Introduction

Deletions involving the chromosome 2p16p21 region are rare, with only six cases reported to date. Herein, we report the first case of a 0.8-Mb deletion at 2p16.3p21 detected with next-generation sequencing (NGS) that includes three Lynch syndrome genes: EPCAM, MSH2, and MSH6. This atypical case of Lynch syndrome due to a contiguous gene deletion was associated with syndromic features. NGS analysis resulted in the implementation of medical management and surveillance guidelines for both the patient and at-risk relatives.

Case

The patient, a 30-year-old Hispanic man who was 5’11” tall and weighed 333 pounds, had a history of developmental delay, cognitive impairment, and distinct physical features. An 8-mm papillomatous right ear lesion was resected by an otolaryngologist, and immunohistochemical analysis identified a sebaceous adenoma lacking MSH2 and MSH6 expression. After referral to a cancer genetics clinic, a Lynch syndrome NGS panel was requested. The results showed deletions of the entire coding sequence for EPCAM, MSH2, and MSH6, which suggested a contiguous gene deletion (Fig. 1).

The Lynch syndrome surveillance protocol (7) was initiated with a referral to a gastroenterologist for upper and lower endoscopies (results pending). The patient was also evaluated by clinical genetics providers, who noted mild macrocephaly and unique physical features (Fig. 2a).

The family history was significant for a brother and maternal uncle with similar appearances and intellectual disabilities who died of unspecified causes at 46 and 22 years of age, respectively (Fig. 2b). There was initial clinical suspicion of a possible chromosomal translocation due to a family history of multiple miscarriages and the similarly affected brother and maternal uncle with intellectual disabilities.

High-resolution karyotyping indicated 46,XY. Whole-genome single-nucleotide polymorphism microarray analysis identified a 0.8-Mb deletion at 2p16.3p21 including EPCAM, MSH2, and MSH6 in addition to C2orf61, CALM2, KCNK12, FBXO11, and other non-coding genes (Fig. 3).

Fig 2a. Patient photo. Signed photo consent was obtained from legal guardian.

Fig 2b. Patient pedigree.

The array results were as follows: ISCN: arr[hg19] 1p22.1(92,236,048-92,548,763)x3, 2p21p16.3(47,380,145-48,131,936)x1. Family studies are planned. The 0.75-Mb chromosome 1p duplication was classified as a variant of uncertain significance and contains 2 OMIM genes, TGFBR3 and BRD7.

Three OMIM genes were included in the 2p21p16.3 deletion: CALM2, KCNK12, FBXO11. The CALM2 gene is associated with established clinical manifestations—specifically, autosomal dominant catecholaminergic polymorphic ventricular tachycardia and long QT syndrome (2, 4). These are severe, early-onset conditions caused by missense mutations (2, 4). In the absence of any known cardiac symptoms in our adult patient, the clinical significance of this whole-gene CALM2 deletion is uncertain.


Fig 4. FISH probes and results for patient from a 2004 case report (2).

Four additional cases were reported in 2011, some of which carried deletions including MSH2 and MSH6 but were several megabases larger than that of our patient or were significantly smaller and involved only MSH6 (1, 5).

Conclusion

To our knowledge, this report is the first of a patient with a contiguous gene deletion at 2p16.3p21 containing EPCAM, MSH2, and MSH6 identified with NGS. No similar variants encompassing these three genes have been found in the ClinGen, DECIPHER, or DGV databases. Contiguous deletions spanning cancer genes are often associated with syndromic features such as cognitive impairment and congenital anomalies and present cancer risks due to the involvement of adjacent genes (3). We believe these associations explain the cognitive impairment and subtle physical differences in our patient.

This case spans several clinical areas, including clinical genetics, cancer genetics, otolaryngology, and gastroenterology, and illustrates the importance of a clinical genetics evaluation for patients with intellectual disabilities and physical findings. The patient’s workup used multiple genetic testing techniques that revealed findings relevant to clinical management, such as the initiation of surveillance protocols for hereditary cancer syndromes with potential implications for family members. This report demonstrates the clinical utility of NGS for identifying unique contiguous multi-gene events and guiding multidisciplinary care.

Literature Review

The first published case of a 2p16.2p21 deletion was described in 2003 in an infant with mild dysmorphic features, acquired microcephaly, nonspecific neuroimaging findings, atrial septal defect, and developmental delay. The deletion was identified through karyotyping and confirmed with whole-chromosome painting; therefore, the precise size and gene content are unknown (6).

A second case, published in 2004, was ascertained in a 37-year-old cognitively impaired woman with mild dysmorphic features, short stature, obesity, and hirsutism (3). Colonoscopy findings revealed a mucinous adenocarcinoma with microsatellite instability. Due to suspicion of a contiguous deletion involving a Lynch syndrome gene, multiplex ligation-dependent probe amplification was pursued with probes containing MLH1 and MSH2. The results indicated a deletion including MSH2, and confirmatory fluorescence in situ hybridization (FISH) suggested the absence of MSH6 and EPCAM, although the precise size of the deletion could not be determined (Fig. 4) (3).

References

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