Training Residents In Genomics

Innovative Approaches Working Group
Universal Team-Based Learning Activity
Exercise 3
Whole-Genome Sequencing

Objectives: By the end of the session, you will be able to:

1. Describe key aspects of informed consent for genomic analyses
2. Describe the process of NGS-data analysis
3. Describe the reporting issues related to incidental findings
4. Use online tools to interpret the clinical significance of genomic data

Team-based Learning Activity:

Case Presentation

The gene panel test that was ordered does not demonstrate a variant that can explain the patient's diagnosis of _____. The patient decides to enroll in a study, similar to the 1000 Genomes Project, that will perform whole genome analysis on a blood sample.

1. **List 3 key components in the informed-consent process for whole-exome and whole-genome sequencing studies. (REVEAL)**
   (10 minutes)

2. **You are asked to specifically review sequencing data to determine whether to call and report specific variants (see the following images; image 1 represents one variant and image 2 represents another variant).**
   (20 minutes)

The variants below are from the original exercise. We would need to find others that could be used that still illustrate the key points in a gene related to the patient's disease or we could perhaps relabel these but real data would be best.

   a. **List 3 criteria you would you use to call a variant. (REVEAL)**

   b. **List 2 criteria you would use to report a variant. (REVEAL)**

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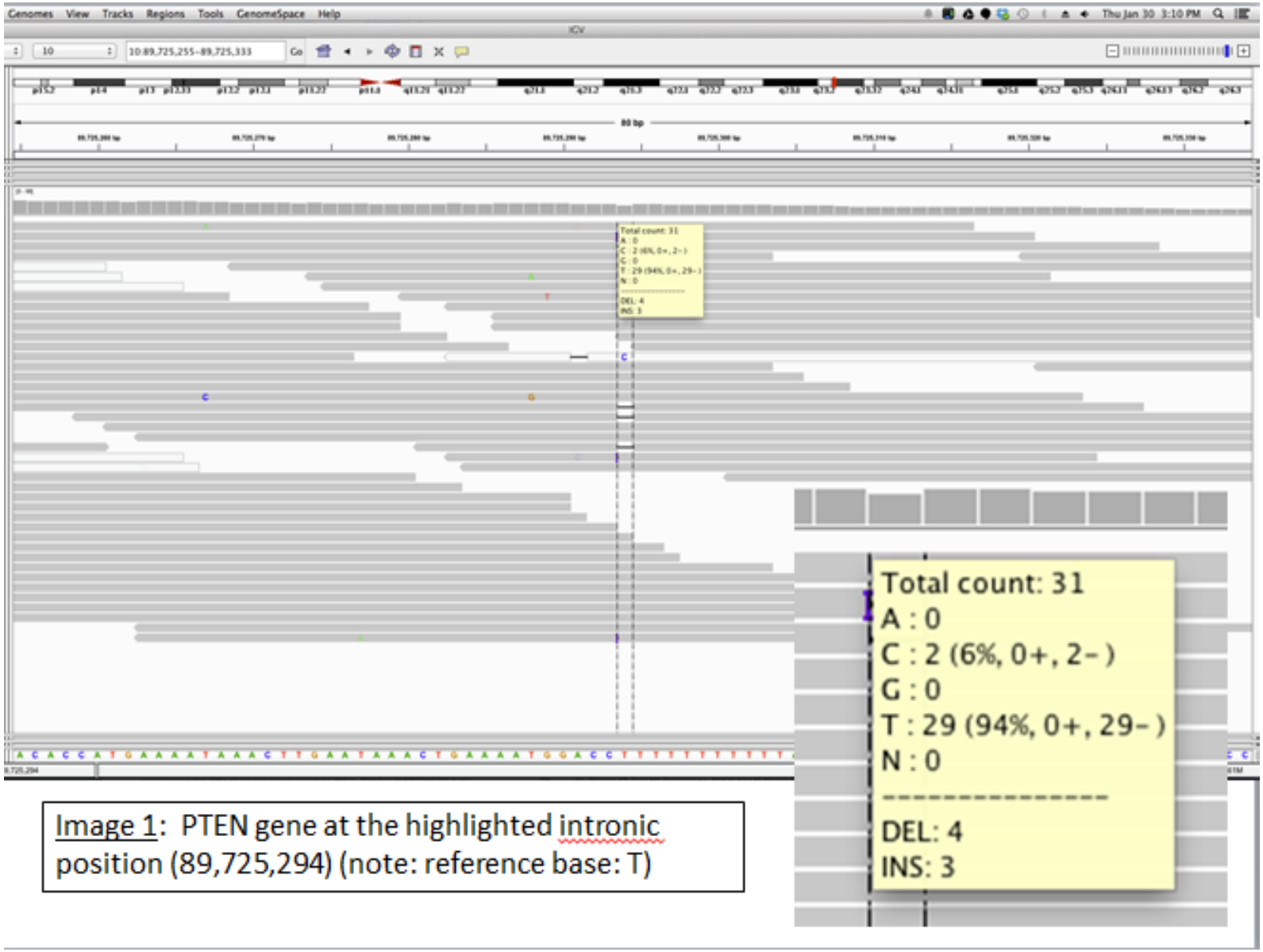

Image 1: PTEN gene at the highlighted intronic position (89,725,294) (note: reference base: T)

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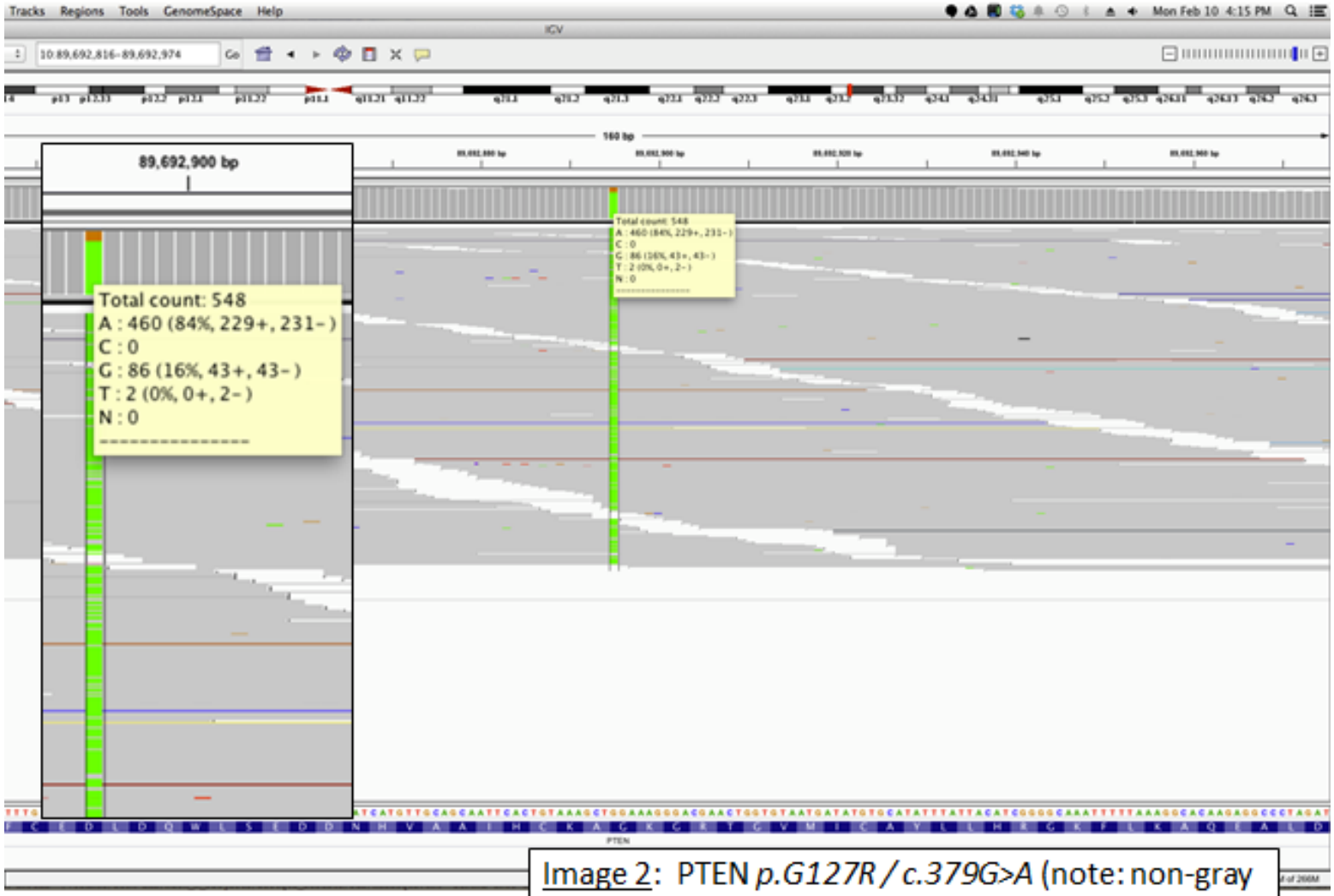

Image 2: PTEN *p.G127R / c.379G>A* (note: non-gray color indicates difference from reference; reference base: G)

c. **Is this gene listed in OMIM (http://www.ncbi.nlm.nih.gov/omim)? if yes, does it have a reported relationship to your patient's diagnosis?**

d. **Using Clinvar (http://www.ncbi.nlm.nih.gov/clinvar/)**

   1. **How many submissions are there for the image 1 and 2 variant?**

   2. **What is the reported clinical significance?**

e. **Based on the criteria you listed, for the variant in each of the 2 images: a) Would you call this variant? Explain your answer in up to 2 sentences. b) Would you report the variant? Explain your answer in up to 2 sentences. If yes, also include up to 2 sentences of sample text explaining how you would report it.**

   1. **Image 1 variant**

   2. **Image 2 variant**

3. **The following germline results are obtained:**

(Variant from exercise 1): (same as in exercise 1)
RYR1: c. 1840C>T (p.Arg614Cys)
CFTR: No variant detected

a. **Using OMIM, (http://www.ncbi.nlm.nih.gov/omim), list the disease(s) with which RYR1 is associated.** (HINT: search using "ryr1")

b. **Using ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), is the RYR1 variant clinically significant?** (HINTS: search using "1840c>t"; review any PubMed links)

Could consider another variant, malignant hyperthermia chosen as an incidental finding with specific significance for a number of specialties

c. **Which of the results should the patient know about? Explain why, in up to 2 sentences for each result. (REVEAL)**

d. The patient is known to have a *CFTR* variant. List 2 reasons why the variant may not have been detected using whole-exome sequencing. (REVEAL)

May consider another variant…this one chosen as one with significance for prenatal screening and the original patient was female