Ambry Genetics®
A Konica Minolta Company

"N of One" is the Loneliest Number:
How a Lack of Corroborating Case Reports is Hindering the Classification of Genes

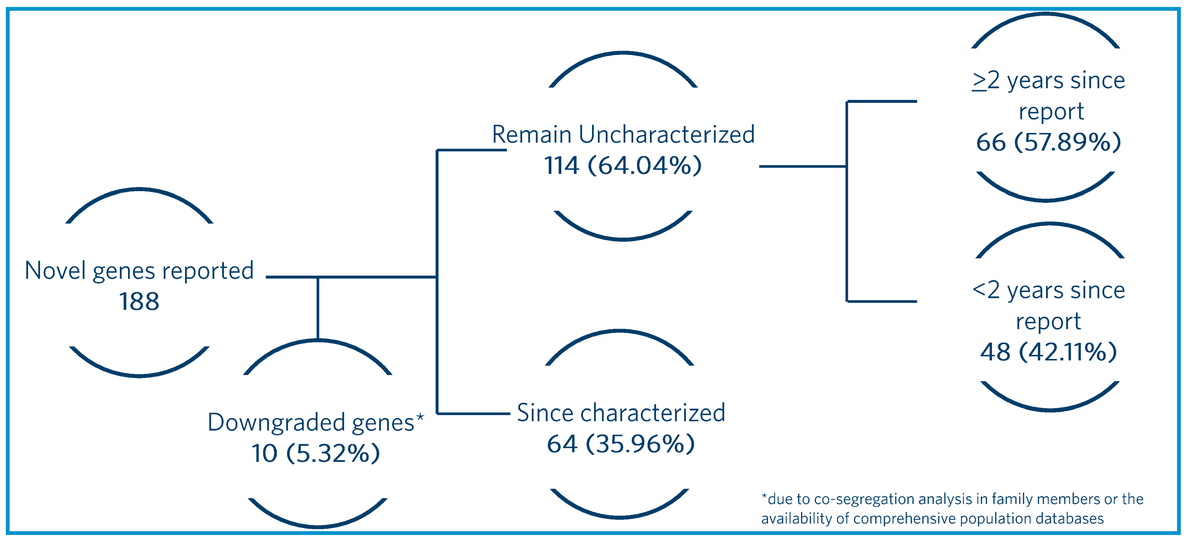
Meghan C. Towne[1], Brian Schoenfeld[1], Kirsten Blanco[1], Kelly Radtke[1], Sha Tang[1], Kelly D. Farwell Hagman[1] and Deepali N. Shinde[1]

[1]Ambry Genetics, Aliso Viejo, CA, 92656

Meghan Towne mtowne@ambrygen.com

BACKGROUND

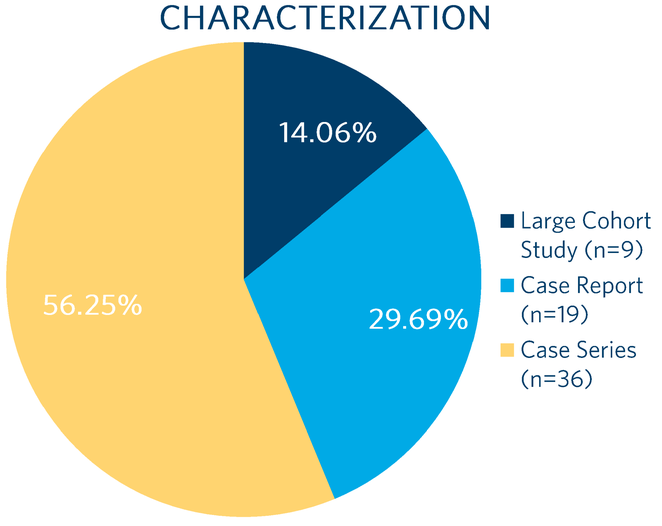
- Aim: To assess the common factors that lead to and prevent gene characterization despite strong evidence
- Diagnostic exome sequencing (DES) has increasing diagnostic rates partially due to discoveries of new gene-disease associations
  - However, the rate of gene discoveries has slowed[1]
  - Remaining gene-disease relationships may include extremely rare disorders for which patients are difficult to ascertain
- Ambry continually evaluates genes based on the literature
  - To determine a clinical validity score
  - To categorize genes as "uncharacterized" (i.e. without an established human disease) or "characterized" [2]
- If DES evaluation for characterized genes is negative or uncertain, uncharacterized genes are assessed
  - Reporting candidate genes has increased DES diagnostic rate by 7.7% [3]



METHODS

- All DES reports with an uncharacterized candidate gene finding over an 8 year period from our clinical laboratory were analyzed
  - 234 cases total
  - 188 different genes uncharacterized at the time of report
- Calculated time to characterization based on:
  - Date of report(s) with uncharacterized gene
  - Date of publication leading to characterization
  - Date of characterization
  - Date of report(s) with characterized gene
- Categorized the type of publication that lead to classification
  - Large cohort study (i.e. DECIPHER or Epi4K consortiums)
  - Case series (≥3 unrelated families)
  - Case report (≤ 2 families)

TYPE OF MANUSCRIPT LEADING TO CHARACTERIZATION



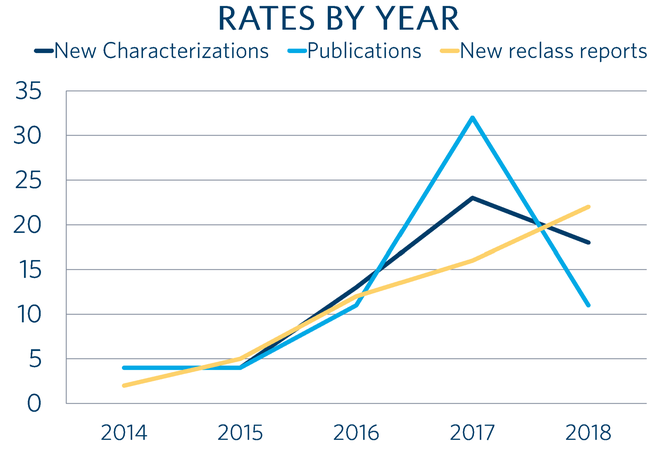
- Case series comprised of 3 or more families most often resulted in gene characterization
- More than half of these case series and case reports included functional analysis (52.78% and 57.89%, respectively)

TIME ANALYSIS (DAYS)

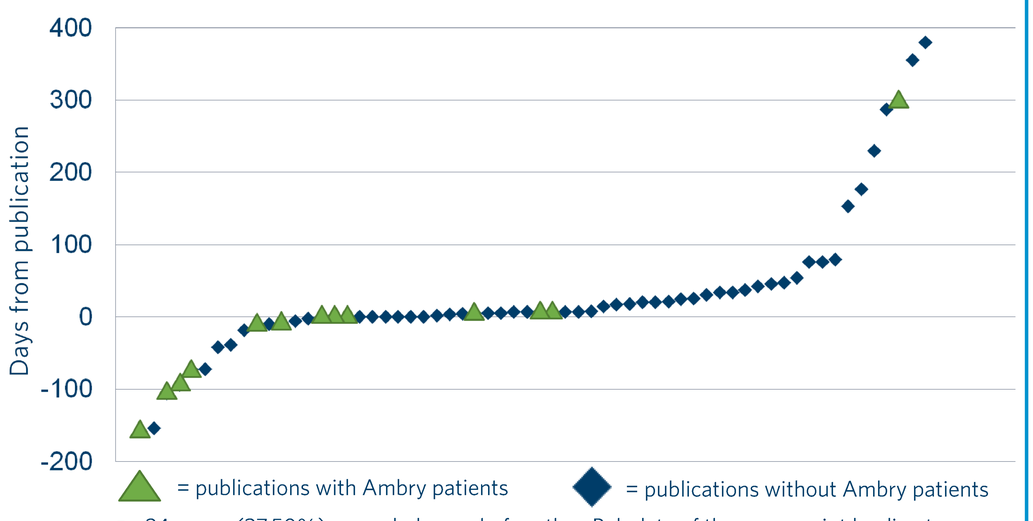
	Average	Median	Range (days)
Publication to characterization (n=64)	19.98	6	(-597 to 380)
Characterization to report (n=61) ±	75.26	58	(0 to 353)
Publication to report (n=61)±	89.38	55	(-244 to 441)

± 3 genes with reports pending at time of analysis

RATES BY YEAR



TIME FROM PUBLICATION TO CHARACTERIZATION



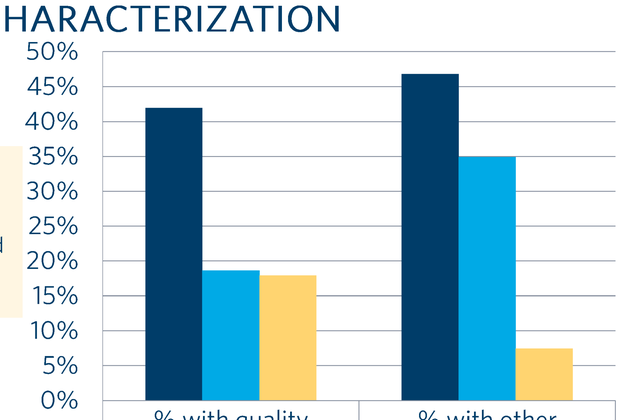
- 24 genes (37.50%) upgraded on or before the ePub date of the manuscript leading to characterization
- 54 genes (84.38%) characterized within 2 months of ePub date
- One outlier (not pictured) was characterized using internal Ambry patient data 597 days before the ePub date of a corroborating manuscript

RESULTS

- 114 genes remain uncharacterized
  - Lack robust patient data to meet criteria for characterization
  - 35.11% of all novel candidate genes reported (n=66) were originally reported ≥2 years ago
    - 87.88% of these genes (n=58) had only 1 novel candidate report issued making these true "n of one" cases
- Patient reports play a major role in characterizing genes and are considered heavily on our classification scheme
  - Both the number of patients reported and the depth of phenotypic description are considered
  - Case series with detailed clinical histories resulted in characterization of a gene in the majority of cases (56.25%)
  - Reports of patient(s) in large cohort studies that lack robust phenotypic descriptions are considered weaker evidence
    - Only resulted in characterization in 14.06% of genes
    - For all but one gene, there was other patient data available
  - Abstracts presented at scientific meetings used to characterize 5 genes
- Nearly half (46.88%) of manuscripts leading to characterization included functional analysis
  - None of the large cohort studies included functional analysis

DETAILED PHENOTYPIC DESCRIPTIONS IN THE LITERATURE LEAD TO FASTER GENE CHARACTERIZATION

Genes uncharacterized for ≥2 years have less patient supporting data and are more likely have a single case reported with no additional supporting patient reports



	% with quality patient data	% with other patient point
Characterized genes	41.94%	46.77%
Genes Unchar < 2 yrs	18.60%	34.88%
Genes Unchar >2 yrs	17.91%	7.46%

TAKE-HOME POINTS

- Ongoing reassessment of uncharacterized genes reported on DES to date has resulted in the establishment of a gene-disease relationship in approximately 1/3 (34.04%)
- Roughly the same percentage (35.11%) have remained as a candidate gene for more than 2 years
  - Mostly comprised of "n of one" cases which do not meet criteria due to lack of patient reports
- Collaborations involving commercial labs may help uncover these elusive gene-disease relationships and can impact clinical reporting categorization in an efficient manner
- Manuscripts which give detailed clinical descriptions of patients are more effective at characterizing genes with a small "n"
- Case series of multiple patients often provide sufficient evidence for characterization
- However, detailed case reports of a single proband may be a more effective option for extremely rare disorders

REFERENCES

1. Boycott KM, *et al.* (2017) *Am J Hum Genet* **100**(5):695-705. PMID: 28475856
2. Smith ED, *et al.* (2017) *Hum Mutat* **38**(5):600-8. PMID: 28106320
3. Farwell Hagman KD, *et al.* (2017) *Genet Med* **19**(2):224-35. PMID: 27513193