The Use of Karyotype Testing in the Diagnosis of Phelan-McDermid Syndrome: Prevalence and Implications

Brittany McLarney, MS, CGC; Emily Vandenboom, MS, CGC; Catherine Ziatz, MD

Abstract

Phelan-McDermid Syndrome (PMS) is a rare genetic condition caused by a deletion on chromosome 22 or a sequence variant in the SHANK3 gene. The majority of people with a diagnosis of PMS have a terminal deletion on chromosome 22. Most often these terminal deletions are identified by chromosomal microarray (CMA). This testing, however, does not identify structural changes such as a ring 22 chromosome. Identifying patients with PMS that have a r(22) is important as there is an increased risk for development of neurofibromatosis type 2 (NF2).

Data from the Phelan-McDermid Syndrome International Registry (PMSIR) was used to determine how many individuals need follow karyotype testing. Sixty-two percent (211/340) of patients with a terminal deletion found on CMA did not provide karyotype results to the PMSIR. There are 129 (38%) patients that provided a karyotype result, 42 (33%) of whom had a r(22) chromosome. Eighty-seven (67%) patients with a karyotype did not have a r(22) chromosome. The analysis performed here shows that r(22) chromosome may be more common than previously thought, reiterating the importance of karyotype testing for patients with a terminal deletion on chromosome 22.

Methods

Registrants of the Phelan-McDermid Syndrome International Registry (PMSIR) 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. Uploaded genetic reports were queried to identify the number of patients with PMS that had terminal deletions and karyotype testing performed as part of the diagnostic work-up. Consent for use of this data for research purposes was previously provided when participant signed up for the registry.

Results

A total of 442 patient genetic reports were collected and analyzed using the PMSIR. Patients with sequence variants, an unclear diagnosis of PMS, a result that would not require a karyotype (such as an interstitial deletion), or if results of the karyotype were unknown/unclear, were removed to leave a sample of 340 patients with a known terminal 22q13.3 deletion. Sixty-two percent (211/340) of patients with a terminal deletion did not provide karyotype results as part of their work-up for PMS (Figure 1). Of the 129 (38%) patients with a karyotype result, 42 (33%) had a r(22) chromosome. Eighty-seven (67%) patients with a karyotype did not have a r(22) chromosome (Figure 2).

Conclusions

As more patients continue to be diagnosed with PMS, and as technology continues to change, it is important to make sure genetic test results provide a complete diagnosis. The presence of a ring 22 chromosome is important to identify in individuals with PMS given the increased risk for development of NF2. In this study one third of patients reviewed had a diagnosis of a r(22) chromosome on karyotype testing, higher than previous reported estimates of 10-15%. Most patients in the PMSIR cohort did not provide karyotype reports, however, and further follow-up should clarify if this testing was considered. It is possible that the karyotype results were not abnormal and deemed unimportant to upload to the registry. This study draws attention to the underreporting of ring 22 in individuals with PMS and highlights the importance of karyotype testing in patients with a terminal 22q deletion to rule out this cytogenetic abnormality.

Key Points

- Karyotype testing should be pursued in patients with a terminal 22q deletion on microarray analysis to evaluate for presence of a ring chromosome.
- Patients with a ring 22 chromosome are at risk for NF2.
- Based on our review, presence of a ring 22 chromosome in the PMS population may be more common than previously thought.

Reference


Introduction

Phelan-McDermid syndrome (PMS) is a rare genetic condition caused by a deletion of genetic material on chromosome 22 or by a sequence variant in the SHANK3 gene. PMS is a neurodevelopmental disorder characterized clinically by varying degrees of intellectual disability, absent or delayed speech development, characteristic facies, and neonatal hypotonia.

Loss of 22q13.3 can be caused by terminal/interstitial deletions, mosaicism for loss of this region, balanced or unbalanced translocations, and ring 22 (r22) chromosomes. Decreased cost, increased sensitivity, and widespread availability of chromosomal microarray analysis has made this a first line test in diagnosis; however, without confirmatory karyotype testing, less common causes of PMS such as ring 22 (r22) chromosomes can be missed. Ring 22 chromosomes are a cytogenic abnormality caused by terminal deletion and fusion of the ends of the p and q arms of the chromosome. They are typically lost within a cell secondary to mitotic instability resulting in monoclonal chromosome 22. Identifying PMS patients with a r(22) is important as monosomy 22 results in loss of the tumor suppressor gene NF2, and thus increases the risk for development of neurofibromatosis type 2 (NF2).