Mosaic Genome-Wide Paternal Uniparental Disomy in an Individual without Features of Beckwith-Wiedemann Syndrome

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Mosaicism for a cell line with genome-wide uniparental disomy (GWUPD) has been reported in a number of individuals in the literature. The level of mosaicism varies between different tissue types including peripheral blood, skin fibroblasts and various other tissues. UPD is paternal in origin (GWpUPD) in most of the reported cases to date. While paternal UPD on chromosomes 6, 11, 14, 15 and 20 are associated with distinct clinical features, the majority of individuals with GWpUPD have features consistent with Beckwith-Wiedemann syndrome (BWS; UPD11), including macroglossia, hepatomegaly, hemihypertrophy and congenital hyperinsulinemic hypoglycemia. Features of other paternal UPD disorders have also been reported, including bell shaped thorax (UPD14) and developmental delay and seizures (UPD15). Tumors or masses are present in a majority of these individuals and are commonly of adrenal, renal and hepatic origin. We present here a 31 year old female whose medical history includes a hepatoma at 6 months of age, bilateral pheochromocytomas diagnosed at 15 and 17 years of age, a cardiac fibroma, multiple benign breast fibroadenomas, multiple juvenile colonic polyps and a pancreatic neuroendocrine tumor at age 31 detected by whole-body rapid sequence MRI. This individual previously failed testing for a hereditary cancer gene panel at another lab due to long stretches of homozygosity. We subsequently performed single-nucleotide polymorphism (SNP) chromosomal array analysis on peripheral blood and cultured skin fibroblasts, which identified GWUPD in the peripheral blood and an apparently heterozygous state in the fibroblasts. Short tandem repeat (STR) analysis detected primarily one allele in peripheral blood, along with a low level peak for a second allele consistent with mosaicism of approximately 7-10%. STR analysis in fibroblasts identified two alleles at an approximate 50% ratio each in fibroblasts, consistent with a heterozygous cell line. Additionally, STR analysis demonstrated the primary allele in the peripheral blood was paternally inherited and therefore consistent with GWpUPD. Both peripheral blood and fibroblasts were tested with a 49 cancer gene panel. No pathogenic mutations were found in any of the genes tested, which included a number of genes associated with juvenile polyps, pheochromocytoma and various other tumors. This individual met diagnostic criteria for juvenile polyposis, which has not been previously reported as a feature associated with mosaic GWpUPD. Further confirmation is needed to determine if juvenile polyposis is a feature of GWpUPD. This is the second reported case of bilateral pheochromocytomas in someone with GWpUPD, highlighting the need to include GWpUPD in the differential diagnosis of pheochromocytomas. Given the high rate and variety of tumors in GWpUPD cases, whole-body MRI should be considered as a screening modality in these individuals. Additionally, the case reported here has normal intelligence and no features of BWS or other paternal UPD disorders, demonstrating the

clinical variability associated with mosaic GWpUPD and that individuals with GWpUPD may be missed by current testing practices.