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Chapter 1 : Big Data: Precision Medicine Research in the Million-Genome Era

Exercise genomics and proteomics. It has been proposed that the exercise-induced increase in mitochon- drial content is the result of the cumulative effects of repeated but transient.

Visualization for Advanced Big Data Analysis Delivering the right therapyâ€"specifically tailored for a patient at the right timeâ€"requires that we understand how individuals differ in their disease course and response to treatment. Fortunately, we can benefit from the current flood of genomic, transcriptomic, proteomic, and epigenomic data, which offers the potential to truly understand the mechanisms of individual response at the molecular level, and turn these discoveries into therapies that can be precisely delivered to those patients who will benefit from them. We are in the million-genome era. In the past few years, we have entered the age of big genomics projects. Initiatives like the U. We already see the benefits of the previous generation of genomics projects. Major genomics projects are growing in size and scope. Since the first large-scale genomics projects were initiated a decade ago, the size and ambition of these projects has grown, with several projects now aiming to accrue over 1 million participants. Numbers Game Why is it that these projects are getting bigger? It turns out that research in precision medicine is very dependent on the number of samples. In many cases, the more individuals from whom we sequence and collect clinical data, the more opportunity there is to uncover the genetic variants and other molecular alterations linked to a host of diseases and traits. An example is in the discovery of genes associated with cancer. Efforts such as TCGA have led to the discovery of many such genes, along with the recognition that cancer is in fact over different diseases, each characterized by specific molecular alterations. The power to detect significantly mutated genes varies by cancer type, but in many cases thousands of samples are needed to detect all the genes involved. Increasing sample sizes for precision medicine research is especially relevant to minority populations, who are currently underrepresented in most research cohorts. For example, there are more than 30, African Americans in the Million Veteran Program cohort right now, and by there will be more than , This unprecedented sample size will provide a real chance to do precision medicine research to develop treatment strategies tailored to this population. Finally, increasing cohort size tackles the problem that not all genetic variants associated with disease are equally common, or equally easy to detect. As the number of sequenced genomes grows, we find that rare variants make important contributions to many diseases. Finding these variants requires large sample sizes, as well as new methods designed to analyze these large samples. By , the annual acquisition of genomic data is anticipated to exceed 2 exabytes 2 million terabytes , and storing, accessing, and analyzing these data will be nontrivial. Based on current infrastructure, most research organizations will struggle to store and manage these data, let alone optimally analyze them. These big genomics projects also gather a spectrum of other data that provides valuable information on causal mechanisms and biomarkers of health and disease. TCGA, for example, comprises not just cancer genomes, but also other data types, including RNA sequencing, proteomic, imaging, and clinical data. The current generation of million-genome studies will not just contain more genomes, but also many more dimensions of data to be stored and analyzed. The increasing volume of genomic data reshapes the way Seven Bridges does science. Over the past decade, an increasing number of sequencers have generated even more genomic data. By , the annual acquisition of genomic data is anticipated to exceed 2 exabytes 2 million terabytes and could be considerably higher. Getting the most from these data will require robust infrastructure and tools for large-scale analysis of multi-omic datasets. Portable Workflows As the size of accumulated genomic data grows, straightforward data-management tasks become increasingly time- and resource-intensive for research professionals. Data sharing, for example, scales poorly. While it is easy to share a text file listing genes of interest by email, sharing the raw data from a whole sequenced genome requires mailing hard drives, and collaborating on these data in a dynamic manner is nigh on impossible. The solution is to employ portable analysis workflows that travel to the data, an approach used in our work with the Million Veteran Program, which takes place across a network of Veterans Affairs VA sites, each with its own data repositories. A researcher within a VA research site can write a description of an analysis she wants to do using an open specification called the Common Workflow Language and submit it to

another VA research site, sending only kilobytes of data. The analysis is done using local resources, without transferring any GB files. In this way, VA researchers can rapidly analyze data across the network. A cost-effective option for many research organizations is to centralize storage, with leading biopharmaceutical companies increasingly turning to the cloud to store and analyze data. Cloud providers offer storage and computation infrastructure, which biomedical software and service providers, like Seven Bridges, build on to create streamlined genomics analysis systems to help research organizations effectively use these data. By using these resources, companies can store multidimensional omics data centrally, where they can be accessed and used by staff around the world. There is no unnecessary data duplication at local sites or infrastructural barrier to data sharing. Making Data More Useful Many research organizations fall into the trap of thinking that vast amounts of data automatically produce insight and returns. For the most efficient precision medicine research, these data are an absolute prerequisite. But there is more to it than thatâ€”researchers need to be able to actually use the data. De-siloing data is identified as a key component to drive success in the U. De-siloing also benefits biopharmaceutical companies, who hold many data assets that are not fully exploited and which are often used just once before being archived. An opportunity exists for the organizations that integrate these data into their ongoing pharmaceutical research and development. Data has great value when it is discoverable, and even greater value when it can be analyzed in the context of other data. As a simple example, researchers can use a whole genome sequence from a patient with a rare disease to find a list of potentially causal variants for further investigation. Moreover, these variants can be filtered effectively when combined with genomic data from , people without the disease. Bringing in the additional , samples can be nontrivial, both because of the size of the data involved and because of different methods of data collection among studies. A major challenge for large-scale precision medicine research is in harmonizing data from different sources. This can be overcome by standardizing nomenclature and developing sophisticated metadata descriptions that enable data integration, and by enabling portable reproducible reanalysis of datasets. Smart, Scalable, Enterprise-Ready Algorithms Maximizing returns from analysis of millions of genomes requires optimization of analytic tools designed for work with smaller datasets, and in some cases a fundamental rethinking of the approach. Delivering the most accurate and most cost-effective research in drug discovery for precision medicine requires tools specifically designed for analysis of millions of genomes. One area where new algorithms promise to help speed and accuracy in precision medicine research in millions of genomes is in the delivery of graph-based genome analysis tools. Moving to graph-based genome representations advances genetic analysis in two key ways. Second, it is a more efficient method to store and analyze vast quantities of genetic data. The volume of NGS data gathered by the massive genomics projects in progress worldwide is informing the development of new data management and analysis methods. By combining purpose-built tools for large-scale analysis of multi-omic data sets with well-annotated data and a well-designed infrastructure layer for storing, accessing, and computing on rich datasets, research organizations can unblock their data-driven projects and maximize the returns from these programs. Building a population genome graph. The genome of any individual can be represented as a path through the graph, which allows the identification of variants not captured by a linear reference, based on comparison against all the variants present in the population.

Chapter 2 : A Neurological Channelopathy in Chronic Fatigue Syndrome (ME/CFS)?

Exercise Genomics encompasses the translation of exercise genomics into preventive medicine by presenting a broad overview of the rapidly expanding research examining the role of genetics and genomics within the areas of exercise performance and health-related physical activity.

Distinct genes are expressed in different cell types, which means that even the basic set of proteins that are produced in a cell needs to be identified. In the past this phenomenon was done by RNA analysis, but it was found not to correlate with protein content. Proteomics confirms the presence of the protein and provides a direct measure of the quantity present. Post-translational modifications[edit] Not only does the translation from mRNA cause differences, but many proteins are also subjected to a wide variety of chemical modifications after translation. Phosphorylation[edit] One such modification is phosphorylation , which happens to many enzymes and structural proteins in the process of cell signaling. Because protein phosphorylation is one of the most-studied protein modifications, many "proteomic" efforts are geared to determining the set of phosphorylated proteins in a particular cell or tissue-type under particular circumstances. This alerts the scientist to the signaling pathways that may be active in that instance. Ubiquitination[edit] Ubiquitin is a small protein that can be affixed to certain protein substrates by enzymes called E3 ubiquitin ligases. Determining which proteins are poly-ubiquitinated helps understand how protein pathways are regulated. This is, therefore, an additional legitimate "proteomic" study. Similarly, once a researcher determines which substrates are ubiquitinated by each ligase, determining the set of ligases expressed in a particular cell type is helpful. Additional modifications[edit] In addition to phosphorylation and ubiquitination , proteins can be subjected to among others methylation , acetylation , glycosylation , oxidation and nitrosylation. Some proteins undergo all these modifications, often in time-dependent combinations. This illustrates the potential complexity of studying protein structure and function. Distinct proteins are made under distinct settings[edit] A cell may make different sets of proteins at different times or under different conditions, for example during development , cellular differentiation , cell cycle , or carcinogenesis. Further increasing proteome complexity, as mentioned, most proteins can undergo a wide range of post-translational modifications. Therefore, a "proteomics" study can quickly become complex, even if the topic of study is restricted. In more ambitious settings, such as when a biomarker for a specific cancer subtype is sought, the proteomics scientist might elect to study multiple blood serum samples from multiple cancer patients to minimise confounding factors and account for experimental noise. Limitations of genomics and proteomics studies[edit] Proteomics gives a different level of understanding than genomics for many reasons: Methods such as phosphoproteomics and glycoproteomics are used to study post-translational modifications. One major factor affecting reproducibility in proteomics experiments is the simultaneous elution of many more peptides than can be measured by mass spectrometers. This causes stochastic differences between experiments due to data-dependent acquisition of tryptic peptides. Although early large-scale shotgun proteomics analyses showed considerable variability between laboratories, [16] [17] presumably due in part to technical and experimental differences between labs, reproducibility has been improved in more recent mass spectrometry analysis, particularly on the protein level and using Orbitrap mass spectrometers. Generally, proteins can either be detected using antibodies immunoassays or using mass spectrometry. If a complex biological sample is analyzed, either a very specific antibody needs to be used in quantitative dot blot analysis qdb , or then biochemical separation needs to be used before the detection step as there are too many analytes in the sample to perform accurate detection and quantification. Protein detection with antibodies immunoassays [edit] Antibodies to particular proteins or to their modified forms have been used in biochemistry and cell biology studies. These are among the most common tools used by molecular biologists today. There are several specific techniques and protocols that use antibodies for protein detection. The enzyme-linked immunosorbent assay ELISA has been used for decades to detect and quantitatively measure proteins in samples. The Western blot can be used for detection and quantification of individual proteins, where in an initial step a complex protein mixture is separated using SDS-PAGE and then the protein

of interest is identified using an antibody. Modified proteins can be studied by developing an antibody specific to that modification. For example, there are antibodies that only recognize certain proteins when they are tyrosine- phosphorylated , known as phospho-specific antibodies. Also, there are antibodies specific to other modifications. These can be used to determine the set of proteins that have undergone the modification of interest. Disease detection at the molecular level is driving the emerging revolution of early diagnosis and treatment. A challenge facing the field is that protein biomarkers for early diagnosis can be present in very low abundance. The lower limit of detection with conventional immunoassay technology is the upper femtomolar range 10 M. Digital immunoassay technology has improved detection sensitivity three logs, to the attomolar range 10 M. This capability has the potential to open new advances in diagnostics and therapeutics, but such technologies have been relegated to manual procedures that are not well suited for efficient routine use. These methods offer various advantages, for instance they are often able to determine the sequence of a protein or peptide, they may have higher throughput than antibody-based and they sometimes can identify and quantify proteins for which no antibody exists. Detection methods[edit] One of the earliest method for protein analysis has been Edman degradation introduced in where a single peptide is subjected to multiple steps of chemical degradation to resolve its sequence. These methods have mostly been supplanted by technologies that offer higher throughput. These methods gave rise to the top-down and the bottom-up proteomics workflows where often additional separation is performed before analysis see below. Separation methods[edit] For the analysis of complex biological samples, a reduction of sample complexity is required. This can be performed off-line by one-dimensional or two dimensional separation. More recently, on-line methods have been developed where individual peptides in bottom-up proteomics approaches are separated using Reversed-phase chromatography and then directly ionized using ESI ; the direct coupling of separation and analysis explains the term "on-line" analysis. Hybrid technologies[edit] There are several hybrid technologies that use antibody-based purification of individual analytes and then perform mass spectrometric analysis for identification and quantification. The number of unique protein species will likely increase by between 50, and , due to RNA splicing and proteolysis events, and when post-translational modification are also considered, the total number of unique human proteins is estimated to range in the low millions. Few of these are new and others build on traditional methods. Mass spectrometry-based methods and micro arrays are the most common technologies for large-scale study of proteins. Mass spectrometry and protein profiling[edit] Main article: Mass spectrometry There are two mass spectrometry-based methods currently used for protein profiling. The more established and widespread method uses high resolution, two-dimensional electrophoresis to separate proteins from different samples in parallel, followed by selection and staining of differentially expressed proteins to be identified by mass spectrometry. Despite the advances in 2DE and its maturity, it has its limits as well. The central concern is the inability to resolve all the proteins within a sample, given their dramatic range in expression level and differing properties. Here, the proteins within a complex mixture are labeled first isotopically, and then digested to yield labeled peptides. The labeled mixtures are then combined, the peptides separated by multidimensional liquid chromatography and analyzed by tandem mass spectrometry. Isotope coded affinity tag ICAT reagents are the widely used isotope tags. In this method, the cysteine residues of proteins get covalently attached to the ICAT reagent, thereby reducing the complexity of the mixtures omitting the non-cysteine residues. Quantitative proteomics using stable isotopic tagging is an increasingly useful tool in modern development. Firstly, chemical reactions have been used to introduce tags into specific sites or proteins for the purpose of probing specific protein functionalities. The isolation of phosphorylated peptides has been achieved using isotopic labeling and selective chemistries to capture the fraction of protein among the complex mixture. Secondly, the ICAT technology was used to differentiate between partially purified or purified macromolecular complexes such as large RNA polymerase II pre-initiation complex and the proteins complexed with yeast transcription factor. Thirdly, ICAT labeling was recently combined with chromatin isolation to identify and quantify chromatin-associated proteins. Finally ICAT reagents are useful for proteomic profiling of cellular organelles and specific cellular fractions. Smith and coworkers at Pacific Northwest National Laboratory. In this approach, increased throughput and sensitivity is achieved by avoiding the need for tandem mass spectrometry, and making use of precisely determined separation time information

and highly accurate mass determinations for peptide and protein identifications. Protein chips[edit] Balancing the use of mass spectrometers in proteomics and in medicine is the use of protein micro arrays. The aim behind protein micro arrays is to print thousands of protein detecting features for the interrogation of biological samples. Antibody arrays are an example in which a host of different antibodies are arrayed to detect their respective antigens from a sample of human blood. Another approach is the arraying of multiple protein types for the study of properties like protein-DNA, protein-protein and protein-ligand interactions. Ideally, the functional proteomic arrays would contain the entire complement of the proteins of a given organism. The first version of such arrays consisted of purified proteins from yeast deposited onto glass microscopic slides. Despite the success of first chip, it was a greater challenge for protein arrays to be implemented. Proteins are inherently much more difficult to work with than DNA. They have a broad dynamic range, are less stable than DNA and their structure is difficult to preserve on glass slides, though they are essential for most assays. The global ICAT technology has striking advantages over protein chip technologies. The technology merges laser capture microdissection LCM with micro array technology, to produce reverse phase protein microarrays. In this type of microarrays, the whole collection of protein themselves are immobilized with the intent of capturing various stages of disease within an individual patient. When used with LCM, reverse phase arrays can monitor the fluctuating state of proteome among different cell population within a small area of human tissue. This is useful for profiling the status of cellular signaling molecules, among a cross section of tissue that includes both normal and cancerous cells. This approach is useful in monitoring the status of key factors in normal prostate epithelium and invasive prostate cancer tissues. LCM then dissects these tissue and protein lysates were arrayed onto nitrocellulose slides, which were probed with specific antibodies. This method can track all kinds of molecular events and can compare diseased and healthy tissues within the same patient enabling the development of treatment strategies and diagnosis. The ability to acquire proteomics snapshots of neighboring cell populations, using reverse phase microarrays in conjunction with LCM has a number of applications beyond the study of tumors. The approach can provide insights into normal physiology and pathology of all the tissues and is invaluable for characterizing developmental processes and anomalies. This relies on genome and proteome information to identify proteins associated with a disease, which computer software can then use as targets for new drugs. For example, if a certain protein is implicated in a disease, its 3D structure provides the information to design drugs to interfere with the action of the protein. A molecule that fits the active site of an enzyme, but cannot be released by the enzyme, inactivates the enzyme. This is the basis of new drug-discovery tools, which aim to find new drugs to inactivate proteins involved in disease. As genetic differences among individuals are found, researchers expect to use these techniques to develop personalized drugs that are more effective for the individual. Most proteins function via proteinâ€”protein interactions , and one goal of interaction proteomics is to identify binary protein interactions , protein complexes , and interactomes. Several methods are available to probe proteinâ€”protein interactions. While the most traditional method is yeast two-hybrid analysis , a powerful emerging method is affinity purification followed by protein mass spectrometry using tagged protein baits. Other methods include surface plasmon resonance SPR , [36] [37] protein microarrays , dual polarisation interferometry , microscale thermophoresis and experimental methods such as phage display and in silico computational methods. Knowledge of protein-protein interactions is especially useful in regard to biological networks and systems biology , for example in cell signaling cascades and gene regulatory networks GRNs, where knowledge of protein-DNA interactions is also informative. Proteome-wide analysis of protein interactions, and integration of these interaction patterns into larger biological networks , is crucial towards understanding systems-level biology. It helps identify main proteins in a particular sample, and those proteins differentially expressed in related samplesâ€”such as diseased vs. If a protein is found only in a diseased sample then it can be a useful drug target or diagnostic marker.

Chapter 3 : Treatment Online

Genomics and proteomics researchers may end up working in different labs and environments, and apply their research in different ways; a genomics researcher, for example, can identify a sequence of DNA coding for the expression of a particular protein, and a proteomics researcher can shed light on what that protein does.

A table of selected channelopathies lists 27 diseases including diabetes mellitus, dilated cardiomyopathy and cystic fibrosis. This list is hardly comprehensive; gene mutations involving sodium ion channels alone are known to cause 20 diseases Kass Ion channels are pores in the membranes through which ions travel often in great volume 1,, and ,, ions a second! The membrane potential is the difference between electrical potential inside and outside the cell. Given their role in maintaining the electric gradients in cells it is not perhaps surprising to find ion channels play a critical role in the functioning of another electrically driven system, the nervous system Cooper and Yeh Four ions are chiefly involved in ion channels. Potassium is typically found in higher concentrations inside the cell and sodium, chloride and calcium are found in higher concentrations outside the cell. Voltage gated ion channels are specialized ion channels found at the synapses that respond to neurotransmitter induced changes in membrane potential. Ion channels and muscle activity A brief overview of the role ion channels play in muscle activity will help to understand the critical role they play in the body. In skeletal muscles ion channels help transmit the signal from the nerve at the neuromuscular junction to the muscles. During the complex interplay between the nerve and muscle that accompanies muscular activity several waves of sodium, calcium, potassium and chloride influx and efflux occur Cooper and Yeh First a raft of ion channel activity involving sodium, calcium and potassium is needed for neurotransmitter release into the nerve synapse. Next calcium ions from the sarcoplasmic reticulum flood the cytoplasm of muscle cells causing muscle contraction. Finally chloride channels open in order the restore the membrane potential to its original state. Mutations in the genes coding for sodium and chloride channels cause myotonia, a disorder of impaired muscle relaxation and heightened muscle contraction. Mutated sodium channel genes cause reduced muscle excitability. Calcium channel gene mutations cause sustained muscle contractions, fever and muscle injury. Cooper and Yeh note that while the ion channel interplay accompanying muscle activity is complex both the number and complexity of ion channels and their activities in the brain far exceeds that in the muscles. The roles played by these ion channels are still poorly understood Cooper and Yeh Chaudhuri and Behan set out their case for disrupted ion channel transport in the central nervous system of CFS patients in a paper Chaudhuri and Behan In this paper they first establish that the kind of fatigue found in CFS also commonly occurs in neurological diseases and that CFS patients respond abnormally to the signaling agents â€" neurotransmitters â€" that drive nervous system functioning. Then they show how altered ion channel functioning could disrupt both the response to neurotransmitters and their production of them. Finally they demonstrate some similarities between CFS and neurological ion disorders and suggest potential causes for ion channel dysfunction in CFS. Tumors of the hypothalamus, a nexus of autonomic and endocrine activity, often first present with severe fatigue, forgetfulness and irritability. Indeed, many symptoms in CFS fatigue, sleep disorder, abnormal sweating, altered temperature, mood disorder, weight changes suggest hypothalamic involvement. This probably occurs either through altered sensitivity of the synaptic receptors â€" increased post synaptic receptivity or decreased pre-synaptic receptivity. The synapse is the empty space between the ending of a nerve and the tissue it excites. This is a key point in this paper. Changes in the sensitivity to neurotransmitters in the nerve synapses could disrupt nerve signal transmission to many parts of the body. Increased numbers of post synaptic receptors would increase the reaction to a neurotransmitter as it bridges the synaptic gap and presumably lead to an overly excitable response. Neurotransmitter receptor number is particularly sensitive to neurotransmitter levels. What roles do channels play in this system? Proper nervous system functioning requires that a complex and reciprocal interaction between ion channels and neurotransmitters take place. Snake and fish toxin often target ion channels. Their sometimes fatal effects illustrates how important ion channel activities are to nervous system functioning. For example, mutations in the genes encoding the receptor for acetylcholine, the neurotransmitter regulating neuromuscular activity, are

often associated with disrupted ion channel functioning. Some ACh mutations alter the number of ion channels, others the rate at which ion channels open and close, still others cause them to open at inappropriate times. An example of this may occur in familial migraine where impaired calcium channel function appears to be related to defective serotonin release Chaudhuri et. There is evidence of abnormal neurotransmitter activity in CFS. Response to a serotonin agonist enhancer â€" busiprone suggests hypersensitive serotonin receptors are present in CFS. CFS patients also often suffer from IBS, a problem that is possibly related to increased colonic activity due to a hypersensitive serotonin response. Norepinephrine FS patients displayed supersensitive central post-synaptic alpha-2 adrenoceptor activity in response to an AR-2 enhancer Morriss et. Increased autoantibodies against IgA muscarinic receptors could indicate reduced IgA muscarinic receptor levels Tanka et. Fifty percent of CFS patients have antibodies to the acetylcholine muscarinic receptor Bell and Vodjani These studies appear to suggest an autoimmune disruption rather than a channelopathy. Ion channel abnormalities are often found in neurological diseases Abnormal ion channel functioning in a wide array of neurological diseases suggests channelopathies are common in these diseases. As noted earlier ion channels play a key role in nervous system functioning. Interestingly fatigue is not an uncommon side effect of a central nervous system channelopathy. Inflammatory demylinating polyneuropathies and multiple sclerosis MS are both associated with ion channel dysfunction. A potassium channel dysfunction is postulated to occur in multiple sclerosis MS , a disease with a similar fatigue presentation as CFS. Antibodies to voltage gated calcium channels occur in neuromyotonia, another fatiguing neurological disease as well as ALS. Interestingly a familial genetic migraine involving a calcium channelopathy is often precipitated by the same stressors stress, exercise, viral infection that exacerbate or appear to initiate CFS. They occur when overly excitable muscle membranes respond to a single nerve impulse with multiple contractions. Graves and Hanna state myotonias should be considered in anyone who complains of muscle stiffness. Although these diseases are genetically based the symptoms they evoke sometimes do not occur until maturity. A sodium channel dysfunction in paradoxical myotonia results in muscle stiffness that increases during exercise and can be precipitated by low temperatures. A recent study found increased oxygen use by the muscles in CFS. A symptom complex called malignant hypothermia-like is used to describe patients who do not have the genetic mutations found in classical MH but who evidence calcium channel dysregulation and a similar symptom presentation. These patients may have an adverse reaction to anesthesia; MH is the most common cause of anesthesia related death Graves and Hanna CFS patients share several features with MH including weakness, muscle stiffness, sympathetic hyperactivity, tachycardia, hemodynamic instability orthostatic intolerance , exercise as a stressor and possibly a poor reaction to anesthestics. The two most common neurological disorders, epilepsy and migraine, are believed to derive from abnormal electrochemical activities in the cortex and brainstem that result in altered neurotransmitter release, cerebral blood flows and ANS functioning. The typical depression in the electrical activity observed after an epileptic episode or migraine attack is believed due to increased extracellular and increased intracellular potassium and calcium levels respectively ion channel dysfunction and altered serotonin sensitivity. Speculation Based on the information in the Chaudhuri paper calcium channelopathies appear to be particularly associated with fatigue. Six of the eight neurological diseases associated with fatigue cited by the authors involve calcium channel abnormalities. The authors note a calcium channel blocker, nimodipine, is partially effective in treating myalgia in CFS Chaudhuri et. There is some evidence for increased intracellular calcium levels in CFS patients. That they did not display the increased serum potassium levels expected in a calcium channelopathy, however, cast doubt on whether the increased calcium levels were due to a channelopathy. The symptoms of CFS patients display some similarities to those found in neurological channelopathies One of the symptoms CFS has in common with ion channel disorders is its fluctuating nature. All known channelopathies of the excitable tissues result in episodic episodes of fatigue. As in CFS some cause symptoms that indicate both peripheral and central disruption. My experience is that it is no more episodic than would probably be expected in a chronic disorder; that is, there are better or worse days but few days with truly dramatic shifts in well-being. CFS patients share with epileptics a predisposition to several autonomic related symptoms such as frequent near syncope fainting and low blood pressure, particularly during TILT table testing. Since the hypothalamus is involved in autonomic

regulation a channelopathy there could conceivably cause symptoms of orthostatic intolerance. CFS patients share with migraine sufferers such symptoms as headache, confusion, increased sensitivity to lights, sounds and smells as well as exacerbated responses to serotonin. Symptom exacerbation during menstruation and muscle pain, disequilibrium and unusual sweating are often seen in both diseases. White brain matter abnormalities and reduced cerebral blood flows are also seen in both diseases and stress, alcohol and caffeine can exacerbate symptoms in both diseases. Transient or chronic fatigue is also common in migraine. Indeed fatigue is a common symptom of a new anti-epileptic drug, dezinamide, targeting sodium channels. Chaudhuri and Behan believe a potassium channelopathy is mostly likely to occur in CFS. Several viruses, including HIV and the picornaviruses are able to alter ion channel flow. Herpesviruses have also been linked, interestingly enough given their history in CFS, to altered ion channel functioning. Ciguatoxin, a neuronal sodium channel disruptor, produces many symptoms, including fatigue, similar to those that occur in CFS. Studies indicate a substantial number of CFS patients have extremely high levels of the ciguatera epitope. Toxic insults from organophosphates, lead, insecticides, pesticides can also alter ion channel activity. Toxins can be key ion channels disrupters because they often attack the membrane surrounding the cell. Some toxins can even create new channels that cause severe ionic imbalances through the leakage of ions out of the cell. Other toxins block ion channel activity by binding to them while others e. Venomous substances produced by scorpions, sea anemones, puffer fish and many other species often target sodium ion channels. Because sodium channel activity is involved in determining the action potential in the first phase of neurotransmitter activity they play a key role in regulating neuronal excitability. Bacterial neurotoxins also often wreak havoc on ion channel activity. Many ion channel binding sites in the nervous system were elucidated using bacterial neurotoxins. Testing the hypothesis The authors recommend three preliminary efforts to establish ion channel dysfunction in CFS patch clamping, a search for humoral antibodies to ion channels, toxin binding studies. Patch clamping, the most valuable method of studying ion channel activity, is an amazing process. In the patch clamp researchers place an extremely small glass or quartz pipet against a cell membrane. By blowing or sucking on it either manually! Ciguatoxin Greatly increased levels of the ciguatoxin epitope, a marker of altered sodium channel activity, in most CFS patients provide the best evidence yet a sodium channelopathy occurs in CFS. Whether these findings reflect a chronic disease process or something more specific to CFS is unclear but research, thankfully, is underway to elucidate the intersection between CFS and ciguatera Pearn , Hokama et. Reports from the AACFS conference indicate, however, that RNase L fragmentation affects the ability of the multi-drug resistant transporter to remove toxins from the cell. Gene microarray studies Perhaps most intriguing of all a recent study found that genes involved in ion channel functioning were among those most prominently altered between CFS patients and controls both prior to and after exercise Whistler et.

Chapter 4 : Suresh C Sikka, PhD | medicine

Which type of genomics studies similarities and differences among the genomes of multiple organisms? Home > Chapter 15 > Self-Quiz.

Their revolutionary insight led to the elucidation of the so-called genetic code, which underpins the central dogma of molecular biology: Subsequently, exploitation of tools from physics and chemistry enabled spectacular advances in genetics, leading to the molecular biology revolution in the late s to early s, and ushered in the era of DNA cloning with its powerful new tools to study biology. The Human Genome Project HGP with its many spin-offs, such as the SNP Consortium, 1 the HapMap Project, 2 and the Protein Structure Initiative , 3 aims to provide a complete working knowledge of the human genome and, in the longer term, proteomics, which together will provide information and the tools necessary for advancing our understanding of human health and disease. Most recently, the advent of new technologies permitting the simultaneous study of many thousands of genes, messenger RNAs, single nucleotide polymorphisms SNPs , proteins, or the products of genes in parallel is producing a flood of information and claims about the role of genes in human disease and behavior. This new knowledge is revolutionizing the field of medical diagnostics and could yield a powerful arsenal of therapies that offer the promise of cures instead of just amelioration of symptoms. Precisely because of this potential, the rise of genomics and proteomics has generated numerous policy battles, of which disputes about intellectual property are but one. This chapter provides background information on the science of genomics and proteomics and their impact on the changing paradigm in genetic or personalized medicine and briefly describes some of the policy debates that have ensued regarding openness and access to genomic and proteomic data as they have affected the conduct of science. Chapter 3 focuses more specifically on intellectual property issues affecting these fields as they have entered the U. Knowledge of the order of the four basesâ€”adenine, guanine, cytosine, and thymine A, G, C, and T â€”within each DNA strand, or sequence, of an organism provides full knowledge of all the genetic information passed from one generation to the next. According to Crick, he and Watson speculated about determining the full sequence of human DNA early on but discarded the idea as one that would not reach fruition for centuries Crick, Astounding progress over the ensuing three decades in the discipline now known as molecular genetics, however, proved their pessimistic estimates incorrect. A DNA fragment from any organism can be inserted or cloned into the bacterium E. In , the Nobel laureate chemist Frederick Sanger developed efficient methods for using these amplified samples of genetic fragments to determine the sequence of the DNA bases and published the entire sequence of some small viral genomes Sanger et al. By the mids, much of the molecular genetics research community was engaged in isolating and sequencing from particular organisms DNA for individual genes of interest. Open, facile access to this relatively limited amount of DNA sequence information became an important priority for molecular biologists and molecular geneticists alike. As a result, in GenBank was established as a nucleic acid sequence database at the Los Alamos National Laboratory and was funded by the National Institute of General Medical Sciences three years later. The GenBank database is designed to provide and encourage access to the most up-to-date and comprehensive DNA sequence information to members of the scientific community. Because protein primary structures now are determined mostly by complementary DNA cDNA sequence analysis, links between the nucleotide and protein sequence databases are common. However, some submitters may claim patent, copyright, or other intellectual property rights in all or a portion of the data they have submitted. There were 37,,, bases in 32,, sequence records as of February Sinsheimer of the University of California, Santa Cruz, formally proposed in the possibility of a concerted effort to sequence the human genome. In , Renato Dulbecco, a Nobel laureate and a member of the Salk Institute, made in the pages of Science magazine a similar proposal to provide the underpinning for the study of cancer Dulbecco, Influential and widely circulated reports by the U. The NRC report recommended that the U. Instead, the program sought to build infrastructure through a variety of projects. These efforts included the exploration of alternative sequencing technologies, the adaptation of existing technologies to the simpler problem of sequencing smaller genomes of laboratory organisms, and the development of low-resolution maps of the

human genome. Other countriesâ€”in particular Britain, France, and Japanâ€”also initiated the HGP, and indeed several early successes came from outside the United States. Despite broad governmental support, the HGP generated considerable controversy in the scientific community. The shift from traditional, hypothesis-driven, small-laboratory, one-gene-, one-protein-at-a-time science to this new data-driven, large-scale engineering program initially engendered resistance in the molecular genetics community. Many felt that the project would become feasible only with the discovery of completely novel sequencing methods that would be orders of magnitude faster and cheaper than previous methods. Others, particularly Craig Venter, then an investigator at NIH, argued that for the human genomeâ€”when much of the sequence was thought to be without function so-called junk DNA â€”a much more efficient strategy would be to sequence only the protein-coding genes through cDNAs, thereby reducing the amount of required sequence by a factor of 10 or more. Despite conservative expectations, rapid progress was made on many fronts. A framework human genetic map soon emerged, with far greater resolution than initially anticipated. Circular DNA molecules, or vectors, were devised for carrying ever-larger amounts of DNA into bacteria, thereby facilitating construction of physical maps of whole genomes. Adaptation of conventional DNA sequencing approaches to highly automated machines yielded a dramatic expansion in global DNA sequencing capacity that produced in rapid succession the sequence of the first bacterial genome H. Given the pragmatic nature of most scientists, it came as no surprise that the enormous utility of these whole genome sequences across the biological scientific enterprise quickly overcame the objections of remaining skeptics. Novel sequencing methods were not required; instead, the basic Sanger method was almost completely transformed by new machinesâ€”developed, for example, by Lloyd Smith, Leroy Hood, and Michael Hunkapiller at the California Institute of Technologyâ€”and software by others, such as Phil Green, to deal with the data. The early enthusiasm for sequencing cDNAs or their cousins, expressed sequence tags ESTs , waned as this information proved to be no substitute for the full genome sequence. However, once a full genome sequence was obtained, both cDNA and EST information proved highly useful in finding genes. EST and cDNA sequencing also provided a rapid means of identifying and characterizing some medically significant genes, opening a path to early intellectual property claims. Venter pursued EST sequencing vigorously, and two companies, Incyte and Human Genome Sciences, devoted extensive resources to capturing these sequences and obtaining patent rights to them see Chapter 3. Based on this initial flurry of success, the international HGP began the systematic sequencing of the human genome in on a pilot scale and in initiated a full-scale effort. Because many investigators wanted to participate in such a historic project, the pilot phase included laboratories throughout the world. The pilot phase was intended to evaluate the cost and quality of the product, select among the variations in sequencing strategies that were still in play, and determine whether performance and economies of scale warranted reducing the number of participants. Funded participants met in early to coordinate their efforts. In a subsequent meeting, the group also considered a proposal to switch from a clone-based strategy to a whole-genome shotgun, or fragment-based, approach. The potential value of rapid access to large parts of the genome and therefore genes was not disputed, but the proponents could not describe a path from the shotgun data to a high-quality complete sequence. The challenges of assembling sequences of individual DNA fragments and in turn assigning all the pieces to specific chromosomal locations in the correct order and orientation were additional concerns. After vigorous debate, the switch in strategy was rejected. The birth of the modern biotechnology industry can be traced to the early s, with the discovery of genetic engineering techniques, such as recombinant DNA methods and hybridoma production. These discoveries were more As the pilot phase drew to a close, the successful groups coalesced around a common strategy and methodology, and a few groups emerged as leaders. Economies of scale also were evident. Most importantly, the pilot phase demonstrated that the strategy was capable of producing high-quality sequences in large contiguous blocks at acceptable costs and that costs were continuing to fall. Funding agencies in the United States and the United Kingdom elected to proceed with a full-scale effort, limiting resource allocations to only a small number of highly successful research teams. ABI surprised the genomics community with their announcement of a joint venture to sequence the human genome using a whole-genome shotgun approach, in direct competition with the international effort. Unlike the public project, their data were to be held by a

company Celera, Inc. Patents would be sought for genes of interest. The scientists leading both the public and private ventures had strong motives to pursue their own courses, and they justified their plans to their funders. A race was on. On June 26, , the public and private groups announced jointly at a White House-sponsored event that each had succeeded in producing an initial draft of the human sequence, with simultaneous publications describing their findings appearing in Lander et al. The international HGP published a full and significantly more accurate human genome sequence in Genome sequences from species across the evolutionary tree continue to flood the databases today. The development of genetic and physical maps and the ongoing release of the human sequence over the past 15 years have greatly increased the number of genetic diseases for which the causative defective, or mutant, gene has been identified. Today the genetic bases for all the major Mendelian single gene diseases are known. Just 15 years ago, only a handful of such genes were known, and the cloning of a gene responsible for human genetic disease became front-page news. Such molecular insights into disease are leading to new strategies for diagnosis and therapy. Definitive diagnoses can be made directly on the defective genes themselves, without the ambiguities of previous indirect phenotypic measures. DNA testing also can be carried out prospectively, permitting action to be taken before overt symptoms develop, an important advantage in genes that predispose individuals to cancer, for example. Tests can even be conducted prenatally, as early as the pre-implantation stage of development, or even in vitro, allowing prospective parents a choiceâ€”a significant benefit in cases of devastating childhood genetic diseases such as Tay-Sachs, sickle cell anemia, or cystic fibrosis. Exploiting molecular insights with which to craft alternative therapies has proven to be more challenging than developing new diagnostic tools, but important progress is being made. To date, success has been limited to a small number of relatively special cases. More encouraging, however, is the growing realization that our knowledge of the precise molecular nature of the genetic defect or mutation can lead to specific therapies that block the consequences of the mutation indirectly. Alternative treatment strategies are aimed at trying to restore protein functions that have been lost as a consequence of mutations. For example, drugs that directly influence the functioning of mutant forms of the cystic fibrosis transmembrane conductance regulator protein are now going into clinical trials with the hope that they will be able to restore sufficient function to alleviate the devastating symptoms of cystic fibrosis. We know, however, that human genetic variation is at the root of many more diseases than these relatively rare single gene disorders. Detailed comparisons of human DNA sequences have demonstrated that two copies of the human genome differ by about 1 base in every 1, In all, there are approximately 3 billion bases in the human genome, which means that the DNA sequences of any two individuals differ at more than 2,, base positions along the DNA double helix. Among such differences are those that underlie heritable variation among individuals for an enormous number of traits, such as eye and skin color. In addition, combinations of particular genetic variations within populations give rise to genetically complicated or multifactorial diseases e. Medical geneticists are just now beginning to use comparative human genome sequencing to understand the extent of genetic variation and to describe the common variants shared across populations. Indeed, understanding how genetic variation leads to individual human variation is one of the great scientific challenges of the twenty-first century. The path forward will inevitably involve an increasingly broad survey of genetic variation across the genome in larger and larger groups of individuals. Correlation of genetic and phenotypic differences will establish causal relationships, ultimately revealing the identities of the multitude of genes that contribute to particular traits. Methods for assaying genetic variation are changing rapidly, with various revolutionary approaches nearing commercial testing. As these cutting-edge technologies are introduced and an increasing number of causal relationships are known, the field of diagnostics will move from its current focus on single genes to a search of all the genes responsible for a particular disease. This knowledge will be critical to realizing the goals of personalized medicine, among other potential benefits, in which drugs are targeted to small groups and even individuals who are likely to benefit from the therapy and unlikely to suffer adverse reactions. For example, Genzyme has just introduced a test based on research from the Massachusetts General Hospital and the Dana-Farber Cancer Center that identifies cancer patients who are more likely to have a favorable response to cancer drugs that target the epidermal growth factor receptor. The scientific community will need freedom to operate to realize these achievements, but concerns exist about the

multitude of existing patents on genes and fragments of the human genomeâ€”with the prospect of even moreâ€”that could impede or even block progress. Early-stage applications are likely to be affected more severely. The success of the initial phase of the HGP and the attendant availability of the human genome sequence and the genomes of numerous other organisms have transformed the study of biology. Most obviously, the full catalog of genes from each genome opens up new avenues of study. No longer does an investigator need to confine his or her inquiries to a single gene or a small set of genes; instead, the behavior of an ensemble of genes can be investigated simultaneously. At the level of science policy, the genome projects have served to validate data-driven or discovery-based approaches as legitimate intellectual competitors of more traditional hypothesis-driven research programs. This constellation of attributesâ€”comprehensiveness, data-driven character, and large scaleâ€”distinguishes genomics from its parent science, genetics. The characteristics of comprehensiveness, scale, and intellectual attitude differentiate proteomics from more traditional ways of studying proteins in much the same way. Interactions between pairs of proteins can be evaluated, not just those of a few likely candidates. Protein identification using mass spectrometric analysis can compare the patterns obtained to what is possible in the genome and quickly identify many of the proteins in a particular mixture, rather than exhaustively characterize each constituent one at a time. In a subdiscipline of proteomics known as structural proteomics, the three-dimensional structures of proteins can be examined in systematic, data-driven projects, rather than focusing on the precise details of a single protein.

Chapter 5 : What is the Difference Between Genomics and Proteomics?

INTRODUCTION. Human genomics is the science that investigates the physical features and properties of the human genome, while human genetics is the science of inheritance, i.e., the transmission of traits across generations.

Tipton ; section editors, Michael N. Bibliographic record and links to related information available from the Library of Congress catalog. Contents data are machine generated based on pre-publication provided by the publisher. Contents may have variations from the printed book or be incomplete or contain other coding. Introduction to Exercise Physiology Chapter 1. The language of exercise Chapter 2. A historical perspective Section II: Exercise and Responses to Biological Systems Chapter 3. The central nervous system and movement Chapter 4. The skeletal and connective tissue systems Chapter 5. Skeletal muscle design Chapter 6. Design and performance relationships Chapter 7. Control of muscle mass Chapter 8. Muscle fatigue Chapter 9. The autonomic nervous system Chapter The respiratory system Chapter The oxygen transport system Chapter Design and control Chapter Cardiac function Chapter Peripheral circulation Chapter The gastrointestinal tract system Chapter Control of energy metabolism Chapter Control of carbohydrate metabolism Chapter Integration of carbohydrate and lipid metabolism. Protein turnover and amino acid metabolism. Mitochondrial biogenesis and exercise training Chapter The immune system Chapter Physiological systems and their responses with exposure to heat and cold. Physiological systems and their responses with exposure to hypoxia. Genomics in the Future of Exercise Physiology Chapter Exercise genomics and proteonomics Library of Congress Subject Headings for this publication: Exercise -- Physiological aspects.

Chapter 6 : Multiple Choice Quiz

2 Genomics, Proteomics, and the Changing Research Environment Since , when Avery, MacLeod, and McCarty published experimental evidence suggesting that DNA serves as the repository of genetic information (Avery et al.,), our understanding of the organization and biological function of DNA has increased dramatically.

Chapter 7 : Proteomics - Wikipedia

Genomics can only show you the sequence of a protein that has a potential to be expressed. The actual levels of that protein within the cell is determined by a number of factors such as transcriptional activation, transcript degradation, translati.

Chapter 8 : Proteomics data analysis course | Immunotechnology

Physiological Systems And Their Responses With Exposure To Microgravity And Bed Rest Section IV: Genomics in the Future of Exercise Physiology Chapter Exercise genomics and proteonomics Library of Congress Subject Headings for this publication.

Chapter 9 : Table of contents for ACSM's advanced exercise physiology

While genomics and proteonomics are currently emerging, exercisenomics may emerge in the future as a field where exercise scientists investigate a series of different factors at different stages in development.