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Maternal Uniparental Disomy of Chromosome 15 and Concomitant *STRC* and *CATSPER2* Deletion-Mediated Deafness-Infertility Syndrome

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TO THE EDITOR

First described in 1956, Prader-Willi syndrome (PWS; MIM 176270) is one of the most illustrative disorders in the field of human genetics due to its characteristic clinical phenotype and unique parent of origin molecular etiology [Gunay-Aygun, et al. 2001]. The majority of PWS cases (~70%) are due to paternal deletion of chromosome 15q11-q13 [Ledbetter, et al. 1981], and ~25% of cases result from maternal uniparental disomy (UPD) of chromosome 15 that originate from a meiosis I (MI) or meiosis II (MII) non-disjunction (NDJ) error with subsequent trisomy rescue [Cassidy, et al. 1992; Mascari, et al. 1992; Nicholls, et al. 1989]. The MI NDJ is more common due to maternal age effect [Matsubara, et al. 2011], yet both MI and MII NDJ result in an increased risk for recessive conditions due to large regions of absence of heterozygosity (AOH) that are hallmark features of most UPD. Paternal deletion of 15q11-q13 is detectable by fluorescence *in situ* hybridization (FISH) and chromosomal microarray (CMA) analysis; however, the maternal UPD of chromosome 15 can also be identified by single nucleotide polymorphism (SNP)-based CMA platforms, which detect AOH in addition to copy number aberrations [Butler, et al. 2008; Papenhausen, et al. 2011]. We report a unique case of PWS due to maternal UPD, which also resulted in a recessive hearing loss syndrome due to biallelic inheritance of a heterozygous deletion from the transmitted maternal chromosome 15.

Our patient presented as a 4-week old male born to non-consanguineous parents. The prenatal course included a positive first trimester screen with an age-related risk for trisomy

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21 of 1 in 43, a nuchal translucency of 1.35 multiples of the median (MOM), PAPP-A of 1.04 MOM, and hCG of 1.87 MOM. Noninvasive prenatal screening (NIPS; MaterniT21 PLUS) was negative for trisomies 13, 16, 18, 21 and 22, as well as for the 1p36, Wolf-Hirschhorn (4p), Cri-du Chat (5p), Langer Giedion (8q), Jacobsen (11q), Prader-Willi/Angelman (PWS/AS; 15q), and 22q11.2 microdeletion syndromes. Chorionic villus sampling and amniocentesis were declined.

The proband was born at 40+4 weeks gestation via elective repeat Cesarean section; Apgars were 9 and 9, birth weight was 3240 g, birth length was 49 cm and head circumference was 36.5 cm, all within normal limits. He had normal suck/swallow at birth but diffuse hypotonia with a weak cry, and was admitted to the NICU for poor feeding, chronic hypoxemia, and hypoglycemia (blood glucose 37–39). Bilateral undescended testes were noted. Head ultrasound showed a subependimal cyst on the left frontal horn, followed by a normal MRI. Echocardiography showed no evidence of congenital heart disease. The child failed the Auditory Brain Response (ABR) hearing screen twice.

Although high resolution peripheral blood G-banded chromosome analysis revealed a normal 46, XY karyotype, clinical CMA analysis using the SurePrint G3 ISCA CGH+SNP 4×180K array (Agilent Technologies, Santa Clara, CA) identified two large regions of AOH spanning 37.7 Mb on 15q11.2-q22.2 and 8.5 Mb on 15q26.1-q26.3 (Fig. 1A), which was highly suggestive of UPD for chromosome 15. Of note, CMA testing is not an independent diagnostic test for UPD due to its inability to detect heterodisomic UPD that does not harbor any AOH. FISH performed on metaphase chromosomes using locus specific probe *SNRPN* (15q11-q13) was normal for two copies of the PWS/AS region (Fig. 1B). However, clinical methylation-sensitive multiplex ligation-dependent probe amplification (MLPA) using the SALSA MLPA ME028 Prader Willi/Angelman probemix (MRC Holland, the Netherlands) demonstrated an abnormal methylation pattern consistent with absence of the paternally derived PWS/AS critical region, which together confirmed the diagnosis of PWS by maternal UPD in the proband. DNA from the proband was also subjected to CMA testing using the CytoScan® HD platform (Affymetrix, Santa Clara, CA). Both CMA platforms detected the two large regions of AOH in the heterodisomic UPD chromosome 15 (Fig. 1A), and given that the pericentromeric region was homozygous in the proband, the maternal NDJ was attributed to a MII error [Papenhausen, et al. 2011].

In addition to the two regions of AOH on chromosome 15, clinical CMA testing also detected a homozygous 55.7 kb deletion (minimum size) of chromosome 15q15.3 located within the 15q11.2-q22.2 region of AOH, which included the *STRC* (exons 1–22) and *CATSPER2* genes. The maximum size of the deletion was 169.6 kb based on neighboring CMA probes (Fig. 1C). Given that biallelic contiguous deletions of *STRC* and *CATSPER2* are a known cause of deafness-infertility syndrome (MIM 611102), the identified homozygous deletion was also considered pathogenic in the proband. This homozygous deletion was subsequently determined to be maternally inherited by CMA testing (Fig. 1C); however, as expected, the 15q15.3 deletion was heterozygous in the mother but transmitted to the proband in both chromosome 15 homologs. The interstitial block of heterozygosity on chromosome 15 identified in the proband by CMA testing was a consequence of maternal

meiotic recombination prior to the MII NDJ and subsequent trisomy rescue after fertilization. The molecular karyotype was reported as:

upd(15)mat.arr[hg19] 15q11.2q22.2(23952738_61658913)x2

hmz,15q15.3(43895633_43951301)x0

mat,15q26.1q26.3(93895094_102398213)x2 hmz.

The *STRC* gene is a major contributor to prelingual hearing loss, as it encodes the large extracellular structural protein stereocilin, which is expressed in the inner ear. Stereocilin anchors the tectorial membrane of the organ of Corti cell structures within the cochlea, and both sequence mutations and deletions of *STRC* can result in autosomal recessive hearing loss (with or without male infertility depending on whether *CATSPER2* is also deleted) [Zhang, et al. 2007]. Notably, *STRC* is challenging to interrogate by most molecular assays as it shares >99% sequence homology with its distal pseudogene, which typically results in low resolution probe spacing for copy number assays [Khan, et al. 2011; Vona, et al. 2015]. The tandem ~100 kb segmental duplications that encompass *STRC*, *CATSPER2* and their pseudogenes, are responsible for the non-allelic homologous recombination-mediated copy number aberrations (deletions and duplications) that are common to this region. As such, lower resolution CMA platforms may not accurately detect *STRC* and *CATSPER2* deletions due to the paucity of unique probes throughout the region, prompting multi-gene hearing loss panels to frequently employ targeted droplet digital PCR for copy number assessment and/or gene sequencing for mutation detection.

UPD was first identified in humans in 1988 when a child was found to have cystic fibrosis due to an isodisomic maternal UPD chromosome 7, which unmasked a heterozygous maternal *CFTR* mutation [Spence, et al. 1988]. Although not all chromosomes have an imprinting-based UPD phenotype, the increased risk for recessive disease associated with UPD has resulted in the discovery of recessive disease genes and/or mutations as well as previously unrecognized UPD chromosomes. Recent examples include UPD chromosome 3 and GM1 gangliosidosis [King, et al. 2014], UPD chromosome 6 and cone dysfunction [Roosing, et al. 2013], UPD chromosome 8 and congenital adrenal hyperplasia [Matsubara, et al. 2014], UPD chromosome 11 and sickle cell disease [Swensen, et al. 2010], UPD chromosome 12 and sulfite oxidase deficiency [Cho, et al. 2013], UPD chromosome 12 and hereditary 1,25-hydroxyvitamin D-resistant rickets [Tamura, et al. 2015], and UPD chromosome 14 and alpha 1 antitrypsin deficiency [Laverdure, et al. 2014].

Our proband adds to these reported cases of an unmasked autosomal recessive disorder due to UPD; however, our case is unique in that it harbors the unfortunate outcome of being affected by both a classic imprinting disorder, PWS (MIM 176270), and a coexisting autosomal recessive disease, deafness-infertility syndrome (MIM 611102), which was transmitted through the maternal UPD chromosome 15. Importantly, given the variable age of onset of *STRC*-mediated deafness and the coexisting PWS symptoms, this second diagnosis may not have been determined until much later. As such, this case also highlights how the increasing resolution of microarray and high-throughput sequencing technologies will not just identify new Mendelian disease genes and disorders, but also can enable

neonatal identification of co-existing genetic diseases that otherwise may not have been detected until later in life.

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References

Butler MG, Fischer W, Kibiryeva N, Bittel DC. Array comparative genomic hybridization (aCGH) analysis in Prader-Willi syndrome. Am J Med Genet A. 2008; 146A(7):854–860. [PubMed: 18266248]

Cassidy SB, Lai LW, Erickson RP, Magnuson L, Thomas E, Gendron R, Herrmann J. Trisomy 15 with loss of the paternal 15 as a cause of Prader-Willi syndrome due to maternal disomy. Am J Hum Genet. 1992; 51(4):701–708. [PubMed: 1357962]

Cho SY, Goh DL, Lau KC, Ong HT, Lam CW. Microarray analysis unmasked paternal uniparental disomy of chromosome 12 in a patient with isolated sulfite oxidase deficiency. Clin Chim Acta. 2013; 426:13–17. [PubMed: 23994568]

Gunay-Aygun M, Schwartz S, Heeger S, O'Riordan MA, Cassidy SB. The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. Pediatrics. 2001; 108(5):E92. [PubMed: 11694676]

Khan WA, Knoll JH, Rogan PK. Context-based FISH localization of genomic rearrangements within chromosome 15q11.2q13 duplicons. Mol Cytogenet. 2011; 4(1):15. [PubMed: 21824424]

King JE, Dexter A, Gadi I, Zvereff V, Martin M, Bloom M, Vanderver A, Pizzino A, Schmidt JL. Maternal uniparental isodisomy causing autosomal recessive GM1 gangliosidosis: a clinical report. J Genet Couns. 2014; 23(5):734–741. [PubMed: 24777551]

Laverdure N, Dabadie A, Alex-Cordier MP, Odent S, Lachaux A. Maternal uniparental disomy 14 revealed by alpha 1 antitrypsin deficiency. Clin Res Hepatol Gastroenterol. 2014; 38(5):604–606. [PubMed: 24636467]

Ledbetter DH, Riccardi VM, Airhart SD, Strobel RJ, Keenan BS, Crawford JD. Deletions of chromosome 15 as a cause of the Prader-Willi syndrome. N Engl J Med. 1981; 304(6):325–329. [PubMed: 7442771]

Mascari MJ, Gottlieb W, Rogan PK, Butler MG, Waller DA, Armour JA, Jeffreys AJ, Ladda RL, Nicholls RD. The frequency of uniparental disomy in Prader-Willi syndrome. Implications for molecular diagnosis. N Engl J Med. 1992; 326(24):1599–1607. [PubMed: 1584261]

Matsubara K, Kataoka N, Ogita S, Sano S, Ogata T, Fukami M, Katsumata N. Uniparental disomy of chromosome 8 leading to homozygosity of a CYP11B1 mutation in a patient with congenital adrenal hyperplasia: implication for a rare etiology of an autosomal recessive disorder. Endocr J. 2014; 61(6):629–633. [PubMed: 24621779]

Matsubara K, Murakami N, Nagai T, Ogata T. Maternal age effect on the development of Prader-Willi syndrome resulting from upd(15)mat through meiosis 1 errors. J Hum Genet. 2011; 56(8):566–571. [PubMed: 21633360]

Nicholls RD, Knoll JH, Butler MG, Karam S, Lalande M. Genetic imprinting suggested by maternal heterodisomy in nondeletion Prader-Willi syndrome. Nature. 1989; 342(6247):281–285. [PubMed: 2812027]

Papenhausen P, Schwartz S, Risheg H, Keitges E, Gadi I, Burnside RD, Jaswaney V, Pappas J, Pasion R, Friedman K, Tepperberg J. UPD detection using homozygosity profiling with a SNP genotyping microarray. Am J Med Genet A. 2011; 155A(4):757–768. [PubMed: 21594998]

Roosing S, van den Born LI, Hoyng CB, Thiadens AA, de Baere E, Collin RW, Koenekoop RK, Leroy BP, van Moll-Ramirez N, Venselaar H, Riemslag FC, Cremers FP, Klaver CC, den Hollander AI. Maternal uniparental isodisomy of chromosome 6 reveals a TULP1 mutation as a novel cause of cone dysfunction. Ophthalmology. 2013; 120(6):1239–1246. [PubMed: 23499059]

Spence JE, Perciaccante RG, Greig GM, Willard HF, Ledbetter DH, Hejtmancik JF, Pollack MS, O'Brien WE, Beaudet AL. Uniparental disomy as a mechanism for human genetic disease. Am J Hum Genet. 1988; 42(2):217–226. [PubMed: 2893543]

Swensen JJ, Agarwal AM, Esquilin JM, Swierczek S, Perumbeti A, Hussey D, Lee M, Joiner CH, Pont-Kingdon G, Lyon E, Prchal JT. Sickle cell disease resulting from uniparental disomy in a child who inherited sickle cell trait. Blood. 2010; 116(15):2822–2825. [PubMed: 20595515]

Tamura M, Isojima T, Kawashima M, Yoshida H, Yamamoto K, Kitaoka T, Namba N, Oka A, Ozono K, Tokunaga K, Kitanaka S. Detection of Hereditary 1,25-Hydroxyvitamin D-Resistant Rickets Caused by Uniparental Disomy of Chromosome 12 Using Genome-Wide Single Nucleotide Polymorphism Array. PLoS One. 2015; 10(7):e0131157. [PubMed: 26153892]

Vona B, Hofrichter MA, Neuner C, Schroder J, Gehrig A, Hennermann JB, Kraus F, Shehata-Dieler W, Klopocki E, Nanda I, Haaf T. DFNB16 is a frequent cause of congenital hearing impairment: implementation of STRC mutation analysis in routine diagnostics. Clin Genet. 2015; 87(1):49–55. [PubMed: 26011646]

Zhang Y, Malekpour M, Al-Madani N, Kahrizi K, Zanganeh M, Lohr NJ, Mohseni M, Mojahedi F, Daneshi A, Najmabadi H, Smith RJ. Sensorineural deafness and male infertility: a contiguous gene deletion syndrome. J Med Genet. 2007; 44(4):233–240. [PubMed: 17098888]

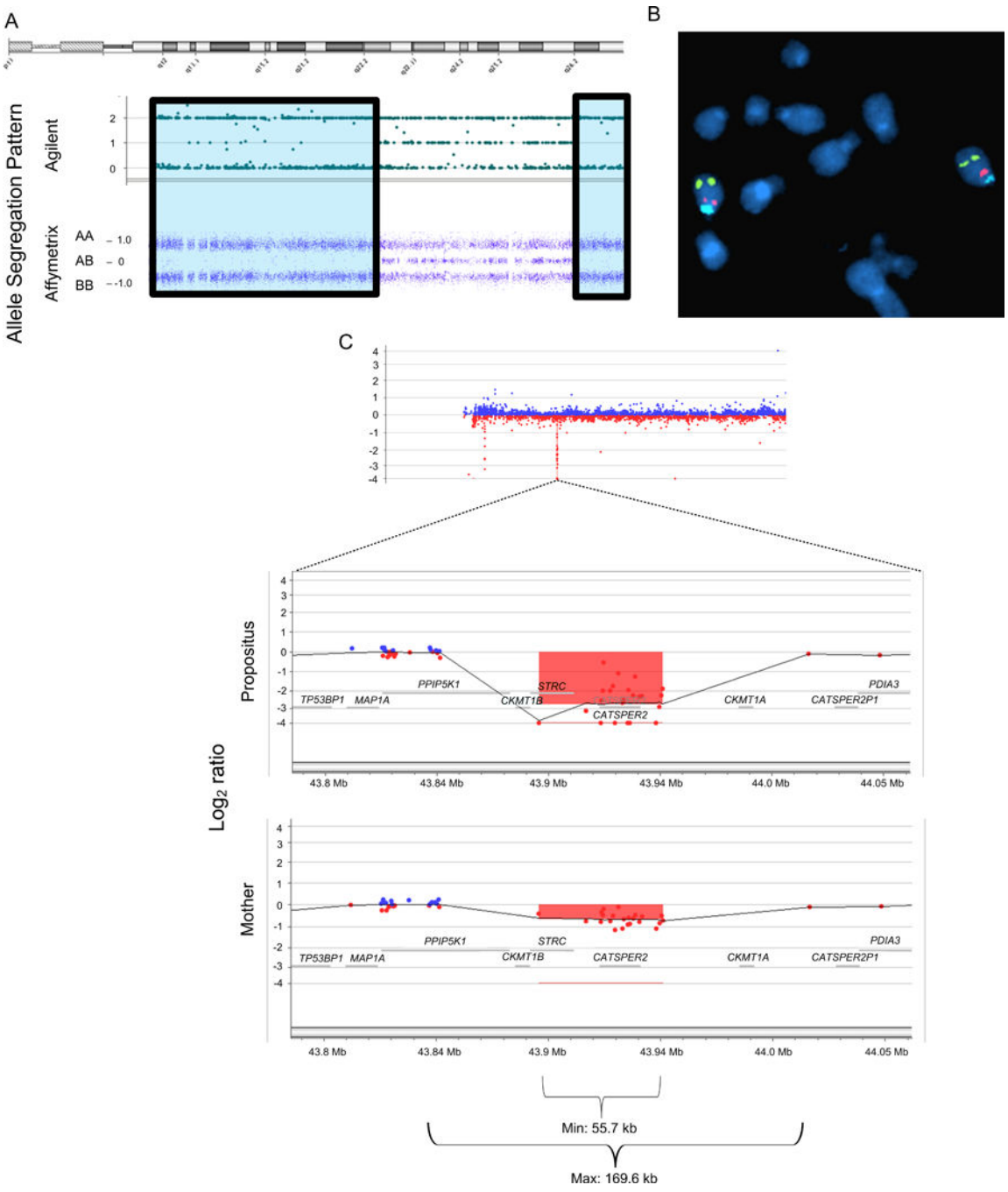

Figure 1.

(**A**) Chromosomal microarray (CMA) analysis of the proband showing absence of heterozygosity (AOH; shaded) on 15q11.2-q22.2 and 15q26.1-q26.3 using both the Agilent (top panel) and Affymetrix (bottom panel) CMA platforms. (**B**) Metaphase FISH using the locus specific probe *SNRPN* (red), co-hybridized with control probes at 15p11.2 (D15Z1; aqua) and 15q22 (*PML*; green), indicating a normal two copy hybridization pattern at the PWS/AS critical region on chromosome 15q11.2. (**C**) Enlarged view of the homozygous

STRC and *CATSPER2* deletion at 15q15.3 by CMA analysis (Agilent) in the proband (top panel) and the transmitted heterozygous maternal deletion (bottom panel).