Never Stop Looking: Dual Diagnoses Due to Updated Gene-Disease Relationships in Exome Patients

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Introduction: Clinical exome data covers so much of the genome that revisiting the sequence files over time can uncover new findings, even in patients with a clinically actionable variant and an apparently complete molecular diagnosis. As new gene-disease relationships (GDRs) are established, additional findings identified through reanalysis can be interpreted as clinically relevant, leading to the addition of a second diagnosis.

Methods: We reviewed reanalysis data of clinical exome patients over 14 years to identify cases with an additional likely pathogenic (LP) or pathogenic variant (PV) due to updated GDRs including newly established reportable GDRs and updates to the mechanism of disease for established GDRs. Cases with dual diagnoses at initial report were excluded. Cases with the addition of a variant of unknown significance (VUS) due to updated GDRs were also excluded.

Results: We found that additional PVs were reported in 29/5778 (0.5%) of exome cases that already had at least one PV/LP finding. On average, additional findings were reported 4 years after initial diagnosis.

Of 19 parental trio cases, 11 of those (57.9%) had a *de novo* finding for the first diagnosis; 13/19 (68.4%) had a *de novo* finding for the second diagnosis and 10/19 (52.6%) had *de novo* findings for both diagnoses. One case with two *de novo* findings had a PV microdeletion and an LP SNV in a gene outside of the CNV region. No additional cases had a CNV finding as one of the diagnoses.

Two cases had homozygous PVs for autosomal recessive conditions for both diagnoses, and in both cases, consanguinity was reported for the parents.

A total of 21/29 (72.4%) of initial PV findings apparently fully explained the patient's phenotype, while 8/29 (27.6%) of initial diagnoses only explained part of the phenotype. Distinct phenotypes from the first diagnosis were explained by additional findings in 10/29 (34.5%) cases. Of cases with phenotypic overlap between the two diagnoses (n=19), 31.6% of additional findings had phenotypic overlap with distinguishing features; and 68.4% of dual diagnoses had complete phenotypic overlap with nonspecific features.

Conclusions: Here, we presented a case series of clinical exome probands who received dual diagnoses over time due to updated GDRs. This study found that 0.5% of exome patients received a second diagnosis over time due to updates to GDRs. Our findings are consistent with previously published data showing that reinterrogation of exome

sequencing due to updated GDRs increases diagnostic yield. Our findings support guidelines recommending exome or genome sequencing as a first-line test, and continued study of GDRs in conjunction with proactive exome reanalysis. This study highlights the relevance of proactive reanalysis even in probands with one diagnosis on exome sequencing to potentially fully explain a proband's clinical phenotype. The presence of multiple dual diagnosis cases with overlapping clinical phenotype without distinguishing features further highlights the need for continued review of exome sequencing data over time to provide patients with a full molecular explanation of their features. Further studies to evaluate the impact of updates to GDRs and proactive exome reanalysis on diagnostic yield among exome patients are warranted.