VEP course April 2019

Cases for workshop Variant classification

using the ACMG recommendations

Please use:

http://www.medschool.umaryland.edu/Genetic_Variant_Interpretation_Tool1.html/

http://wintervar.wglab.org/

http://exac.broadinstitute.org/

http://gnomad.broadinstitute.org/

And data sources from:

https://www.acmg.net/docs/Standards Guidelines for the Interpretation of Sequence Variants.p df

Optional web services:

http://umd-predictor.eu/index.php

https://loschmidt.chemi.muni.cz/predictsnp2/

http://www.umd.be/HSF3/index.html

Case 1:

Female counselee asks for genetic counseling in her 9th week of pregnancy (G2P1).

She previously had a carrier screening test from a diagnostic laboratory, that reported her to be carrier of a variant in the DMD gene (NM_004006).

Variant is:

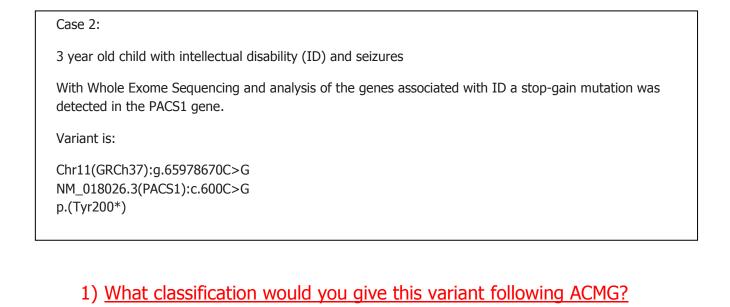
ChrX(GRCh37):g.31525569T>C c.8219A>G p.(Asp2740Gly)

1) What classification would you give this variant following ACMG?

2) Would the classification justifying prenatal testing?

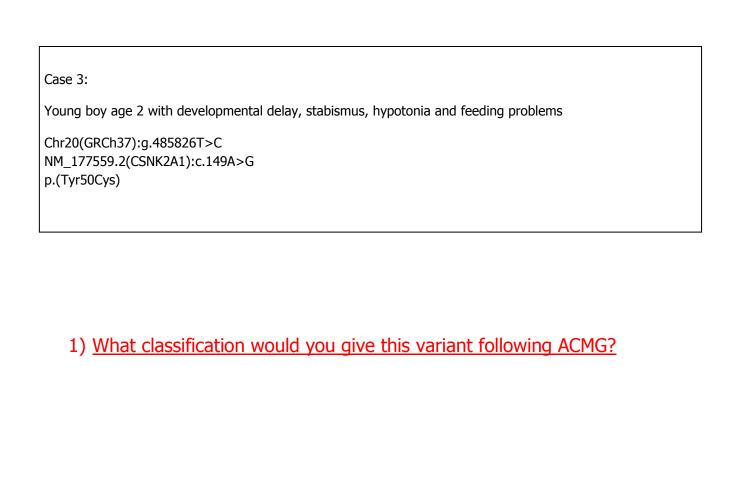
See also:

https://www.nature.com/articles/gim2017174



2) What is special about the PACS1 gene that should be taken into

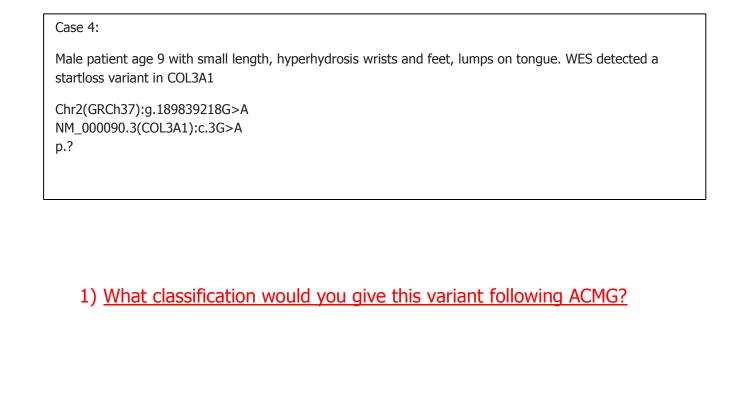
account?



2) What criteria tips the balance?

https://www.nature.com/articles/gim201842.pdf

Please also check:



2) Why is this variant likely not a LOF variant?

Case 5: Female patient age 25 with clinical phenotype that could fit with Aicardi-Goutières syndrome Sequence analysis of the IFIH1 gene detected two variants: - Chr2(GRCh37):g.163144803del; NM_022168.3(IFIH1):c.937del; p.(Met313fs) - Chr2(GRCh37):g.163130423C>A; NM_022168.3(IFIH1):c.2336G>T; p.(Arg779Leu)

1) What classification would you give both varians following ACMG?

2) Which variant(s) should be reported?

Case 6 (adapted from Andreas Laner workshop 11/17):

Female patient age 38 with breast cancer. Mother and maternal aunt were also affected with breast cancer at ages 45 and 59.

Gene panel analysis (ATM, BRCA1, BRCA2, CDH1, CHEK2, NBN, PALB2, PTEN,RAD51C, RAD51D, STK11 and TP53) revealed a variant in CHEK2.

Variant is:

Chr22(GRCh37):g.29121087A>G

NM_007194.3:c.470T>C

p.(Ile157Thr)

1) What classification would you give this variant following ACMG?