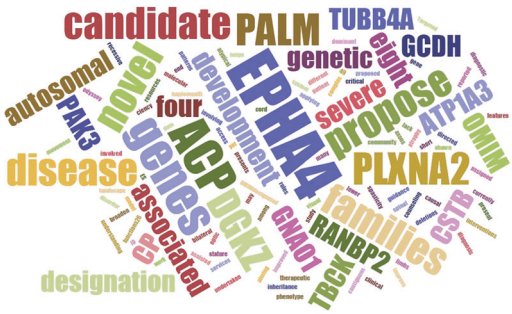
IN THIS ISSUE

Genome sequencing leads to targeted therapies in atypical cerebral palsy

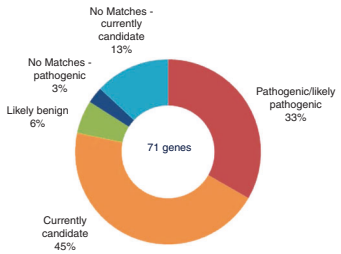
https://doi.org/10.1038/s41436-018-0376-y



Cerebral palsy (CP) is a group of permanent disorders that affect the development of movement and posture. The condition affects 0.2–0.3% of live births, making CP one of the most common neurological disorders to present in childhood. Oxygen deprivation leading to damage of the fetal or infant brain has been thought to be the primary etiology, but brain asphyxia only explains less than 10% of cases. In this issue, Matthews et al. report the diagnostic yield and impact on management of next-generation sequencing in individuals with atypical CP. The researchers recruited 50 children and adults with atypical CP from 49 families to participate in the study. Participants must have displayed impaired or lost motor function at birth or within the first year of life as well as one or more of the following: severe intellectual disability, progressive neurological deterioration, other abnormalities on neurological examination, multiorgan disease, congenital anomalies outside of the central nervous system, an abnormal neurotransmitter profile, family history, or brain imaging findings not typical for cerebral palsy. In addition, biochemical testing, neuroimaging, and chromosomal microarray by a neurologist and/or clinical geneticist did not identify an etiologic diagnosis. The researchers performed exome and genome sequencing and collected detailed clinical and biochemical information and family histories from hospital records. The analysis revealed a molecular diagnosis in a surprising 65% of families. In 57% of families, known disease genes were causative. In four cases, the investigation identified novel candidate genes (*DGKZ*, *EPHA4*, *PALM*, *PLXNA2*) that currently do not have an associated disease designation in the OMIM compendium. The analysis allowed many families in the study to move on from the diagnostic odyssey and led to improved genetic counseling. Additionally, eight families with eight different causal genes were able to undertake targeted therapeutic interventions as a result of the analysis, demonstrating the power of exome sequencing in diagnosis of atypical CP. —*V. L. Dengler, News Editor*

Data sharing via online matching tools helps identify novel disease genes

https://doi.org/10.1038/s41436-018-0383-z



Over the last ten years, exome sequencing (ES) has become a powerful means to identify the genetic root of heterogeneous conditions such as intellectual disability and multiple congenital anomalies. However, many results remain nonconclusive. Lack of connections between scientists and clinicians hinders the identification of cases with similar phenotypes and gene variants. In this issue, Bruel et al. report their experience using a free, online data exchange platform called GeneMatcher (http://www.genematcher.org) to identify novel disease-causing genes. GeneMatcher is one of seven data-sharing tools under the Matchmaker Exchange project (http://www.matchmakerexchange.org), a web-based platform developed for researchers and medical professionals to share genotype and phenotype data. The idea behind sharing tools is to connect professionals interested in the same phenotypes or gene variants. Variants in genes identified in a unique affected family require supporting evidence to prove pathogenicity. Documentation of recurrence of pathogenic variants in the same gene in unrelated affected cases is one method of proving pathogenicity. Approximately three to five affected cases with variants in the same gene are sufficient for proof of pathogenicity, but in many instances a novel variant is identified in a single individual. Matching those single cases with additional cases with similar phenotypes and variants in the same gene can be quite useful. In the new study, Bruel and colleagues identified 71 novel candidate genes via ES. Then they shared their findings on GeneMatcher. Sixty of the 71 candidate genes (84%) found matches through the online tool. The number of matches per gene ranged from 1 to 34. On average, the researchers found 4.2 matches per gene. The matches enabled the researchers to confirm that 23 of the 60 matched genes (39%) are disease causing. The platform also enabled the researchers to determine that 6 of the 60 matched genes (10%) are likely benign. Thirty-three percent of the matched candidate genes were novel genes implicated in rare diseases. Response times between data submission and first match varied from a few minutes to a few months, but the median time was 4 hours. The matches inspired international collaborations and will result in future publications on more than half of the matched genes (28/60, 51%). In the last four years, submissions to GeneMatcher have grown from 500 genes to more than 8000 as of January 2018. The number of submitters has increased as well. The authors conclude that as more scientists and clinicians know about and make use of the data-sharing tools, the chances of determining the molecular basis of rare phenotypes will improve. —*V. L. Dengler, News Editor*

Genetics in Medicine (2019) https://doi.org/10.1038/s41436-019-0574-2