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Supplemental information

Scaling national and international improvement in virtual gene panel curation via a collaborative approach to discordance resolution

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Table S1. Common sources of discordant gene inclusion or rating on diagnostic panels and further recommendations for practice.

Gene-disease validity assessments	
New evidence since original assessment	*HARS2* rating upgraded to diagnostic on Hearing Loss panel due to publication of 6 unrelated families in 2019.[1; 2] Mode of inheritance for *SCN8A* changed from mono-allelic to both mono-allelic and bi-allelic due to reports of families with bi-allelic variants and more severe phenotype in 2019.[3] **Recommendation**: new evidence for gene-disease relationships should be sought proactively on a regular basis.
Reappraisal of historical gene-disease associations	Association between *HOXA11* and radioulnar synostosis with amegakaryocytic thrombocytopenia downgraded to Amber as two families reported in 2000, and none since. Association between *KIRREL3* and intellectual disability (ID) downgraded to Red as the genetic variants originally reported are present at a high frequency in population datasets. Association between *TUBA8* and cortical malformations downgraded to Red as publication reporting alternative diagnosis in original families identified.[4] **Recommendation**: evidence for gene-disease associations should be critically appraised, especially those predating genome-wide approaches to gene discovery and the existence of large reference population datasets. Academic publishers should encourage an evidence-based approach to asserting gene-disease associations, particularly in subject reviews.
Gene-disease associations reported in isolated populations	*PET100* promoted to Green on ID panel: initially founder variant in eight Lebanese individuals reported, but one further family in different population identified, as well as functional data. **Recommendation**: caution should be exercised when gene-disease associations rest on evidence solely derived in isolated populations as the reported variant could be in linkage disequilibrium with the true causative variant which affects a different gene.
Use of unpublished evidence from diagnostic	Association between *FAM20C* and craniosynostosis rated as Green due to personal communication with research group reporting unpublished cases.

laboratories and research groups	**Recommendation**: unpublished evidence should be used judiciously when provenance can be established, and ideally the primary data supporting variant classification reviewed. Decisions based upon unpublished or private data should be explained in as much detail as is possible (the PanelApp software enables comments to be made which are publicly available).
Differential weighting of functional evidence	*HOMER2* rating unresolved: two families reported with mono-allelic variants and deafness. Bi-allelic mouse model has deafness, but mice with mono-allelic variants have normal hearing. **Recommendation**: detailed gene curation schemes such as the ClinGen framework are particularly well suited to objectively resolving edge cases.
Quality of evidence	*GRIA1* rating unresolved: multiple reports of *de novo* variants in large intellectual disability cohort studies, but paucity of phenotypic, segregation, or functional data. **Recommendation**: higher thresholds should be applied where novel gene-disease associations are reported without robust supporting evidence. Publishers should encourage the inclusion of case-level data where possible.
Panel inclusion decisions	
Inclusion due to phenotypic overlap	*ALMS1* included in ciliopathy panels, despite Alstrom syndrome not being considered a ciliopathy. **Recommendation**: careful consideration should be given to genes that need to be included in panels due to phenotypic overlap and to providing guidance that promotes panel co-application or more extended analysis.
Inclusion of gene family members	Inclusion of *PEX* genes in disorders of cortical malformation unresolved: only some have published evidence documenting cortical malformations. **Recommendation**: a consistent approach should be adopted to this scenario and clear guidance and explanation provided to clinical and diagnostic users (e.g. co-application of other panels such as Peroxisomal Disorders encouraged if all genes are not included).
Tractability of variant types by different Next	Inclusion of *PRDM13* remains unresolved: the only variant types reported are non-coding variants upstream of the gene which

Generation Sequencing (NGS) assays and sample types	may not be tractable by all assays (e.g., exome sequencing). **Recommendation**: a consistent approach should be adopted to this scenario and clear guidance provided to clinical and diagnostic users (e.g., the gene is included in the panel but analysis and reporting are dependent on technical factors).
Proportion of individuals with the disorder who have a particular phenotypic manifestation	Inclusion of Fanconi anemia (FA) genes on the ID panel remains unresolved: ~20% of individuals with FA have ID. **Recommendation**: clinical guidance is required for this decision, and consideration of the scope of the panel, established clinical pathways for testing as well as risk of incidental findings.

References:

1. Demain, L.A.M., Gerkes, E.H., Smith, R.J.H., Molina-Ramirez, L.P., O'Keefe, R.T., and Newman, W.G. (2020). A recurrent missense variant in HARS2 results in variable sensorineural hearing loss in three unrelated families. Journal of human genetics 65, 305-311.
2. Karstensen, H.G., Rendtorff, N.D., Hindbaek, L.S., Colombo, R., Stein, A., Birkebaek, N.H., Hartmann-Petersen, R., Lindorff-Larsen, K., Hojland, A.T., Petersen, M.B., et al. (2020). Novel HARS2 missense variants identified in individuals with sensorineural hearing impairment and Perrault syndrome. European journal of medical genetics 63, 103733.
3. Wengert, E.R., Tronhjem, C.E., Wagnon, J.L., Johannesen, K.M., Petit, H., Krey, I., Saga, A.U., Panchal, P.S., Strohm, S.M., Lange, J., et al. (2019). Biallelic inherited SCN8A variants, a rare cause of SCN8A-related developmental and epileptic encephalopathy. Epilepsia 60, 2277-2285.
4. Diggle, C.P., Martinez-Garay, I., Molnar, Z., Brinkworth, M.H., White, E., Fowler, E., Hughes, R., Hayward, B.E., Carr, I.M., Watson, C.M., et al. (2017). A tubulin alpha 8 mouse knockout model indicates a likely role in spermatogenesis but not in brain development. PloS one 12, e0174264.

Table S2. Journals reviewed as part of the PanelApp rare disease updates

	Journal name
1	American Journal of Human Genetics
2	American Journal of Medical Genetics
3	Annals of Clinical and Translational Neurology
4	Annals of Neurology
5	Brain
6	Cell
7	Clinical Genetics
8	European Journal of Human Genetics
9	Genetics in Medicine
10	Human Molecular Genetics
11	Human Mutation
12	Journal of Clinical Investigation
13	Journal of Medical Genetics
14	Nature
15	Nature Communications
16	Nature Genetics
17	Neurology
18	Neurology Genetics
19	PLOS Genetics
20	Science