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Gene panels for skeletal dysplasia and epilepsy: Maximizing clinical utility through careful design, regular review, and clinician-laboratory collaboration

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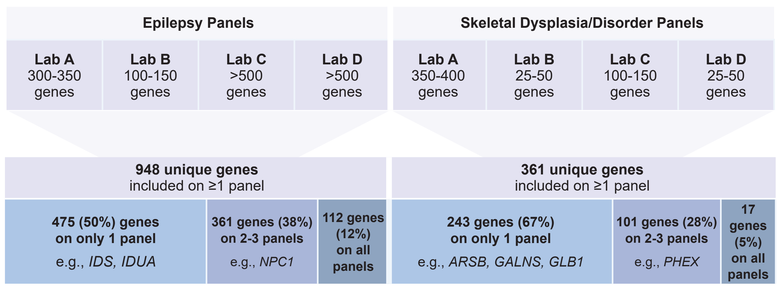
Background

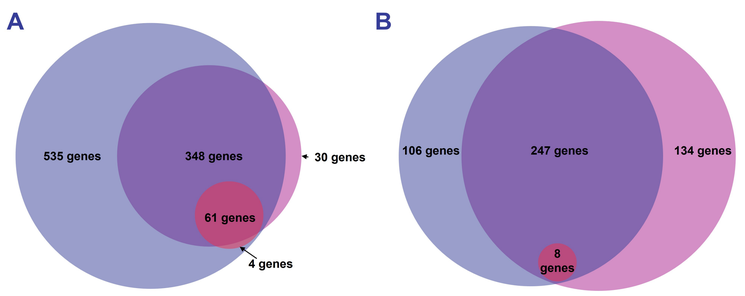
- Advances in sequencing technology have made gene panels more accessible, flexible, comprehensive, and efficient
- Lack of gene panel standardization represents a barrier to timely and accurate diagnosis of rare conditions with treatment or other management options available
- In 2019-2020, the ACMG published a Technical Standard for diagnostic gene panel design,[1] however, there remains a lack of standardization of genes included on panels offered by clinical laboratories
- The ACMG Technical Standard provides a framework, but relies on individuals to interpret and apply to specific phenotypes and does not provide guidance on follow-up recommendations
- Comprehensive symptom- or disease-directed gene panels for epilepsy and skeletal dysplasia/disorder (SD) offer a high-throughput testing option that can reduce the diagnostic burden associated with rare, heterogenous disorders with overlapping and non-specific symptoms (e.g., lysosomal storage disorders, or LSDs)
- The lack of standardization of epilepsy and SD panels can be seen through comparing commercially-available panels marketed for these conditions:
  - When looking at all genes included in panels from 4 major labs in the US/Europe, over half of genes are included at only one lab (**Figure 1**); rare/treatable conditions, including LSDs, are frequently excluded from panels

Figure 1. Epilepsy and Skeletal Dysplasia/Disorder Panels are heterogeneous and frequently exclude rare/treatable conditions



- Public tools have been introduced to facilitate selecting genes to include on phenotype-directed gene panels
  - Comparing two of these tools, ClinGen[2] and PanelApp[3], with genes included on any of the 4 panels from **Figure 1**, further demonstrates the lack of standardization of panels and associated resources for epilepsy and SD (**Figure 2**)

Figure 2. Comparison of ClinGen, PanelApp, and (A) Epilepsy and (B) Skeletal Dysplasia/Disorder Panels demonstrates lack of standardization



ClinGen	*Includes "definitive", "strong", and "moderate" gene-disease associations from Gene Curation Expert Panels: Epilepsy (last accessed: Jan 16, 2022), Skeletal Disorders (last accessed: Jan 16, 2022)*
PanelApp	*Includes Green annotations from: Genetic epilepsy syndromes (v3.0), Skeletal dysplasia (v3.3)*
Panels	*Includes genes on ≥1 of 4 commercial lab Epilepsy/SD panels in initial analysis*

Objective

- To develop practical considerations for the design of gene panels for epilepsy and SD including phenotype/gene-specific guidance on gene selection, reflex testing, and reporting

Methods

- Expert opinion was developed through multiple surveys, and subsequent discussions with a group of molecular genetic laboratory and clinician specialists (N=10) from the US, Europe, the Middle East, Turkey, and Brazil to capture both laboratory and clinical as well as regional perspectives/differences

Results

The principal barriers to using epilepsy and SD gene panels in clinical practice were identified by the expert group as:

Includes insufficient genes
Limited familiarity with testing
Inconclusive results

Practical Considerations to ACMG Technical Standard for Epilepsy and Skeletal Dysplasia

- To acknowledge the evolving nature of clinical genetics and need for durable guidance, we focused on a process (**Figure 3**) versus a static list of genes
- Given availability of approved treatments and confirmatory testing methods (e.g., enzyme testing), we recommend that metabolic conditions and treatable conditions are included on gene panels for epilepsy and/or SD
- In addition to the considerations presented here, partnership with external bodies (e.g., MetabERN in EU for inborn errors of metabolism, ILAE for epilepsy) could amplify efforts to standardize, and increase clinician familiarity with, gene panels for epilepsy and SD
- The considerations presented here are intended to be a condition-specific supplement to, not a replacement for, the core the ACMG Technical Standard[1]

Figure 3. Epilepsy/SD-specific considerations mapped to ACMG Technical Standard

Summary of process described in ACMG Technical Standard

Define intended use of gene panel

Select genes

Consider technical limitations

Reporting

Please refer to Bean et al., 2019[1] for general recommendations within each step above

Practical Consideration	Resources	Epilepsy/SD Examples
1 Consider all GAD and GADDx spanning both *common* and *rare* causes of the disorder to maximize clinical utility (yield) – Alternatively, use a tiered approach in which an extended panel is used to expand the list of genes tested if the core panel does not yield satisfactory findings	▪ ClinGen[2] ▪ PanelApp[3] ▪ HGMD[4] ▪ ClinVar[5] ▪ Literature	**Literature:** Nosology of Skeletal Dysplasia[6]
2 Consider clinical heterogeneity through collaboration with lab and clinician peers; for example, consider: – Spectrum of diseases (consider classical and atypical phenotypes) – Phenotype at presentation (early diagnosis)	▪ Peer-to-peer collaboration (clinician and lab collaboration)	**Consider differential diagnoses at patient presentation:** – Epilepsy: CLN2 disease (*TPP1* gene) typically presents with unprovoked seizures before progressing to a syndromic presentation **Consider the spectrum of phenotypes for each gene:** – SD: Morquio A syndrome (*GALNS* gene) has classical and nonclassical presentations with variable clinical symptoms and age at presentation
3 Consider impact on clinical management including availability of targeted therapies, pharmacogenomics, and interventional clinical trials	▪ ClinGen Expert Working Groups[2] ▪ Regulatory agencies, e.g., FDALabel[7], EMA[8], ClinicalTrials[9], EudraCT[10] ▪ PharmGKB[11] ▪ Literature	**Example genes with clinical implications:** – **Epilepsy:** ALDH7A1[a], *CHD2*[b], *PCDH19*[b], *SCN1A*[b], *SLC2A1*[a], *TPP1*[c], *TSC1/2*[b,c] – **SD:** *ALPL*[c], *ARSB*[c], *COL1A1*[b,c], *COL1A2*[b,c], *FGFR3*[b,c], *GALNS*[c], *IDS*[c], *IDUA*[c], *PHEX*[c]
4 Consider reflex testing with orthogonal methods (e.g., enzyme activity) or providing information on follow-up testing to facilitate follow-up of inconclusive results – Including genes for conditions with non-sequencing confirmatory test available can increase clinical utility while reducing burden of inconclusive results (e.g., VUS)	▪ Genetic Test Registry[12] ▪ Orphanet[13] ▪ Local Labs ▪ Literature	**Epilepsy examples:** *PPT1*[d], *TPP1*[d] **SD examples:** *ARSB*[d], *GALNS*[d], *GLB1*[d], *IDS*[d], *IDUA*[d], *SGSH*[d]

GAD, gene associated with Mendelian disorder; GADDx, gene associated with differential diagnosis; VUS, variant of uncertain significance

[a]non-pharmacological therapy impacting disease course available (e.g., ketogenic diet); [b]clinical trial(s) available; [c]therapy approved in US, Europe, and/or other region(s); [d]biochemical genetic (enzyme) testing

Conclusions

- Gene panels for epilepsy and SD should include genes for both common and rare genetic conditions (e.g., lysosomal storage diseases) and be regularly reviewed to ensure completeness and continued appropriateness of genes included
- Where available, orthogonal confirmatory testing methods should be leveraged to increase clinical utility by clarifying inconclusive results (e.g., VUS) and shortening the diagnostic odyssey
- Collaboration and knowledge sharing among/between laboratories and clinicians is recommended to facilitate panel design, results interpretation, and follow-up testing
- Partnership with global/regional external bodies could amplify efforts to standardize gene panels for epilepsy and SD

References

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