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.pdf

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

Case 2:

3 year old child with intellectual disability (ID) and seizures

With Whole Exome Sequencing and analysis of the genes associated with ID a stop-gain mutation was detected in the PACS1 gene.

Variant is:

Chr11(GRCh37):g.65978670C>G
NM_018026.3(PACS1):c.600C>G
p.(Tyr200*)

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

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

Case 3:

Young boy age 2 with developmental delay, stabismus, hypotonia and feeding problems

Chr20(GRCh37):g.485826T>C
NM_177559.2(CSNK2A1):c.149A>G
p.(Tyr50Cys)

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

2) What criteria tips the balance?

Please also check:

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

Case 4:

Male patient age 9 with small length, hyperhydrosis wrists and feet, lumps on tongue. WES detected a startloss variant in COL3A1

Chr2(GRCh37):g.189839218G>A
NM_000090.3(COL3A1):c.3G>A
p.?

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

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?