Step A: Functional grading

5 – FE – Functional Effect: Known LoF or GoF variant
4 – LFE – Likely Functional Effect – or known Hypomorphic Allele
3 – HFE – VUS with Hypothetical Functional Effect – or a de novo VUS
0 – VUS without hypothetical functional effect
2 – LNF – Likely Normal Function
1 – NF – Normal Function

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):

<table>
<thead>
<tr>
<th>Class</th>
<th>Step A + Step B</th>
<th>Variant class</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0-2</td>
<td>Not reported – and clinical grading unnecessary</td>
</tr>
<tr>
<td>F</td>
<td>3</td>
<td>Not reported</td>
</tr>
<tr>
<td>E</td>
<td>4-5</td>
<td>Variant-of-interest (VOI) group, reporting optional</td>
</tr>
<tr>
<td>D</td>
<td>6-7</td>
<td>Risk factor (RF) group, reporting recommended if clinical match</td>
</tr>
<tr>
<td>C</td>
<td>8</td>
<td>Pathogenic (P), unknown or low (lifetime &lt;20%) penetrance</td>
</tr>
<tr>
<td>B</td>
<td>9</td>
<td>Pathogenic (P), moderate penetrance (lifetime 20-40%)</td>
</tr>
<tr>
<td>A</td>
<td>10</td>
<td>Pathogenic (P), high penetrance (lifetime &gt;40%)</td>
</tr>
<tr>
<td>X</td>
<td>5-10</td>
<td>Secondary/incidental/unsolicited/opportunistic finding</td>
</tr>
</tbody>
</table>

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):
PATH – Heterozygosity for a dominant likely pathogenic variant was detected
PATH – Heterozygosity for a dominant pathogenic variant was detected
PATH – Heterozygosity for a dominant pathogenic variant of moderate penetrance was detected
PATH – Heterozygosity for a dominant pathogenic variant of high penetrance was detected

Incidental/unexpected findings, i.e. class X (5-10):
IF – A genetic variant unrelated to the clinical question was detected
IF – No obvious match between genotype and phenotype. Further clinical investigations necessary

Suggestion for integration of ACMG criteria in the ABC system:

Step A
FE
PV51 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)