GENOMIC NEUROLOGY WORKSHOP C180: DEVELOPING PRACTICAL KNOWLEDGE OF TOOLS AND CONCEPTS THROUGH CASE STUDIES I.

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Introduction:
An understanding of genomic testing is becoming critical for best practice in neurology. Such testing, often based on the state of the art genomic concepts and technology, is rapidly entering clinical care and is being used in diagnosis, as well as to guide drug therapy. A "genomically literate" neurologist understands the utility and limitations of current genomic testing and applications, is able to obtain clinically relevant information from available websites/databases and apply and explain results to patients.

There is limited education in genomics during medical school and residency training. Educational sessions often focus on didactic knowledge as opposed to practical hands-on experience dealing with patient's genomic test data. Once in practice, time is limited for further didactic training. Thus, it is our belief that understanding and utilizing the current growing list of websites containing genomic information is the most efficient approach to incorporating genomic information into a clinical practice. Otherwise, this knowledge deficit translates to limit the practicing neurologist in appropriate ordering and interpretation of genomic testing and use of genomic information to provide optimal patient care.

The first part of this educational session will provide refresher information on genetic and genomic principles. Then we will focus on testing for neurological conditions including appropriateness of testing and interpretation of results. By using a team-based learning approach (TBL), students not only learn from instructors but from each other. Team teaching by its nature encourages the student to actively participate and often lowers learning anxieties. By using a case-based approach and providing hands-on instruction in use of online genomics tools, participants will learn and apply practical information directly related to providing optimal patient care.

Pre-workshop materials

While it is not required, it is suggested that participants complete the pre-workshop materials to be able to "hit the ground running" to complete the performance-based objectives of the workshop. We utilize several websites in this class. There addresses are listed below.

1) **Clinvar** is a website designed to provide documentation about the importance of a genetic variant in contributing to a disease phenotype. It is populated by both clinical laboratories as well as literature. It has been designated as a primary website to hold documented DNA variants for clinical use.
2) **Polyphen-2** is a website where an computer algorithm predicts the amount of damage to a protein's function that occurs when changing a single amino acid in a protein's structure.
3) For those who feel they need more background, here is the full set of modules from a YouTube series. We would like to acknowledge Kiran Musunuru MD, PhD, MBA, for his excellent work creating these modules. **Module 4** is clinically relevant to our discussions, discussing the types of DNA variations and there functional effect.

Module 1- Basic Concepts and potential applications of Genetics and Genomics:
https://www.youtube.com/watch?v=gxsYk7oPX-I&feature=youtu.be

Module 2 - Basics of molecular biology: transcription and translation - http://youtu.be/3zfpd00xKLw

Module 3 - The genome and DNA variants - http://youtu.be/S3L1_wPcHi8

Recommended: Module 4 - Coding variants - http://youtu.be/q7BrTFeH9BM

Module 5 - Noncoding variants - http://youtu.be/JSGE0MM_Wrg

Module 6 - Genotyping and sequencing to determine the identity of DNA variants - http://youtu.be/I4GwreLZO6c

Module 7 - Monogenic traits and disorders: dominant, recessive, co-dominant - http://youtu.be/cIMO_BpJA5o

Module 8 - Monogenic traits and disorders: Mendel's first law - http://youtu.be/IfVvUhn2dUI

Module 9 - Monogenic traits and disorders: Mendel's second law - http://youtu.be/WkchNwcVzVw

Module 10 - Pedigrees and Mendelian transmission of disease - http://youtu.be/OV953iixs54

Module 11 - Linkage studies - http://youtu.be/hcNsaK2Zs74

Recommended: Module 12 - Next-generation sequencing studies - http://youtu.be/WTK7DnZFMZg

Module 13 - Common variants and linkage disequilibrium - http://youtu.be/G5GBlFf-950

Module 14 - Genome-wide association studies - http://youtu.be/dvFNinls_2M

Module 15 - Risk prediction in complex diseases - http://youtu.be/3syc5qSkj6w

Module 16 - Pharmacogenomics - http://youtu.be/PsxL3GWDu4c

4) We will ask the participants to try and answer several preparatory questions. These will get the participants thinking about core concepts.

Workshop Structure: Each exercise consists of three components:

1) Pre-activity lecture: This lecture will review pre-workshop materials and provide answers to the preparatory questions. In this way, we will ensure participants have the needed background to complete the exercise.
2) Team-based learning activity: Participants will work in small teams to answer clinically relevant genomics questions using online tools
3) Post-activity review: Faculty will review the answers to the activity with the larger group and answer questions

Part 1:

The patient is a 20-year-old, woman who was referred for a history of focal seizures. Seizures began in childhood, and were initially considered to be night terrors as a child. Later, physicians diagnosed panic attacks after puberty. The seizures consisted of bicycling movements of her legs of which she had no recall, and usually occurred as she began to doze off to sleep or shortly before she awoke. Sometimes she experienced auras, consisting of a feeling of shivering or falling. The seizures became less frequent as she became an adult but still occur. Previous neuro-imaging with cranial MRI was normal. Examination in your office is normal.

You suspect cryptogenic focal epilepsy, rule out known genetic focal epilepsies such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).

1. You want to use molecular testing to see if you can make a diagnosis of ADNFLE. What are some of the general concerns you may have in sequencing this patient?

2. List ways that knowing the results of ADNFLE gene testing could be helpful for this patient

Part 2:

Upon talking to her mother about her father's medical history, the patient learns that her father had undergone some sort of genetic testing as part of a research study in the 1990s. Her mother is able to find an old report from that study that documents the presence of a mutation in the gene cholinergic receptor, neuronal nicotinic, alpha polypeptide 4 (CHRNA4), specifically the S284L variant.

You refer the patient for targeted testing for the CHRNA4 variant reported in her father and find that she has the same variant, plus another variant in the CHRNA4 gene, R148W.

3. Using ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), what is the reported clinical significance of the variants and based upon what evidence?
[Search using "CHRNA4 S284L", click on the relevant link, and review the information contained in the page, including the PubMed links]. Repeat for R148W.

4. Using PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), what is the variants' predicted impact on protein function and clinical significance for the patient? [Use "CHRNA4" [all capital letters] for "Protein or SNP identifier", "284" for "Position", "S" for "AA1", and "L" for "AA2"; after hitting "Submit Query", you will need to hit "Refresh" on the following page until the job is completed]. Repeat for R148W.

Part 3:

You meet the patient to go over the test result i.e., the two CHRNA4 variants.

5. In discussing the available data with the patient and to help determine further medical care, what would you conclude is the clinical significance of the variants in this patient(benign or pathogenic) and why?

6. What could be done to further examine the clinical significance of these variants'?