When Symptoms Don't Make Sense: The Power of Diagnostic Tools for Identifying Dual Diagnoses

Carli Andrews[1], Christina Settler[1], Mathew Chau[1,2], Weimin Bi[1,2], Hongzheng Dai[1,2], Christine Eng[1,2], Pengfei Liu[1,2], Linyan Meng[1,2], Nichole Owen[1,2], Janice Smith[1,2], Carlos Bacino, Liesbeth Vossaert[1,2], Fan Xia[1,2], Xiaonan Zhao[1,2]

1) Baylor Genetics, Houston, TX 77021, USA
2) Dept. of Molecular & Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA

OBJECTIVES

The diagnostic odyssey is common in individuals with genetic disease, requiring them to see an average of 8 physicians and spend an average of $19K on less informative testing over 5-7 years, receiving 2-3 misdiagnoses along the way. Chromosomal microarray analysis (CMA) and whole exome sequencing (WES) are powerful clinical tools when patients present with unusual phenotypes or incongruent symptoms for a specific genetic disease. Between 2 to 7% of individuals with genetic conditions have a dual diagnosis on exome sequencing. Here we present a case series of individuals with dual diagnoses of more than one genetic disease using these tests.

METHODS

We performed a retrospective study of patients who had concurrent WES and CMA or WES only tests ordered between 2018 and 2022. Fifteen representative previously reported dual diagnosis cases were selected and met the following criteria: (1) WES and CMA each provided a diagnosis (2) WES and CMA both provided information to support dual diagnosis and (3) dual diagnosis via WES only.

RESULTS

In this cohort, 15 patients who had both tests received a dual diagnosis. Patient ages ranged from 6 days to 23 years old, and all but one case had multiple indications for testing (Figure 2). Among these, 6 cases (6/15, 40%) were ordered as stat cases. Indications included multiple congenital anomalies (MCA), complex congenital heart disease (CHD), intellectual disability/developmental delay (ID/DD), seizures, hypotonia, brain abnormalities, kidney abnormalities, dysmorphic features, psychiatric illnesses, skeletal abnormalities, failure to thrive (FTT), and intrauterine growth restriction (IUGR). The most common indication was intellectual disability and/or developmental delay (n=7) followed by dysmorphic features (n=6) (Figure 1). These dual diagnosis cases were divided into three categories. For most cases (n=10), WES and CMA provided distinct diagnoses where each test explained part of the phenotypes. In three cases, WES and CMA provided a unifying diagnosis where both results contributed to the patient's phenotype or had overlapping features. Two cases received a dual diagnosis by SNVs in WES only.

TABLE 1

Age/ Gender	Indication	WES Results	CMA Results	Disease Association
6 d.o F	Complex CHD, dysmorphic features, cystic hygroma	De novo pathogenic variant identified in the CHD7 gene	15q11.2 del	• Charge syndrome • 15q11.2 microdeletion syndrome
4 m.o M	Polyhydramnios, DD, motor delay, breathing/ swallowing difficulties, FTT, hypotonia, high arched palate	De novo pathogenic variant identified in the ACTA1 gene	15q11.2 del	• Nemaline myopathy Type 3 • 15q11.2 microdeletion syndrome
1 m.o M	Seizures, microcephaly, ID, DD, ataxia, aniridia, renal abnormalities, possible rhabdomyoma, genitourinary anomalies, encephalitis, skin hypopigmentation	De novo pathogenic variant identified in the TSC1 gene	11p14.2p13 del	• Tuberous sclerosis • WAGR syndrome
1 y.o M	Delayed speech and language development, motor delay, abnormality of the basal ganglia, ataxia, macrocephaly	• De novo Pathogenic variant in the MAPK8IP3 gene • De novo likely pathogenic variant in GABRB3 gene	n/a	• NDD with or without variable brain abnormalities • Developmental and epileptic encephalopathy Type 43
23 y.o F	Porphyria, DD, cleft lip and palate, psychiatric illness, increased serum iron, fatigue, abdominal pain	Pathogenic variant identified in the HFE gene	16p12.2 del	• Hemochromatosis • 16p12.2 microdeletion

Table 1: 5 out of 15 case details

FIGURE 1

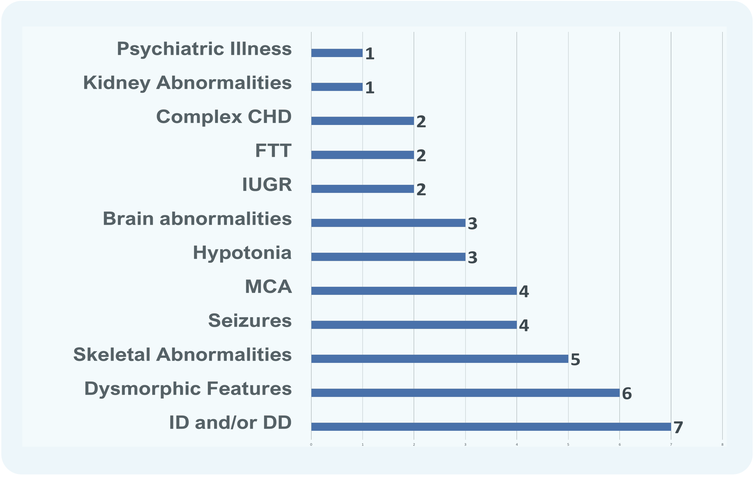

Figure 1: Indications for testing in Dual Diagnoses Cases (N=15)

FIGURE 2

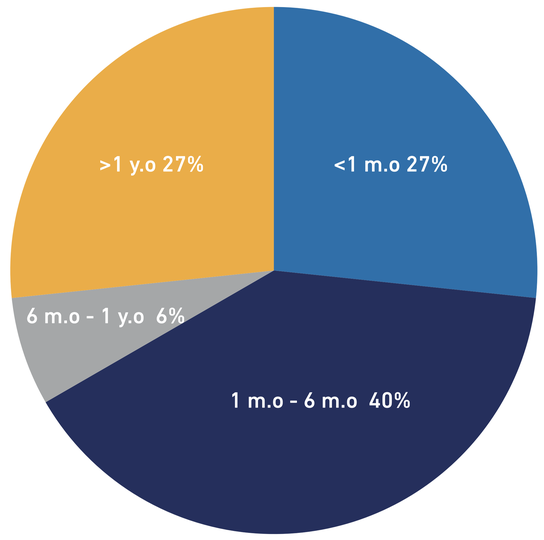

Figure 2: Age distribution of cases

FIGURE 3

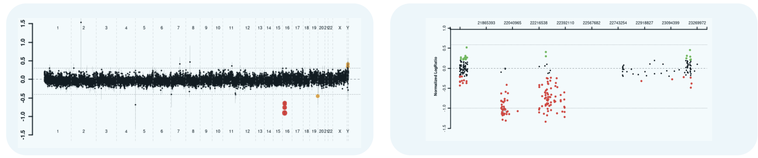

Figure 3: CMA Plot for 16p12.2 del case

CONCLUSIONS

The diagnostic odyssey for patients can be long and arduous. Patients with dual diagnoses are more likely to fall into this category, thus clinicians need diagnostic tools that efficiently and effectively provide diagnoses, especially in patients with unclear clinical presentations due to multiple underlying etiologies. Clinicians need a clear understanding of genetic testing technologies and how to capitalize on the advantages of these complementary tests. In this cohort we demonstrate the utility of performing exome sequencing and chromosomal microarray with the detection of 13/15 dual diagnoses being made by both exome sequencing and CMA. Whole exome sequencing and CMA, as well as whole genome sequencing, offer a comprehensive analysis of disease-causing single nucleotide variants and copy number changes.