Double take! Mosaic Li Fraumeni syndrome in Monozygotic Twins

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NGS has increased our ability to detect mosaicism in individuals undergoing multigene panel testing (MGPT). However it is exceedingly rare to identify mosaic mutations in twins, especially in genes associated with hereditary cancer syndromes. Here we report on monozygotic (MZ) twins found to have the same mosaic TP53 mutation. The proband, a female with a personal history of breast cancer diagnosed at age 34, was identified to carry a pathogenic TP53 mutation via full gene analysis. Her unaffected twin sister also tested positive for the mutation. NGS confirmed mosaicism in both twins, as the minor allele frequency (MAF) was lower than expected for a heterozygous carrier and below 40% in both. Sanger sequencing of the TP53 mutation with two independent primer sets also confirmed the presence of the mutation at lower than expected MAF in both twins. The presence of this mutation across multiple methodologies is most consistent with mosaic Li Fraumeni syndrome (LFS). Follow-up testing on a benign lymph node tissue specimen from the proband also demonstrated mosaicism. Identification of the TP53 mutation in multiple tissues suggests that the mosaicism resulted from a postzygotic mutational event early in development, prior to twinning. Another possibility is that a postzygotic TP53 mutation occurred in the proband, followed by the transfer of stem cells with the mutation through placental vascular anastomoses to the bone marrow of her sister. To our knowledge, this is the first report of classic mosaicism associated with LFS in a MZ twin pair. Studies have demonstrated that a significant proportion of TP53 mutations identified by MGPT display abnormal NGS metrics. The vast majority of results from ancillary testing from these cases are consistent with aberrant clonal expansion and the majority are likely due to clonal hematopoiesis of indeterminate potential. Despite the somatic origin for the majority of TP53 alterations with abnormal NGS metrics, this case highlights the importance of follow-up germline testing in MZ twins when mosaicism is found in a sibling.