Review: ***The Role of Gene-Sequencing Projects in the Study of Human Disease.***

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Introduction:

Gene sequencing is the processes of identifying the order of individual base pairs in a given piece of DNA (beyonddiscovery.org, 1996). The discovery of gene sequencing came as the unanticipated by-product of the cumulative efforts of many decades of study by biologists, chemists, mathematicians and computer scientists attempting to elucidate the structural and functional nature of DNA. With the progression of DNA characterization techniques from the initial discovery of its molecular structure, to the discovery of restriction endonucleases and bacterial cloning, to the development of chromosomal staining, the Southern Blot and positional cloning, and finally, to the advent of the PCR (Polymerase Chain Reaction) and the didoxy method and its automation by powerful computational tools, it has become possible to rapidly sequence large pieces of DNA (Alberts et. al, 2001). This ability has made possible the field of genomics— the sequencing and dissection of the entirety of the genetic make-ups of organisms, called their 'genomes'. As of today, the sequencing of the genomes of 60-100 species, including mice, yeast, fruit flies, and human beings, has been carried as far to completion as possible given current technological limitations (Peltonen and McKusick, 2001). The implications of these genomic sequencing projects to the study of human illnesses are indeed tremendous (Bork and Copley, 2001).

Explanation:

It is speculated that between 3000 and 4000 human diseases have a genetic component (beyonddiscovery.org, 1996). Most of these diseases are caused by Single Nucleotide Polymorphisms (SNPs)- mutations at single nucleotides on the concerned genes, which may range from thousands to millions of nucleotides in length. It is thus necessary to know the exact nucleotide sequence of a disease-associated gene both in its un-mutated

standard genomic state and in individuals expressing mutant phenotypes in order to determine the single nucleotide discrepancy that results in the development of the mutant (diseased) phenotype. With the roughly completed human genome at our fingertips, DNA samples can be taken from subjects at risk for mutations associated with certain familial illnesses and cross-referenced against genomic databases to determine susceptibility, a process called genetic screening (Peltonen and McKusick, 2001).

The usefulness of gene sequencing projects in the study of human diseases is not limited to human gene sequencing projects alone. Most genes linked to heritable human illnesses are basic survival genes that have been conserved throughout eukaryote evolution. That is, the human ortholog of a gene that encodes a given protein in a lesser eukaryote usually encodes an identical or very similar protein in humans (Hariharan and Haber, 2003). For example, the faulty expression of a human gene encoding a transcription mismatch repair protein called MSH2 results in a familial form of colorectal cancer called hereditary non-polyoposis colorectal cancer (HNPCC) 85-90% of the time (beyonddiscovery.org, 1996). Recent experimental data show the MSH2 gene to be highly conserved in eukaryote evolution. MSH2 homologues can be found performing essentially the same function in everything from yeast to plants such as *Arabidopsis thaliana* (Ade' et. al, 2001). This finding underscores the major benefit of using non-human gene sequencing projects in the study of human diseases: Once orthologs are identified in non-human organisms their expression pathways can be manipulated in ways that would be ethically and chronologically impossible in human studies (Peltonen and McKusick, 2001). The experimental technique of modifier screening is one such example (Hariharan and Haber, 2003). In modifier screening populations of organisms known to exhibit a mutant phenotype are irradiated or treated with chemicals to induce genetic mutations. Individuals who exhibit enhancement or suppression of the mutant phenotype are then separated and screened for telltale genetic markers, which may then provide insight into what to look for when screening the homologous pathway in humans.

The study of genomics as it relates to human illness is still in its infancy and faces many immediate technical and societal dilemmas (Peltonen and McKusick, 2001). For instance, gene sequencing projects have provided compelling resolutions to questions regarding monogenic diseases – those associated with one gene – but Quantitative Trait Locus (QTL) disorders – those associated with the expression and interaction of several genes – are much more difficult to characterize with current technologies. Other technical problems include the lack of understanding of the role of intronic non-coding regions of DNA involved in activation and regulation of genes, the inability to sequence vast portions of repetitious, theoretically gene-free regions of DNA that may be involved in genetic disease pathways (called heterochromatin) (Bork and Copley, 2001), and the need to further understand the role of environmental interaction with genes in human disease metabolism (Peltonen and McKusick, 2001). Some Societal issues include the fact that the ability of medical professionals to diagnose genetic disorders often surpasses their ability to treat them, the need for innovative therapeutic methods to help people diagnosed with genetic illnesses or high susceptibility to genetic illnesses, and the potential necessity of legally imposed protocols for companies with respect to access to their clients' or employees' genetic profiles (beyondiscovery.org, 1996).

Conclusion:

As humanity passes through the 21st century biomedical practice will be defined primarily by the further elucidation of the genetic character of ourselves and related species (Peltonen and McKusick, 2001). The focal points of genetic research will be progressively resolved and give way to new ones. The focus on structural genomics will be replaced by an emphasis on functional genomics, the study of monogenic disorders will be eclipsed by the study of multifactorial disorders, and the efforts to sequence entire genomes will lead to efforts to sequence the entire protein complements of those genomes – 'proteomics'. Ultimately, the efficiency and success of the advancement of the field of genetic characterization in

the context of human disease will depend mainly on the ability of professionals and public institutions to synergize the advancement of technology with the advancement of sensitive political and ethical and humanitarian concerns.

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