A Unique Case of Male/Female Chimerism in Buccal Specimen Due to a Bone Marrow Transplant

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OVERVIEW
Over the past decade microarray technology has allowed the detection of chromosomal aberrations not routinely seen with standard analysis. However, it has also provided a better understanding of specimens from patients received in the laboratory. Here we describe a unique case of a 21 year old female with a clinical history of dysautonomia, cataracts, anxiety and short stature, and a history of acute lymphoblastic leukemia. Buccal swab was performed and sent in for SNP/CN microarray analysis which identified a sex chromosome mosaicism with 85% of cells with XX and ~15% of cells with XY suggestive of chimerism. Based on the sex chromosome findings and the unusual pattern allele tracks and homozygosity seen, this was believed to be due to a bone marrow transplant from a male sibling, which was subsequently confirmed by the referring physician. Interestingly, the array also identified a mosaic 12 Mb interstitial deletion of 15q14-q21.1. However, this deletion was only present in ~15% of the sample suggestive that the deletion is in the male transplant donor rather than in the proband. By report this sibling has learning disabilities, which to date does not have an underlying etiology, but may be associated with the deletion. Overlapping deletions of this 15q deletion have been reported with clinical features that include craniosynostosis, congenital heart defects, limb abnormalities, urinary abnormalities and bone maturation. In this complicated array there were also multiple chromosomes identified with regions of allele homoygosity totaling 41.1 Mb, suggesting a distant parental relationship or common decent. This case highlights the clinical utility of the SNP microarray analysis in allowing the correct delineation of complex findings. In this patient it clearly indicated the true nature of the chimerism prior to clinical information being available and it was able to indicate that the deletion appears to be in the donor rather than proband.

PROBAND HISTORY
21 year old female with a clinical history and reason for referral include dysautonomia, cataracts, anxiety and short stature, and a history of acute lymphoblastic leukemia at 6.5 years and a relapse 12 years of age. Patient was sent in for SNP microarray analysis on a buccal specimen (Images 1-3). The parents are reported to be 5th degree relatives. Siblings include a 27 year old male with developmental delay and learning difficulties and was the bone marrow transplant donor for proband. Additionally there is a sister with scoliosis and a brother with ADHD but reportedly normal cognition.

EVALUATION CRITERIA
• Copy numbers gains >500 kb and losses >200 kb, including one OMIM gene are reported in this analysis.
• Gains/losses of >25 Kb within clinically significant genes or regions.
• UPD testing is recommended for patient results demonstrating a long contiguous region of homozygosity (ROH) in a single chromosome of >20 Mb interstitially or >10 Mb telomERICally (15 and 8 Mb, respectively, for imprinted chromosomes).
• Contiguous homozygosity of >8 Mb within multiple chromosomes suggests common descent.
• A high level of allele homozygosity due to numerous short ROH (associated with a geographically or socially limited gene pool) is reported at the 99th percentile.

RESULTS AND CONCLUSION
• SNP microarray analysis on a buccal specimen received from proband showed sex chromosome mosaicism with ~85% of cells XX and ~15% of cells showing XY (Image 1-2). In addition, autosomal allele differentiation showed long stretches of three allele combinations, alternating with additional heterozygote combinations in the remainder of the genome (Image 3). The two findings are consistent with the history of a bone marrow transplant from the male sibling.
• Long stretches of allele homozygosity >8 Mb was also observed in multiple chromosomes which is consistent with common descent. Family history confirmed parents are 5th degree relatives.
• The mosaic deletion seen on buccal analysis, which was only seen in ~15% of the sample suggests that the deletion is more likely found in the male transplant donor.
• The a 12 Mb 15q14q21.1 mosaic deletion arr[hg19] 15q14q21.1(35,720,282-47,731,825)x1~2. seen in buccal analysis. Percentage mosaicism of 15q deletion is at ~15%. The mosaic deletion was not seen in the skin microarray analysis.

DISCUSSION
This case highlights the clinical utility of microarrays in identifying chimeric states in patients, even if the information is not initially provided. Furthermore, it highlights the importance of understanding that donor chimerism can be seen in buccal specimens from patients who receive allogenic transplant. Testing of other tissues such as skin may help in differentiating donor genotype from recipient.