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Broad Implications of Sustained, Proactive Clinical Validity Curation

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BACKGROUND

- Our understanding of phenotypic spectrums expands as discoveries of new gene-disease associations continue to increase
- However, there remains a lack of clinical validity assessment standards and guidelines for disease naming
- Reference databases are valuable resources for evaluating gene-disease associations but have limitations
  - OMIM[1] and HGMD[2] have on average 3-4 disease associations per gene, including potentially duplicated disease entries
  - Some genes have >100 distinct disease associations listed in HGMD
  - Collaborative efforts such as ClinGen[3] provide helpful insight into this issue; however, the scope is limited
- Genetic testing labs must conduct comprehensive and standardized curation of gene-disease associations to:
  - Develop panel tests for genes with clear clinical utility
  - Efficiently reclassify exome data based on newly characterized gene-disease associations

METHODS

- Our clinical laboratory developed standardized guidelines for curating and scoring the clinical validity of gene-disease associations[4]
  - A team of scientists proactively curate literature weekly
  - Evidence supporting new gene-disease associations are categorized based on scoring metrics **[Figure 1]**
- Here, we describe how this internal clinical validity database is used for developing and updating panel offerings run on an exome backbone
  - Gene relevance for inclusion on a neurodevelopmental disorders (NDD) panel is assessed
  - Only characterized disease associations are included
  - Smaller phenotypically-driven panels are also created
  - Curated gene lists are compared to other similar products on the market
  - Reasons that genes are excluded from one or more panels are evaluated
  - Panel gene content is assessed quarterly

FIGURE 1: CONTENT OF CLINICAL VALIDITY DATABASE

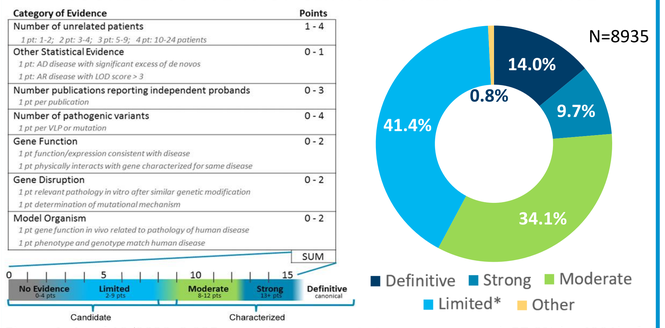

Figure 1: As of 12/2020, 8,935 gene-disease associations were curated. 57.8% (n=4291) of these relationships are classified as moderate or higher and are associated with one of 3272 genes. This represents ~16% of genes in the genome, emphasizing the need for ongoing curation efforts as new gene-disease discoveries are made.

RESULTS

- In August 2020, 1406 genes associated with NDD were identified for a comprehensive neurodevelopmental panel
  - Genes were further assigned to smaller, phenotypically-focused panels
- Two other labs have similar products in terms of clinical indication and scope **[Figure 2]**
  - Our panel included 60 unique genes, of which 50.0% (n=30) were characterized in the last 2 years
  - Major reasons for omitting genes from our NDD panel include:
    - Limited clinical validity evidence
    - Characterized disease association was outside the phenotypic scope
- From concept to launch, the process took 2.5 months
- Clinical validity database is continuously updated **[Figure 3]**
  - 42 genes were added at the 1st two quarterly reviews **[Table 1]**
  - After 6 months, the gene content increased by 3.0%

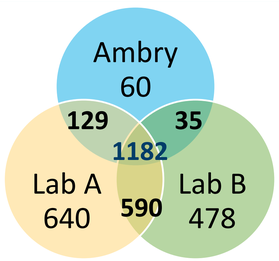

FIGURE 2: GENE CONTENT OF NDD PANELS AT 3 LABS

Figure 2: Of 1406 genes offered on our comprehensive NDD panel, 1182 (84.1%) were on all three panels. 129 (9.2%) were shared between Ambry and Lab A; 35 (2.5%) were shared between Ambry and Lab B. At panel launch, Ambry offered 60 (4.3%) unique genes that were not available on the panels of Lab A or Lab B.

FIGURE 3: NEWLY CHARACTERIZED GENE-DISEASE ASSOCIATIONS 2020 – 2021

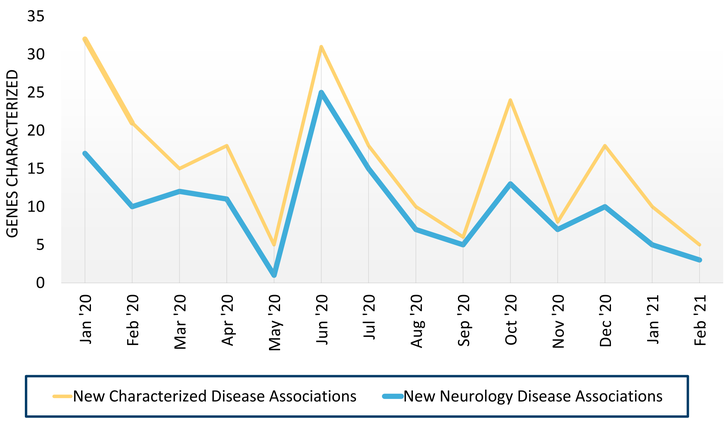

Figure 3: On average, 15 gene-disease associations are characterized per month, out of which about 10 have neurology disease associations.

TABLE 1: NEW GENE ADDITIONS AT QUARTERLY REVIEW AFTER PANEL LAUNCH

Gene Name	Inheritance	Date of Characterization
ATP6AP2	XLR	7/2/2020
CBY1	AR	11/6/2020
CDK8	AD	3/29/2019
CEP85L	AD	12/3/2020
CPE	AR	10/02/2020
FAM50A	XLR	10/2/2020
GABRA5	AD	8/31/2020
GAD1	AR	7/30/2020
GLRA2	AD	7/9/2020
GLUL	AR	10/23/2020
HPDL	AR	11/6/2020
HS2ST1	AR	12/4/2020
JARID2	AD	10/27/2020
KAT8	AD	11/6/2020
KCNN2	AD	9/15/2020
LARGE1	AR	5/4/2017
LARS	AR	12/18/2020
LMNB1	AD	11/3/2020
MADD	AR	8/14/2020
MAPK1	AD	7/31/2020
MDH2	AR	9/28/2020
MED25	AR	8/28/2020
MED27	AR	1/15/2021
MFSD2A	AR	5/4/2017
NAPB	AR	5/4/2017
NDUFA12	AR	10/23/2020
NEMF	AR	10/20/2020
NKX2-2	AR	8/28/2020
NLGN1	AD	8/31/2020
PCYT2	AR	10/2/2020
PDSS1	AR	10/28/2020
PEX11B	AR	10/23/2020
PIGH	AR	12/31/2020
PSPH	AR	10/23/2020
PUM1	AD	8/31/2020
RLIM	XLR	9/29/2020
SCAF4	AD	7/31/2020
SCAMP5	AD	1/8/2021
SHMT2	AR	11/4/2020
TBC1D2B	AR	7/16/2020
UBE4A	AR	1/15/2021
VPS4A	AD	12/24/2020

Table 1: Panel gene content is assessed quarterly for additional genes meeting inclusion criteria. 27 genes were added at the 1st quarterly review and 15 genes were added at the 2nd quarterly review. After 6 months, the gene content increased by 3.0%

TAKE-HOME POINTS

- Proactive and sustained clinical validity curation has wide reaching benefits
  - Defining accurate and distinct phenotypes
  - Impacting panel design, panel updates, and redesign
  - Increasing diagnostic rates through proactive reclassification
- Relying on reference databases like HGMD and OMIM alone for clinical validity assessment may result in including genes with imprecise or limited disease associations on clinical testing platforms.
- This is especially true for NDDs which display a more rapid rate of new gene-disease discoveries compared to other phenotypes.

REFERENCES

1. OMIM: https://www.ncbi.nlm.nih.gov/omim/
2. Stenson, PD *et al.* (2020) *Hum Genet* **139**(10): 1197-1207 (PMID: 32596782)
3. ClinGen: https://clinicalgenome.org/
4. Smith, ED *et al.* (2017) *Hum Mutat* **38**(5): 600-608 (PMID: 28106320)