Abstract

Phelan-McDermid Syndrome (PMS) is a rare genetic condition. Traditionally, PMS has been most commonly the result of a large deletion on the terminal end of chromosome 22 (including critical gene, SHANK3). It is not surprising, however, that as new testing technology becomes accessible to clinicians, the types of diagnostic variants being seen has evolved. There is a clear shift in the diagnosis of PMS, as more sequence variants in SHANK3 are found using next generation sequencing (NGS) panels and whole exome sequencing (WES). The use of sequencing has identified cases of PMS that would have otherwise been missed on chromosomal microarray. The diagnosis of patients with PMS using multiple forms of testing technology has forced deeper investigation into genotype-phenotype associations.

We utilized data from clinical questionnaires in the Phelan-McDermid Syndrome International Registry (PMSIR) to evaluate for potential phenotypic patterns related to chromosomal deletions versus SHANK3 variants. One of the most common features of PMS is lack of speech. Of the 197 patients with deletions and available data regarding their speech development, 48 (24.4%) are verbal. Of the 14 patients with pathogenic SHANK3 variants, 4 (28.6%) are verbal. Additional research is needed to further define the PMS phenotype based on genetic test results to compare differences between deletions and SHANK3 variants. As more individuals are diagnosed with PMS based on results from NGS panels and whole exome sequencing, we expect to be able to offer additional insight for phenotypic expectations.

Methods

The PMSIR contains three main surveys, each consisting of 100 questions: a clinical questionnaire, a developmental questionnaire, and an adult and adolescent questionnaire. Multiple searches were performed using the search and export function in the PMSIR. Registrants are asked to upload genetic reports to their entry when they enroll with the registry. These genetic reports are then reviewed by genetic counselors and a geneticist to curate the relevant genetic information into a master genetic file. This process serves two purposes:

1. to confirm the diagnosis of the patient in the registry

2. to provide genetic information to researchers using PMSIR data.

A search was performed to pull responses from all registrants that answered the relevant question related to speech (Figure 2). The question reviewed was “With PMS, some children develop understandable verbal speech while others do not. If the patient is over age 2, please choose the response that most closely matches your child’s abilities today.” The registrants that answered this question were then compared with the registrants that have genetic information available.

Results

The values pulled from the genetic file showed an average of 29 people per year, for the past ten years, being diagnosed with PMS based on 22q13.3 deletion (Figure 3). Beginning in 2012, an average of five people per year were found to have a sequence variant in SHANK3 that led to a diagnosis of PMS. One person in the registry was diagnosed with PMS from a sequence variant prior to 2012. These numbers do not include variants of unknown significance (VUS) and thus are likely an underestimation of PMS diagnosis due to SHANK3 variants. As more people are found to have sequence variants the VUSs could be reclassified. Currently there are three registrants that have a VUS; they were not included in this analysis as a PMS diagnosis cannot yet be confirmed.

In this study, we looked at speech as a phenotypic variable (Figure 4). Of the 197 patients with PMS with deletions and available data regarding their speech development, 48 (24.4%) of them are verbal. Of the 14 patients with PMS with pathogenic SHANK3 variants, 4 (28.6%) of them are verbal. Of note, 12 of the 14 registrants have frameshift variants within SHANK3.

Conclusions

As more patients are identified with pathogenic variants, it will be interesting to review the phenotype for PMS and the variability associated with the disorder. The percentages of verbal patients identified in this project look to be similar between those with deletions and those with sequence variants; however, due to the small number of patients with a sequence variant, it is difficult to predict whether a pattern will emerge. Though we chose to focus on speech development, other phenotypic features of PMS could be analyzed to see if genotype-phenotype trends exist.

As more sequence variants are identified additional research will be needed to further define the PMS phenotype. Comparing phenotypic data of patients with large deletions versus sequence variants could potentially provide additional information for the presentation of PMS.

As more individuals are diagnosed with PMS based on results from NGS panels and whole exome sequencing, we expect to be able to offer additional insight for phenotypic expectations. The data in the PMSIR will lead to potential research projects that could help define PMS and the variability based on genotype. Recent studies have suggested the possibility of modifier genes in the 22q13 region. This may add another layer of complexity to an already variable condition, emphasizing the need for future endeavors.

Reference