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BRIEF REPORT

Multiple tumors due to mosaic genome-wide paternal uniparental disomy

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Abstract

Mosaic genome-wide paternal uniparental disomy is an infrequently described disorder in which affected individuals have signs and symptoms that may resemble Beckwith–Wiedemann syndrome. In addition, they can develop multiple benign and malignant tumors throughout life. Routine molecular diagnostics may not detect the (characteristic) low level of mosaicism, and the diagnosis is likely to be missed. Genetic counseling and a life-long alertness for the development of tumors is indicated. We describe the long diagnostic process of a patient who already had a tumor at birth and developed multiple tumors in childhood and adulthood. Furthermore, we offer clues to recognize the entity.

KEYWORDS

body asymmetry, paternal uniparental disomy, syndrome, tumors

1 | INTRODUCTION

Uniparental disomy (UPD) occurs when the two copies of a (part of a) chromosome are derived from one parent only. If this chromosome contains imprinted gene(s), this can result in human disease due to loss of gene function and can lead to congenital anomalies, intellectual disability, and other health problems.¹

If both copies of (a part of) a chromosome are derived from the father, this is called paternal UPD (patUPD). Five syndromes are associated with patUPD: transient neonatal diabetes mellitus (patUDD6), Beckwith–Wiedemann syndrome (BWS) (patUPD11), Kagami–Ogata

syndrome (patUPD14), Angelman syndrome (patUPD15), and patUPD20.²

PatUPD of the whole genome is lethal in utero, as it presents as hydatidiform mole.³ If UPD of the whole genome is present in a mosaic state, it can be compatible with life. In 1995, mosaic genome-wide paternal UPD (MGWpatUPD) was first described in a patient with BWS and a Wilms tumor.⁴ Since then, 17 additional cases have been described (Table 1).^{3,5–17}

Here, we describe a female with multiple benign and malignant tumors, occurring at various ages, in whom eventually MGWpatUPD was diagnosed. We compare the findings in this

Abbreviations: BAF, B-allele frequency; BWS, Beckwith–Wiedemann syndrome; GOM, gain of methylation; IC, imprinting center; LOM, loss of methylation; MGWpatUPD, mosaic genome-wide paternal uniparental disomy; MS-MLPA, methylation-specific multiplex ligation-dependent probe amplification; SNP, single-nucleotide polymorphism; UPD, uniparental disomy.

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TABLE 1 Overview and characteristics of patients with MGWpatUPD in the literature

This report	Hopman ¹⁷ 2016		Darcy ¹⁶ 2015		Bertoin ¹⁵ 2015		Ohtsuka ¹⁴ 2014		Kalish ¹³ 2013		Kalish ¹³ 2013		Gogiel ³ 2013		Johnson ¹² 2013		Feigenberg ¹¹ 2012		Yamazawa ¹⁰ 2011		Romanelli ⁹ 2011		Wilson ⁸ 2008		Wilson ⁸ 2008		Reed ⁷ 2008		Giurgea ⁶ 2006		Bryke ⁵ 2004		Hoban ⁴ 1995									
	†39	2	0.5	21	23	7	20	6	†0.3	†0.08	13.3	18	†30	21	14	2.2	4	4	10.8	4																						
Age at last report (years)	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F							
Sex	MS-MLPA, SNP array B: <5%	SNP array B: >95%	SNP array B: 50–60	SNP array B: ND, FI: 12%	SNP array B: 91%, P: 83%	SNP array B: 30%, FI: 30%, S: 10%	STRa B: 44%–88%, FI: 0%	SNP array B: 85%, P: 90%	SNP array B: 10%, P: 85%	SNP array B: 64%	SNP array B: 91%, T: 70%	MS-MLPA, MS-SNuPE	SNP array B: 85%, S: 64%, U: 79%	SNP array B: >90%, FI: <10%	SNP array B: 17%	MS-PCR B: ND	SNP array B: >90%, FI: <10%	SNP array B: 17%	MS-PCR B: ND	MSa STRa B: +, S: 0%, P: 100%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%	MSa STRa B: +, S: 0%							
Analysis (% GWpatUPD)	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Tumors (see Table 2)	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
patUPD6 symptoms																																										
TNDM																																										
patUPD11 symptoms BWS																																										
Prematurity (< 37 weeks)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Macrosomia (< P90)	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
PMD	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Macroglossia	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Ventral wall defects	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Body asymmetry	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Visceromegaly	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hyperinsulinism or transient hypoglycemia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Ear abnormalities ^d	-	+	-	-	-	-	+	+	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
patUPD14 symptoms Kagami-Ogata syndrome																																										
Skeletal abnormalities ^e		-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

(Continues)

TABLE 1 (Continued)

	This report 2016	Hopman ¹⁷ 2015	Darcy ¹⁶ 2015	Bertoin ¹⁵ 2015	Ohtsuka ¹⁴ 2014	Kalish ¹³ 2013	Kalish ¹³ 2013	Kalish ¹³ 2013	Gogiel ³ 2013	Johnson ¹² 2013	Feigenberg ¹¹ 2012	Yamazawa ¹⁰ 2011	Romanelli ⁹ 2011	Wilson ⁸ 2008	Wilson ⁸ 2008	Reed ⁷ 2008	Giurgea ⁶ 2006	Bryke ⁵ 2004	Hoban ⁴ 1995
											Inbar-								
PMD	+										+	+							
Ventral wall defects	-	+	+	+	+	+	+	+	+	+	+	+							
Developmental delay	-	-	-	-	-	-	-	-	-	-	+	-	+	±	+	±	±	±	+
patUPD15 symptoms																			
Angelman syndrome																			
Developmental delay	-	-	-	-	-	-	-	-	-	-	+	-	+	±	+	±	±	±	+
Happy demeanor ^f	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Seizures	-	-	-	-	-	-	-	-	-	-	-	± ^g	+	-	-	-	± ^g	-	+
Speech impairment	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	+
Gait ataxia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
patUPD20 symptoms																			
PHP-1b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Macrosomia (< P90)	-	-	+	+	+	+	- (P85)	- (P75)	+	- (P50)	+	+	+	+	+	+	+	-	-
Nephrocalcinosis	-	-	±	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-
Adrenal hyperplasia	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+
Other features	UTIs	T21, ht, cd, hp	T21, ht, cd, hp	AR cu, nb	RDS, nb, ASD	PS	hk	UAO	nb	ht, ks	ht, CRI, HEP, CMM, AK with ESRD	ht, CH							

Abbreviations: AK with ESRD, atrophic kidney with end-stage renal disease; AR cu, autosomal recessive cystinuria; ASD, atrium septal defect; B, blood; BWS, Beckwith–Wiedemann syndrome; cd, clinodactyly; CH, capillary hemangioma; CMM, cardiac myectomy; CRI, chronic respiratory insufficiency; F, female; Fi, fibroblasts; HEP, hypertensive encephalopathy; hk, hyperkalemia; hp, hyperpigmentation; ht, hypotonia; ks, kidney stones; MSa, microsatellite analysis; MS-MLPA, methylation-specific multiplex-ligation-dependent probe amplification assay; MS-PCR, methylation-specific polymerase chain reaction amplification; MS-SNUPE, single-nucleotide primer extension; nb, not detected; P, pancreas; patUPD, paternal uniparental disomy; PHP-1b, pseudohypoparathyroidism type 1b; PMD, placental mesenchymal dysplasia; PS, pulmonary stenosis; RDS, respiratory distress syndrome; S, saliva; SNP, single-nucleotide polymorphism; STRa, STR analysis; T, tongue; T21, trisomy 21; TNDM, transient neonatal diabetes mellitus; ToF, tetralogy of Fallot; UAO, upper airway obstruction; UTIs, urinary tract infections

^a Skin biopsy taken from the hypertrophic limb.

^b Partial loss of the maternal allele demonstrated.

^c Mosaic paternal isodisomy for every chromosome was proven by STR analysis.

^d Anterior linear ear lobe creases and/or posterior helical ear pits.

^e Fitting patUPD14, such as coat hanger appearance of ribs, bell-shaped thorax.

^f Fitting patUPD15.

^g Hypoglycemic seizures.

[†] Deceased.

patient with earlier reported individuals and offer clues for recognition.

2 | CASE DESCRIPTION

The index case was the third child of healthy, nonconsanguineous Dutch parents (aged 32 and 34 years). Weight at birth after 35 weeks of gestation was 2520 g (P50-75). The placenta was remarkably large, weighing 1890 g (>P98). Immediately after birth and later during life, she developed multiple benign tumors (please see Table 2 for an overview of all tumors). At one year of age, a body asymmetry became apparent, with the left side being larger. General health was good; growth and cognition were undisturbed.

She had two children, one of whom was born with tetralogy of Fallot without other abnormalities. When she was 37 years, a malignant adrenocortical tumor from the right adrenal gland was surgically removed. At 39 years, she developed a yolk sac tumor in the sacral region, which could only partly be removed due to massive local invasion. Curative therapy was not possible and she died within a few months' time.

Tumor material and peripheral blood were examined using methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) and single-nucleotide polymorphism (SNP) array (please see Supporting Information for additional information).

3 | RESULTS

In 1997, at 19 years of age, diagnostic testing for BWS was performed by Southern blot analysis on lymphocytes. No methylation defect was detected in imprinting centers (IC) 1 and IC2. At 38 years of age, methylation studies IC1 and IC2 were repeated using MS-MLPA on lymphocytes, which seemingly showed again a normal methylation of IC1 and IC2 (Supporting Information Figure S2a).

Because of her subsequent malignancy at age 39, her laboratory results were reevaluated because of the clinical suspicion of MGWpatUPD. Reevaluation of the previously performed MS-MLPA ME030 (BWS/SRS) did demonstrate a low mosaicism around the detection level of the technique. This was confirmed by SNP array analysis in blood, which showed an apparent normal female profile (Supporting Information Figure S3a), with an aberrant broadening of the B-allele frequency (BAF) around the 0.5 line fitting low-level percentage of mosaicism.

Subsequent analysis with MS-MLPA ME034 (MLID) showed a low mosaic loss of methylation (LOM) of all tested maternally methylated loci and low mosaic gain of methylation (GOM) of all tested paternally methylated loci (Supporting Information Figure S2b), indicative for a low mosaic MGWpatUPD.

Subsequently, MS-MLPA of DNA isolated from frozen adrenocortical tumor (Supporting Information Figure S2c and d) showed 80% loss of maternal methylation, and SNP array analysis in the same material showed an aberrant BAF pattern for the complete genome (Supporting Information Figure S3b). Both strongly suggest a high level ($\pm 95\%$)

MGWpatUPD in the tumor. SNP array analysis of the yolk sac tumor material from the sacral region showed a similar aberrant BAF profile, and many gains and losses of (large parts of) chromosomes (Supporting Information Figure S3c).

Results were discussed with the patient and her family, explaining that this *de novo* genomic imbalance was most likely the cause of her asymmetry and recurrent tumors, and that this implies no increased cancer risks for her offspring and other relatives.

4 | DISCUSSION

The occurrence of several tumors and asymmetrical body growth as present in the index case can be associated with MGWpatUPD. The initial methylation studies, 20 years ago, could not establish this diagnosis, as the level of mosaicism for the UPD was below the detection threshold of the methylation test. Sensitivity of diagnostic genetic tests has improved since then. Still, even today sensitivity of testing is not complete, which should be taken into account in evaluating results of such testing in the light of a suspected clinical diagnosis.

In patients with MGWpatUPD, the BWS phenotype is predominant; in individuals with a BWS phenotype, an MGWpatUPD might remain unrecognized if methylation analyses are restricted to a single UPD region, e.g., 11p15.^{18,19} To check for this, methylation tests at various loci should be undertaken if methylation testing for 11p15 is suggestive for patUPD (loss LIT1 and gain H19). Due to the mosaicism, aberrations may not be detectable in DNA derived from leucocytes, so other tissues may need to be studied to prove MGWpatUPD.

The presented patient is the oldest reported individual with an MGWpatUPD; the other patients range in age from 1 month to 30 years (Table 1).³⁻¹⁷ Obviously, all patients are female, as an androgenetic lineage (containing two Y chromosomes and no X chromosome) is not viable.

The predominance of the BWS phenotype may, in part, be explained by the mosaic distribution of the UPD. Signs and symptoms in a particular tissue may occur only if the mosaicism reaches a threshold level, which can differ between tissues within the same patient. Until now, this has not been studied in detail. Paternal UPDs of chromosomes 6, 14, 15, and 20 have been reported only in a nonmosaic state.¹⁸ Paternal UPD11 has been demonstrated to occur only in a mosaic state, leading to BWS.¹⁹ Likely, tissue-specific effects of imprinted genes allow low-level mosaic paternal UPD11 to cause signs and symptoms, and inhibits symptoms of the other low-level mosaic paternal UPDs.¹³

Fifteen of 19 patients (79%) previously reported with MGWpatUPD developed tumors, and 12 of them developed more than a single tumor (Table 2). The four patients in whom no tumor was described were < 13.5 years. Four of the seven women aged 17 years or older had breast fibroadenomas. The variability of the nature of the tumors and the age at which these develop hampers effective surveillance. We suggest general life-long vigilance in individuals with MGWpatUPD, because more targeted surveillance seems not well possible. The true frequency of developing tumors in patients with MGWpatUPD remains uncertain due to the (likely) ascertainment bias in reported individuals.

TABLE 2 Occurrence and tumor spectrum in patients with MGWpatUPD

Patients	Age (years)	Tumors	Age (years)	MGWpatUPD percentage	M/B
This report	39	Fibroepithelial polyp mandible left	0		B
		Liver hemangioma	0		B
		Tumor umbilicus; not further classified	1		B
		Breast fibroadenoma left	17		B
		Breast fibroadenoma left	17		B
		Breast fibroadenoma left	35		B
		Adrenocortical tumor right adrenal gland; biphasic epithelial/mesenchymal tumor, either yolk sac tumor or clear-cell carcinoma	36	95%	M
		Adrenocortical tumor left adrenal gland	37		M
		Yolk sac tumor sacral region	39	95%	M
Romanelli ⁹	30	Wilms tumor	4.4		M
		Adrenocortical virilizing adenoma	20	86%	M
		Melanocytic nevus right mandibular region	27		M
		Pancreatic adenocarcinoma (ductal)	28.5		M
		Liver metastasis	29		M
Ohtsuka ¹⁴	23	Multiple breast fibroadenomas	16		B
		Ovarian adenofibroma	16		B
		Multiple breast fibroadenomas	17		B
Bertoin ¹⁵	21	Bilateral cortical hyperplasia	0.1		B
		Virilizing adrenal tumor	16	86%	M
		Virilizing adrenal tumor recurrence	18	79%	M
		Virilizing adrenal tumor recurrence	21	94%	M
		Multiple breast fibroadenomas	>21	30%	B
Wilson ⁸	21	Pheochromocytoma right adrenal	8		M
		Pheochromocytoma left adrenal	9.5		M
		Three extra-adrenal paragangliomas (i.e., pheochromocytoma)	15		M
Inbar-Feigenberg ¹¹	20	Paraumbilical hemangioma	0.4		B
		Choledochal cyst	0.8		B
		Hamartomous tumor heart	13		B
		Hepatic cysts			B
Gogiel ³	18	Liver hamartoma	0.1		B
		Steroid cell tumor ovary	12	100%	M
		Breast fibroadenoma	18		B
Wilson ⁸	14	Cystic adrenomegaly	Prenatal		B
		Hemangioendothelioma	0.4		B
		Hepatoblastoma	1.3		M
		Pheochromocytoma	11		M
Yamazawa ¹⁰	13.3	No tumors			
Bryke ⁵	10.8	Hepatic hyperplasia	1.5		B
		Pheochromocytoma	10.8		M
Kalish ¹³	7	Liver hemangioma	0.1		B
		Liver hamartoma	0.1	80%	B
Kalish ¹³	6	Bladder polyps	0.1	95%	B
		Hepatic hemangiomas	0.2		B
Hoban ⁴	4	Wilms tumor	0.9		M

(Continues)

TABLE 2 (Continued)

Patients	Age (years)	Tumors	Age (years)	MGWpatUPD percentage	M/B
Giurgea ⁶	4	No tumors			
Reed ⁷	2.2	Hepatic mesenchymal hamartoma	0.9	60%	M
Hopman ¹⁷	2	No tumors			
Darcy ¹⁶	0.5	Hepatoblastoma	0.3		M
		Wilms tumor	0.5		M
Kalish ¹³	0.3	Adrenocortical hyperplasia	0.2	95%	B
Johnson ¹²	0.08	No tumors			

Abbreviations: B, benign; M, malignant.

We conclude that in every child or adult, who develops multiple different benign and malignant tumors with one or more signs or symptoms fitting a paternal UPD, an imprinting disturbance should be considered, especially MGWpatUPD. Routine molecular diagnostic procedures may not be sufficient to detect a low level of mosaicism, and the clinical suspicion should lead to directed testing in multiple tissues. If MGWpatUPD is diagnosed, adequate genetic counseling is possible and a life-long alertness for developing additional tumors is indicated.

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CONFLICTS OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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