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Non-Pathological Paternal Isodisomy of Chromosome 2 Detected From a Genome-Wide SNP Scan

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TO THE EDITOR

Uniparental disomy (UPD) occurs when both homologs of a chromosomal pair come from the father (paternal UPD) or the mother (maternal UPD). Depending on the mechanism by which it arises [Engel, 2006; Robinson, 2000], it can lead to heterodisomy (where both homologous chromosomes from the same parent are present), isodisomy (where two copies of the same homologous chromosome from the same parent are present), or a mix of the two. UPD has been detected much more frequently for certain chromosomes (6, 7, 14, 15, 16) than for others (1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 13, 20, 21, 22, X), and it has yet to be observed for chromosomes 18 or 19 [Engel, 2006; Kotzot and Utermann, 2005]. While there may be real differences in the frequencies of UPD across the chromosomes, much of the frequency differences reported in the literature probably reflect differential ascertainment: UPD in certain chromosomes causes syndromes that are easily diagnosed.

Paternal isodisomy of chromosome 2 is comparatively rare in the literature [Kotzot and Utermann, 2005], and all previous cases of it have been found via genetic analyses of patients with diseases or phenotypes that suggested genetic abnormalities. Thompson et al. [2002] identified uniparental isodisomy in a 34-year-old otherwise healthy patient with retinitis pigmentosa who was homozygous for the MERTK mutation at 2q14.1. This patient was suspected of UPD because the father was heterozygous for the mutation but the mother was not a carrier [Thompson et al., 2002]. Similarly, Kantarci et al. [2008], Petit et al. [2005], and Chavez et al. [2000] discovered paternal isodisomy of chromosome 2 in follow-ups of cases of abnormal inheritance of Donnai–Barrow syndrome, Crigler–Najjar type I syndrome, and steroid 5-alpha-reductase 2 deficiency, respectively.

In the current report, we describe the first case of full paternal isodisomy of chromosome 2 from a population-based sample for which no clinical phenotype was apparent. The focal individual (Twin 1) was a dizygotic twin male. Phenotypic and genomic data for Twin 1, his co-twin sister, and both parents were collected as a part of a genome-wide association study (n = 461 twins plus siblings and 215 parents) on the Brisbane Adolescent Twin Sample (for details, see Wright and Martin, 2004). Genomic DNA was extracted from whole blood and genotyped on the Affymetrix® Human Mapping 50K Array Xba GeneChip. Informed consent was collected from participants and their parents, and all procedures and protocols were reviewed and approved by the QIMR Human Research Ethics Committee.

Both parents of Twin 1 self-reported their ethnicity as Samoan, which was supported by principal components analysis of the identity-by-state matrix from 50K autosomal SNPs. Despite repeated attempts, the mother of Twin 1 could not be contacted, and so information on pregnancy, birth, and childhood are not available. Twin 1 was 22 years of age at the time of a follow-up examination by a clinical geneticist. Other than a 2/3 toe syndactyly on one foot, Twin 1 was of normal appearance and had no other apparent physical abnormalities. His head circumference was 60.5 cm, and his height of 171 cm was normal for his family. His full-scale IQ assessed previously at age 16 by the Multi-dimensional Aptitude Battery was 95 (verbal IQ = 96 and performance IQ = 94), comparable to the IQ of his co-twin sister (88) but lower than the sample average of 112. He reported needing tutoring in junior school, but he successfully completed high school. He has basic

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reading and math skills, enjoys art and playing sports, and is currently employed at a manual labor job. There was no history of behavioral problems or significant medical problems. While we note that, given the information on Twin 1 available to us, we cannot rule out any pathology associated with the UPD, the degree of pathology must be minor enough to have escaped detection to date.

During routine genomic quality control procedures, Twin 1 came to our attention because virtually his entire chromosome 2 (5258 of 5274 SNPs) was homozygous; the 16 (0.3%) heterozygous calls were infrequent enough to be consistent with genotyping errors. This occurred for no other chromosome in the sample. The average homozygosity in a sliding 100 SNP window (about 5 Mb in length, or 2% of the chromosome), as well as the locations of all Mendelian errors for chromosomes 1 and 2 of Twin 1 and his co-twin are shown in Figure 1. In addition to the complete homozygosity on chromosome 2, Twin 1 had a Mendelian error of maternal origin at nearly every location where such an error was possible on chromosome 2, for a total of 734 maternal Mendelian errors of maternal origin and one of paternal origin. In comparison, Twin 2 did not show complete homozygosity and had only seven Mendelian errors (three of maternal and four of paternal origin) on

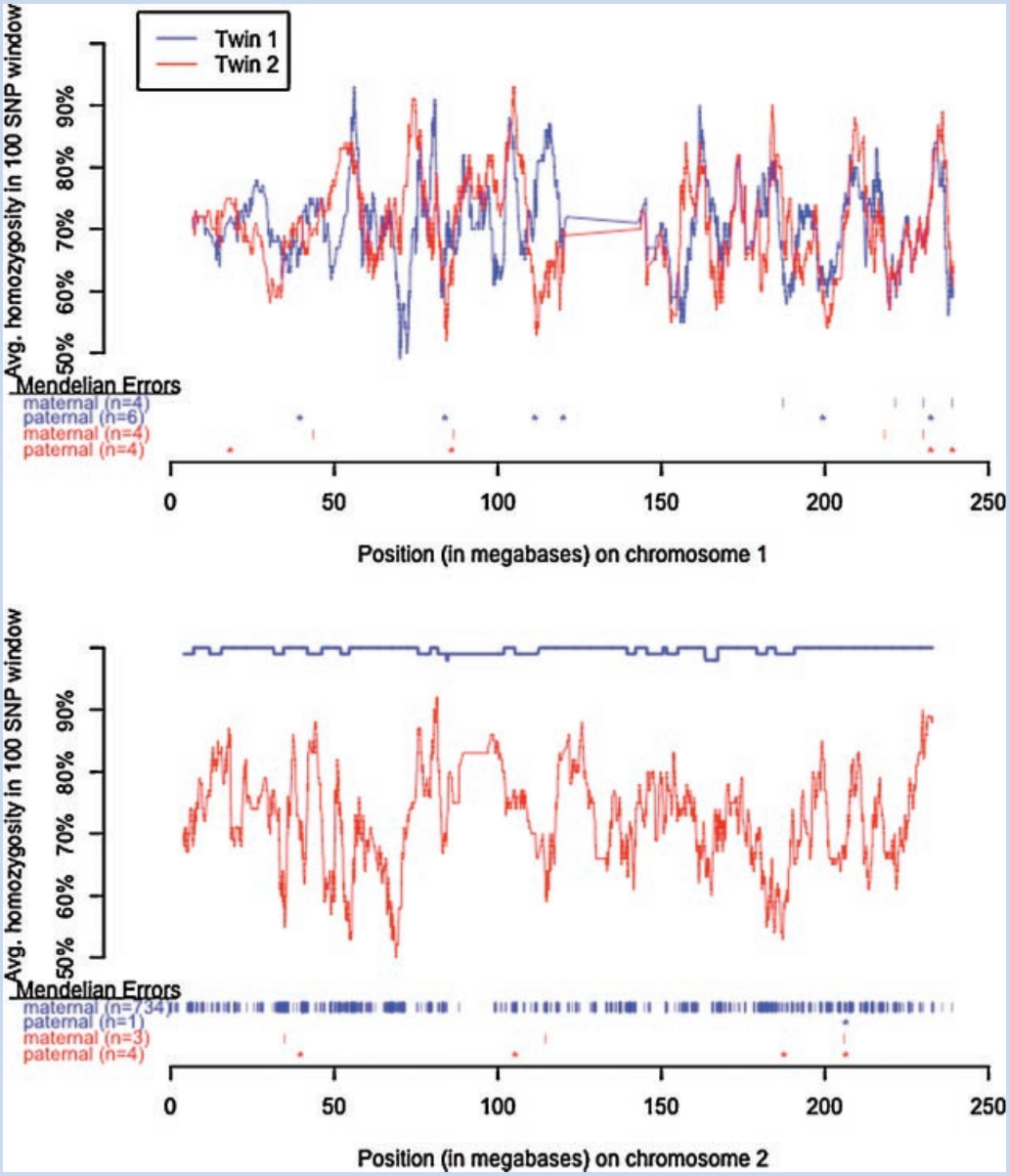

FIG. 1. The average homozygosity for the focal twin (blue) and his DZ co-twin (red) in a 100 SNP window sliding along chromosome 1 (top panel) and chromosome 2 (bottom panel). The locations of Mendelian errors are shown as hatch marks (maternal in origin) or asterisks (paternal in origin) below the homozygosity information. The average homozygosity for Twin 1 outside of chromosome 2 (74%) was similar to that of his co-twin (73%) and somewhat higher than the overall sample average homozygosity (71%).

chromosome 2. The homozygosity and locations of Mendelian errors for chromosome 1 shown at the top of Figure 1 (results were similar for the other 20 autosomes, not shown) demonstrate that the UPD is restricted to chromosome 2, and also rules out any potential sample mix up in the family or non-maternity of the mother of Twin 1. Inspection of the marker intensity data (results not shown), which appeared normal for all chromosomes of Twin 1, rules out a monosomy of chromosome 2. Last, the rate of missing calls for Twin 1 on chromosome 2 was 0.7%, which was low (20th percentile) compared to the missing calls on chromosome 2 in the rest of the sample. SNPs are called "missing" when the genotype calling algorithm cannot determine which allele an individual has at a given locus, and is symptomatic of poor data quality, duplications, or mosaicism [Ting et al., 2006]. Thus, the low level of missingness on chromosome 2 for Twin 1 and the very consistent signal of homozygosity across the chromosome argue against mosaicism for the isodisomy.

Excluding chromosome 2, the percent of the genome in homozygous runs (defined as 25+ homozygous SNPs in a row spanning at least 1 Mb in distance) for Twin 1 (9.6%) was similar to that of his co-twin (10.3%), but much higher than that typical in the full sample (mean = 4.5%, sd = 1%). At first glance, this might seem to indicate inbreeding. However, both parents of the twins themselves also had very high levels of homozygosity, with the father and mother having 11.0% and 11.1% of their genomes, respectively, in runs of homozygosity. Moreover, an unrelated South Sea Islander family also showed inflated (12.1–13.6%) percentages of the genome in homozygous runs. These observations suggest that the background levels of homozygosity observed outside of chromosome 2 in Twin1 and Twin 2 are unrelated to the paternal isodisomy or to inbreeding. Rather, the inflated homozygosity levels in the two South Sea Islander families are probably caused by reduced genetic diversity in South Sea Islander populations or to the use of SNPs that are uninformative (e.g., low minor allele frequencies) in such populations.

Robinson [2000] discussed four mechanisms by which UPD arises. The complete homozygosity of chromosome 2 in the present case implies isodisomy and, therefore, makes the gametic complementation and trisomic rescue mechanisms unlikely, both of which should lead to some level of heterodisomy and heterozygosity [Robinson, 2000]. Furthermore, the normal levels of missingness for chromosome 2 in Twin 1 weigh against a somatic recombination event, which should lead to various levels of mosaicism for the isodisomy [Robinson, 2000]. Instead, we believe that the present observation of paternal isodisomy is most consistent with monosomic rescue, such that a normal paternal gamete paired with a maternal gamete nullisomic (or otherwise abnormal) for chromosome 2, leading to replication of the paternal homolog and, therefore, to paternal isodisomy of the full chromosome [Robinson, 2000].

Several cases of UPD in twins have been documented before, mostly for monozygotic twins discordant for a syndrome suggestive of UPD (e.g., Beckwith–Wiedemann syndrome) [Kotzot and Utermann, 2005]. In such cases, an early somatic recombination event is the likely cause, and some degree of mosaicism for the UPD is typically observed. Nevertheless, twins are not expected to be at increased risk for UPD, and our results do not suggest otherwise.

In addition to being the first demonstration of full paternal isodisomy of chromosome 2 for which no clinical phenotype was apparent, this case is only the fourth UPD case discovered using genomewide marker data (previous reports include Abecasis et al., 2004; Field et al., 1998; Xiao et al., 2006). Because UPD cases where no clinical phenotype is evident must usually go undetected, population-based genomewide data offer a clearer way of inferring both the frequency and typical clinical significance of UPD than studies based on clinical samples. Our results raise the possibility that many cases of UPD fail to generate notice because of the lack of any obvious phenotypic manifestations. The present observation of one case of UPD from among 676 subjects, along with the three previous serendipitous population-based findings of UPD, may also suggest that the frequency of UPD is higher than previously thought (the base-rate of UPD has been crudely estimated to be around 1/5000 births; Robinson, 2000).

Our results also highlight the potential for using dense SNP chips for detecting UPD rather than relying on the more traditional approach of using microsatellite data. Most modern SNP chips (with >10K SNPs) are more dense and, despite being much less polymorphic than microsattelites, have much greater informational content than microsatellite panels (e.g., Tayo et al., 2005). Bruce et al. [2005] demonstrated that using SNP information in the way we have done here results in very high power for detection of UPD and its breakpoints.

Unfortunately, routine data cleaning procedures in genomewide association studies, which include removing "bad samples" with high homozygosity and high Mendelian error rates, are likely to lead to missed opportunities to document UPD in many population-based genomewide datasets. The present results suggest the need for researchers using genomewide data to follow up on putative bad samples in order to check whether there is spatial clustering of homozygosity and (if available) Mendelian errors, both of which are diagnostic of UPD. Analyses of large population-based, genomewide datasets—many of which are now publicly available (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap)—should allow a much clearer understanding of the frequency and typical clinical significance of this fascinating non-Mendelian mechanism of inheritance.

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