate methods in molecular biology and creation of machines to automate laborious processes led the Genomics to grow as one of the main fields in Biology. The outstanding progress and the eager to understand the human body called the interest of many scientists to decipher the human genome. This discussion started in the middle of the 1980s, and, despite many scientists had considered the idea a waste of money and not informative, there were many of them believing that this accomplishment would be exceptionally promising for medicine and pharmacology, and, therefore, favorable to launch the ambitious Human Genome Project. This wave occurred in many countries around the world, and, in the United States, the government-funded Human Genome Project was launched in 1990. Initial estimative was a cost of $3 billion and 15 years of research. However, the cost was a little lower and the first draft of the human genome was announced in 2001[21], and the complete human genome was announced in 2003, 2 years before the expected[22]. This achievement involved the collaboration among several universities and institutes located in different countries, but the success of this ambitious project was greatly due to the expansion of internet, development of more powerful computers, and the use of computational methods to process the incredible amount of information that genomics data generates. Nowadays, Computational Biology, or Bioinformatics, is essential for modern genetics and molecular biology.

The conclusion of the human genome revealed that we have way less genes than expected for the level of complexity of a human being. Yet, most of the DNA in our chromosomes had no apparent function. Actually, less than 5% of our genome corresponded to genes. This pattern was recapitulated on the following genome projects that aimed other organisms. In this context, the first decade of this century had a strong focus on sequencing of genomes. The idea was that the availability of this data would allow a genome-wide view of how genes interact and, therefore, pinpoint the roots of genetic diseases and any kind of individual trait that would be relevant. Accordingly, genomes from different populations around the world and individuals with different kinds of diseases were sequenced. Availability of this massive amount of data allowed for the first time the statistical studies with high power to identify correlations between human traits and punctual marks or mutations in the genome. This method was called Genome-Wide Association Studies (GWAS) and has been broadly used for this purpose[23-26]. However, as mentioned before, less than 5% of human genome corresponded to functional genes and the remaining was a “dark matter” considered garbage. Hence, looking only at the information coming from genes, supposedly to be the only functional part of the genome, led to a considerable number of inconclusive studies[25]. Later on, some works started shedding light on the dark matter, and what was before considered junk began to become as essential as the coding-protein regions of the genome[27]. For instance, several non-coding RNAs with essential regulatory functions were found along the genome[28-29], and, intriguingly, the gigantic DNA molecules that comprise the chromosomes are spatially very well organized in the nucleus, and same group of cells will display the same pattern[30]. This organization creates functional domains required for proper functioning of the genome and cell health. Accordingly, nowadays, most of the genome is functionally annotated[27].

The advances in genomics kept going at fast pace and today, 13 years after the conclusion of the Human Genome Project, companies offer this service at a cost of about $1000 and it takes only a few days for any individual to get his/her genome fully sequenced. We have a very well knowledge of the genomic features and it has been used for diagnosis, paternity and forensic tests, counseling, and prediction of diseases and application of better methods for treatment and/or to delay diseases onset. Furthermore, recently a new RNA/protein complex able to edit genomes was found in bacteria. This complex, called CRISPR/Cas system, is an adaptive mechanism developed by bacteria to avoid DNA infection, such bacteriophage and exogenous plasmids. This system was studied and adapted as a molecular tool, and today it is the most sophisticated genetic technology to make unprecedented ease and precise genetic engineering in mammal cells[31]. It is not only useful to study genes and genomes, but also extremely important for development of future strategies for genetic therapy[32]. In addition to practical applications, a whole lot regarding human evolution is known. As a curious example, genome sequencing of the ancient species Neanderthal and Denisovan[33-34], revealed that *Homo sapiens* interacted and bred with these 2 species, and the genomes of modern human being retain from 2 to 6% of DNA from archaic human species[35-36].

Altogether, it seems there is no limits for knowledge; the interest on learning about ourselves and create solutions for our problems have led us to a deep understanding of life. Here I discussed a tiny bit about the history of Genetics. However, nowadays, comprehensive studies targeting DNA, RNAs, proteins, or metabolites are trivial in science. The final goal is integrating all these studies to understand the tiniest detail of a cell. Despite the progress we have seen in all these fields, life is puzzling and the answer for several points is extremely intricate. However, the scientific community will keep tackling these points and keep pushing the frontiers of the knowledge outward.

REFERENCES

1. Inomata T, MacLellana J, Triadana D, Munsonb J, Burhama M, Aoyamac K, et al. Development of sedentary communities in the Maya lowlands: coexisting mobile groups and public ceremonies at Ceibal, Guatemala. Proc Natl Acad Sci USA. 2015;112(14):4268-73. DOI: http://dx.doi.org/10.1073/pnas.1501212112
2. Darwin CR. On the origin of species by means of natural selection, or the preservation of favoured races in the struggle for life. London: John Murray; 1859.

3. Hillman G, Hedges R, Moore A, Colledge S, Pettitt P. New evidence of Lateglacial cereal cultivation at Abu Hureyra on the Euphrates. Holocene. 2001;11(4): 383-93. DOI: http://dx.doi.org/10.1191/095968301678302823
4. Allard RW. History of plant population genetics. Annu Rev Genet. 1999;33:1-27. DOI: http://dx.doi.org/10.1146/annurev.genet.33.1.1
5. Cooke R. Prehistory of Native Americans on the Central American Land Bridge: Colonization, Dispersal, and Divergence, J Archaeological Res. 2005;13(2):129-87. DOI: http://dx.doi.org/10.1007/s10804-005-2486-4
6. Miko I. Gregor Mendel and the principles of inheritance. Nature Education. 2008;1(1):134.
7. Sutton WS. On the morphology of the chromosome group in Brachystola magna. Biol Bull. 1902;4(1):24-39.
8. Griffith F. The significance of pneumococcal types. J Hyg (Lond). 1928;27(2):113-59.
9. Hershey AD, Chase M. Independent functions of viral protein and nucleic acid in growth of bacteriophage. J Gen Physiol. 1952;36(1):39-56.
10. Watson JD, Crick FHC. A structure for deoxyribose nucleic acid. Nature. 1953;171(4356):737-8.
11. Meselson M, Stahl FW. The replication of DNA in Escherichia coli. Proc Natl Acad Sci USA. 1958;44(7): 671-82.
12. Shapiro J, Machattie L, Eron L, Ihler G, Ippen K, Beckwith J. Isolation of pure lac operon DNA. Nature. 1969;224(5221):768-74.
13. Jackson DA, Symons RH, Berg P. Biochemical method for inserting new genetic information into DNA of simian virus 40 - circular SV40 DNA molecules containing lambda phage genes and galactose operon of escherichia-coli. Proc Natl Acad Sci USA. 1972;69(10):2904-9.
14. Baltimore D. RNA-dependent DNA polymerase in virions of RNA tumour viruses. Nature. 1970; 226(5252):1209-11. DOI: http://dx.doi.org/10.1038/2261209a0
15. Temin HM, Mizutani S. RNA-dependent DNA polymerase in virions of Rous sarcoma virus. Nature. 1970;226(5252):1211-13. DOI: http://dx.doi.org/10.1038/2261211a0
16. Lehman IR, Bessman MJ, Simms ES, Kornberg A. Enzymatic synthesis of deoxyribonucleic acid. I. Preparation of substrates and partial purification of an enzyme from Escherichia coli. J Biol Chem. 1958; 233(1): 163-70.
17. Klenow H, Henningsen I. Selective elimination of the exonuclease activity of the deoxyribonucleic acid polymerase from escherichia coli b by limited proteolysis. Proc Natl Acad Sci USA. 1970;65:168-75.
18. Chien A, Edgar DB, Trela JM. Deoxyribonucleic acid polymerase from the extreme thermophile Thermus aquaticus. J Bacteriol. 1976;174:1550-7.
19. Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. Proc Natl Acad Sci USA. 1977;74(12)5463-7.
20. Sanger F, Air GM, Barrell BG, Brown NL, Coulson AR, Fiddes CA, et al. Nucleotide sequence of bacteriophage phi X174 DNA. Nature. 265(5596):687-95. DOI: http://dx.doi.org/10.1038/265687a0
21. International Human Genome Sequencing Consortium; Lander ES, Linton ML, Birren B, Nusbaum C, Zody MC, et al. Initial sequencing and analysis of the human genome. Nature. 2001;409(6822):860-921. DOI: http://dx.doi.org/10.1038/35057062
22. International Human Genome Sequencing Consortium Finishing the euchromatic sequence of the human genome. Nature. 2004;431:931-945. DOI: http://dx.doi.org/10.1038/nature03001
23. Hindorff LA, Sethupathy P, Junkins HA, Ramos EM, Mehta JP, Collins FS, et al. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. Proc Natl.Acad Sci USA. 2009;106(23):9362-7. DOI: http://dx.doi.org/10.1073/pnas.0903103106
24. Cooper GM, Shendure J. Needles in stacks of needles: finding disease-causal variants in a wealth of genomic data. Nat Rev Genet. 2011;12:628-40. DOI: http://dx.doi.org/10.1038/nrg3046
25. Maurano MT, Humbert R, Rynes E, Thurman RE, Haugen E, Wang H, et al. Systematic localization of common disease-associated variation in regulatory DNA. Science. 2012;337(6099):1190-5. DOI: http://dx.doi.org/10.1126/science.1222794
26. Hou L, Zhao H. A review of post-GWAS prioritization approaches. Front Genet. 2013;4:280. DOI: http://dx.doi.org/10.3389/fgene.2013.00280
27. The ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. Nature. 2012;489(7414):57-74. DOI: http://dx.doi.org/10.1038/nature11247
28. Lee RC, Ambros V. An extensive class of small RNAs in Caenorhabditis elegans. Science. 2001;294(5543): 862-4. DOI: http://dx.doi.org/10.1126/science.1065329
29. Rinn JL, Chang HY. Genome regulation by long noncoding RNAs. Annu Rev Biochem., 2012;81: 145-66. DOI: http://dx.doi.org/10.1146/annurev-biochem-051410-092902
30. Lieberman-Aiden E, van Berkum NL, Williams L, Imakaev M, Ragoczy T, Telling A, et al. Comprehensive mapping of long-range interactions reveals folding principles of the human genome. Science. 2009; 326(5950): 289-93. DOI: http://dx.doi.org/10.1126/science.1181369

31. Doudna JA, Charpentier E. The new frontier of genome engineering with CRISPR-Cas9. Science. 2014;346(6213). DOI: http://dx.doi.org/10.1126/science.1258096
32. Cox DB, Platt RJ, Zhang F. Therapeutic genome editing: prospects and challenges. Nat Med. 2015;21(2):121-31. DOI: http://dx.doi.org/10.1038/nm.3793
33. Meyer M, Kircher M, Gansauge MT, Li H, Racimo F, Mallick S, et al. A high-coverage genome sequence from an archaic Denisovan individual. Science. 2012; 338(6104):222-6. DOI: http://dx.doi.org/10.1126/science.1224344
34. Prüfer K, Racimo F, Patterson N, Jay F, Sankararaman S, Sawyer S, et al. The complete genome sequence of a Neanderthal from the Altai Mountains. Nature. 2014;505(7481):43-9. DOI: http://dx.doi.org/10.1038/nature12886
35. Reich D, Green RE, Kircher M, Krause J, Patterson N, Durand EY, et al. Genetic history of an archaic hominin group from Denisova Cave in Siberia. Nature. 2010;468:1053-60. DOI: http://dx.doi.org/10.1038/nature09710
36. Vattathil S, Akey JM. Small Amounts of Archaic Admixture Provide Big Insights into Human History. Cell. 2015;163(2):281-4. DOI: http://dx.doi.org/10.1016/j.cell.2015.09.042

Resumo

O desenvolvimento das civilizações e a tecnologia de melhoramento genético de culturas e animais têm sido controlados pelos seres humanos por mais de 10.000 anos. Apesar do termo “Genética” ter começado a ser utilizado há poucos séculos, a sua prática é antiga e responsável pelo progresso da sociedade humana ao ponto que vivemos atualmente. Os recentes avanços neste campo começaram com as teorias sobre evolução, desenvolvimento de modelos matemáticos para prever características de interesse e estudos a nível celular. A explosão de conhecimento na genética que tem ocorrido nas últimas décadas associada aos avanços da internet e computadores levaram ao surgimento de um novo campo dentro da genética: genômica. Neste texto são discutidos a transição da genética à genômica e alguns dos principais fatores responsáveis por este progresso. Atualmente a genômica faz parte de vários estudos que envolvem ciências da vida e os resultados obtidos estão levando a extraordinarias descobertas acerca da precisa regulação dos genomas; estes achados têm sido cruciais para entender doenças humanas e para o desenvolvimento de tratamentos médicos personalizados e mais precisos.

Palavras-chave: desenvolvimento, modelos matemáticos, genética, genomas.