The ABC system in brief October 2023

Step A: Functional grading

5 – FE – Functional **E**ffect: Known LoF or GoF variant
4 – LFE – Likely **F**unctional **E**ffect – or known **H**ypomorphic **A**llele
3 – HFE – VUS with **H**ypothetical **F**unctional **E**ffect – or a **de novo** VUS
0 – VUS without hypothetical functional effect
2 – LNF – Likely **N**ormal **F**unction
1 – NF – Normal **F**unction

Step B: Clinical grading

0 – NO MATCH variant, i.e. the gene is unlikely to be linked to the phenotype – or no clinical information
1 – VOI - variant of potential interest in a gene that fits the phenotype
2 – RISK FACTOR variant for the phenotype (recessive or oligo/multifactorial)
3 – Dominant pathogenic variant of low or unknown penetrance
4 – Dominant pathogenic variant of moderate (>20%) penetrance
5 – Dominant pathogenic variant or high (>40%) penetrance

Classification: Combined grade (A+B) gives the variant class (F to A):

Class		
0	Step A 0-2 + no step B = 0-2	Not reported – and clinical grading unnecessary
F	Step A + step B = 3	Not reported
E	Step A + step B = 4-5	Variant-of-interest (VOI) group, reporting optional
D	Step A + step B = 6-7	Risk factor (RF) group, reporting recommended if clinical match
C	Step A + step B = 8	Pathogenic (P), unknown or low (lifetime <20%) penetrance
B	Step A + step B = 9	Pathogenic (P), moderate penetrance (lifetime 20-40%)
A	Step A + step B = 10	Pathogenic (P), high penetrance (lifetime >40%)
X	Step A + step B = 5-10	Secondary/incidental/unsolicited/opportunistic finding

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Step C: Standard variant comments

A+B grade 0-2:
0 NORMAL findings
A+B grade 3-7, i.e. classes F (3) , E (4-5) and D (6-7):
1 NORMAL findings – no pathogenic or likely pathogenic variants were detected
2 NORMAL findings – no pathogenic variants that could be related to the phenotype were detected
3 NORMAL findings – no pathogenic variants that could explain the phenotype were detected
4 VOI – A genetic variant of potential interest was detected
5 VOI – Heterozygosity for a recessive genetic variant of potential interest was detected
6 VOI – Hemizygosity for a genetic variant of potential interest was detected
7 VOI – Homozygosity for a genetic variant of potential interest was detected
8 RISK FACTOR – A genetic variant that increases susceptibility for this phenotype was detected
9 RISK FACTOR – Heterozygosity for a recessive genetic variant of interest was detected
10 PATH – Likely compound heterozygosity for recessive pathogenic variants was detected
11 PATH – Homozygosity for a recessive pathogenic genetic variant was detected
A+B grade 8-10, i.e. classes C (8), B (9) and A (10):

12 PATH – Heterozygosity for a dominant likely pathogenic variant was detected

13 PATH – Heterozygosity for a dominant pathogenic variant was detected

14 PATH – Heterozygosity for a dominant pathogenic variant of moderate penetrance was detected

15 PATH – Heterozygosity for a dominant pathogenic variant of high penetrance was detected

Incidental/unexpected findings, i.e. class X (5-10):

16 IF – A genetic variant unrelated to the clinical question was detected

17 IF – No obvious match between genotype and phenotype. Further clinical investigations necessary

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Suggestion for integration of ACMG criteria in the ABC system:

Step A

FE	PVS1 PS1 PS3	1 criterium is enough to grade as FE
LFE	PP1-Strong PM4 PM5	2 criteria or more: upgrade to FE
HFE	PS2 PS4 PM1 PM2 PP2 PP3 PP5	3 criteria or more: upgrade to LFE
fVUS	not enough data to grade variant	
LNF	BS1 BS2 BS3 BP1 BP2 BP3 BP4 BP5 BP6 BP7	
NF	BA1	

Step B

cVUS	BS4, no clinical match, or no clinical Information	
VOI	gene fits phenotype	
RISK FACTOR	PM3 PP4 PP5	1 criterium is enough to grade as RF
PATH	known pathogenic (AR or AD)	
PATH	known pathogenic (AD, mod.)	
PATH	known pathogenic (AD, high)	