

## SHORT REPORT

# Genome-wide paternal uniparental disomy mosaicism in a woman with Beckwith–Wiedemann syndrome and ovarian steroid cell tumour

Magdalena Gogiel<sup>1</sup>, Matthias Begemann<sup>1</sup>, Sabrina Spengler<sup>1</sup>, Lukas Soellner<sup>1</sup>, Ulf Göretzlehner<sup>2</sup>, Thomas Eggermann<sup>\*1</sup> and Gertrud Strobl-Wildemann<sup>3</sup>

Uniparental disomy (UPD) of single chromosomes is a well-known molecular aberration in a group of congenital diseases commonly known as imprinting disorders (IDs). Whereas maternal and/or paternal UPD of chromosomes 6, 7, 11, 14 and 15 are associated with specific IDs (Transient neonatal diabetes mellitus, Silver–Russell syndrome, Beckwith–Wiedemann syndrome (BWS), upd(14)-syndromes, Prader–Willi syndrome, Angelman Syndrome), the other autosomes are not. UPD of the whole genome is not consistent with life, in case of non-mosaic genome-wide paternal UPD (patUPD) it leads to hydatidiform mole. In contrast, mosaic genome-wide patUPD might be compatible with life. Here we present a 19-year-old woman with BWS features and initially diagnosed to be carrier of a mosaic patUPD of chromosome 11p15. However, the patient presented further clinical findings not typically associated with BWS, including nesidioblastosis, fibroadenoma, hamartoma of the liver, hypoglycaemia and ovarian steroid cell tumour. Additional molecular investigations revealed a mosaic genome-wide patUPD. So far, only nine cases with mosaic genome-wide patUPD and similar clinical findings have been reported, but these patients were nearly almost diagnosed in early childhood. Summarising the data from the literature and those from our patient, it can be concluded that the mosaic genome-wide patUPD (also known as androgenic/biparental mosaicism) might explain unusual BWS phenotypes. Thus, these findings emphasise the need for multilocus testing in IDs to efficiently detect cases with disturbances affecting more than one chromosome.

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## INTRODUCTION

Non-mosaic genome-wide paternal uniparental disomy (patUPD) is commonly known to be lethal. It is usually associated with complete hydatidiform mole, a condition characterised by the hydropic degeneration of villi and absence of the embryo. In contrast to non-mosaic genome-wide patUPD, its mosaic status—also known as androgenic/biparental mosaicism—is compatible with life and has been reported for several times (Table 1).<sup>1–7</sup> For non-mosaic genome-wide patUPD, different formation mechanisms have been suggested, which mainly occur from prefertilisation stages (for review, refer Van den Veyver and Al-Hussaini<sup>8</sup> and Golubovskiy<sup>9</sup>). Mosaic genome-wide patUPD is probably the result of a normal conception followed by post-zygotic errors.<sup>10</sup>

Mosaic genome-wide patUPD carriers show a broad phenotypic range but in all patients Beckwith–Wiedemann syndrome (BWS) and/or Wilms tumour (WT) were the initial clinical diagnoses (Table 1). In both BWS and WT, (epi)genetic alterations within 11p15.5 can be detected, including paternal UPD 11p15 (upd(11p15)pat) (for review, refer Choufani *et al*<sup>11</sup>). BWS was initially called EMG syndrome from its three main features exomphalos, macroglossia and (neonatal) gigantism. Additional signs include neonatal hypoglycaemia, hemihypertrophy, organomegaly, earlobe creases, polyhydramnion,

haemangioma and cardiomyopathy. In 5–7% of children, embryonal tumours (most commonly WT) are diagnosed. In addition to the aforementioned BWS features, single genome-wide patUPD carriers present symptoms overlapping with those of other imprinting disorders.<sup>6,7</sup> As aforementioned, the BWS phenotype does not only comprise dysmorphic and metabolic features, but is also associated with a significantly increased risk for embryonal tumours. As a result, the majority of the genome-wide patUPD patients develop BWS-associated cancers, such as WT or hepatoblastoma.

## Case report

We report on a patient referred to genetic counselling because of BWS features. Her non-consanguineous parents were healthy. The patient has two healthy older brothers and a healthy younger sister. The mother had one miscarriage. Patients and parental chromosomes were normal.

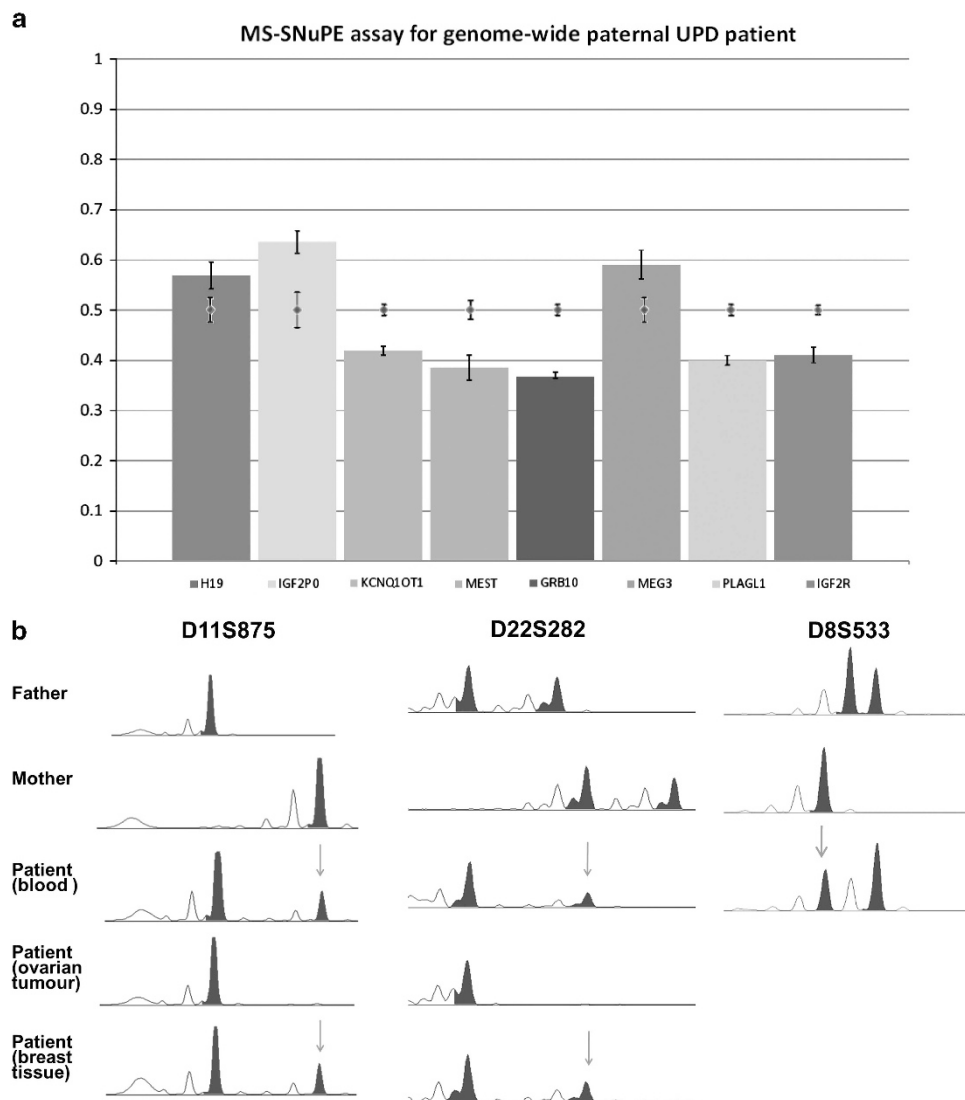
The patient was spontaneously born at 37 gestational weeks. Polyhydramnion was reported. During pregnancy, the mother showed a severe weight gain, but maternal diabetes was not diagnosed. The newborns length was 52 cm (>P90), weight 3850 g (>P90) and head circumference 34,5 cm (P75–P90). The placenta was reported to be hypertrophic (2000 g), the umbilical cord was thick (2 × 2 cm at the

<sup>1</sup>Institute of Human Genetics, RWTH Aachen, Aachen, Germany; <sup>2</sup>Gynaecological Hospital, Department of Gynaecology, Ehingen, Germany; <sup>3</sup>Praxis für Humangenetik, Ulm, Germany

\*Correspondence: Professor T Eggermann, Institute of Human Genetics, RWTH Aachen Pauwelsstr. 30, D-52074 Aachen, Germany. Tel: +49 241 8088008; Fax: +49 241 8082394; E-mail: teggermann@ukaachen.de

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**Figure 1** Molecular studies in the patient with genome-wide patUPD. (a) MS-SNuPE results for eight imprinted loci, for each locus two different CpGs were tested. The paternally methylated loci H19, IGF2P0 and MEG3 loci showed an increased methylation ( $nMI > 0.5$ ). In contrast a reduced methylation index ( $nMI < 0.5$ ) can be observed for the maternally methylated loci, *PLAGL1*, *IGF2R*, *GRB10*, *MEST* and *KCNQ1OT1* corresponding to a genome-wide patUPD. The control ranges are presented as dots (including SDs) for each locus. (the results of the two different CpG loci and from different bisulfite treatments are summarised and SDs are given; for details, refer Begemann *et al.*<sup>12</sup>) (b) Genotyping results of three microsatellite markers (D11S1758 (11p15), D22S282 (22q13), D8S533 (8q13.1)) in the patient and her parents. Patients' DNA from peripheral blood and breast tissue showed a reduction of the maternal allele (red arrows) and an increased signal of the paternal allele, indicating a mosaic patUPD condition. In ovarian tumour DNA, complete genome-wide patUPD was detectable.

genome-wide microsatellite-typing studies in lymphocyte DNA, and thereby confirmed mosaic paternal UPD for 16 autosomes (Figure 1b, Supplementary Table 1), markers on the other 6 autosomes were not informative. All informative markers showed a strongly increased peak height of the paternal allele and a lower intensity of the maternal allele. A third paternal allele corresponding to a paternal uniparental heterodisomy was never observed. In DNA from ovarian cancer, tissue typing of seven markers revealed complete non-mosaic genome-wide patUPD, whereas analysis of breast tissue DNA showed the same mosaic patUPD pattern like DNA from peripheral blood (Figure 1b).

## DISCUSSION

The clinical findings and course in our patient with mosaic genome-wide patUPD illustrates the broad phenotypic range in carriers of this rare molecular disturbance. However, the preponderant clinical signs

in this entity are hyperinsulinemia, organomegaly, umbilical hernia and hemihypertrophy (Table 1), features typically associated with BWS and 11p15 aberrations. Interestingly, a clinical overlap with other imprinting disorders has been reported only for two patients in the literature, though a more complex phenotype might be expected due to different loci affected by the aberration<sup>1,7</sup>. The situation is similar to that in multilocus methylation defect (MLMD) carriers where numerous imprinted loci are affected but the chromosome 11p phenotypes (BWS, Silver–Russell syndrome/SRS) are dominant (for review, refer Eggermann *et al.*<sup>13</sup>). One might therefore assume that the clinical signs in mosaic genome-wide patUPD (and MLMD) are influenced by further factors, such as tissue-specific mosaicism, tissue and development specific level of imprinted gene expression or interaction between imprinted genes/domains.

Moreover, mosaic genome-wide UPDpat is associated with a significantly increased predisposition for cancer development. Five of the so far described 10 patients showed paediatric tumours (pheochromocytoma, hepatoblastoma, pancreatic tumour, adrenocortical neoplasia) (Table 1). This finding is in agreement with the observation that UPD is generally important as a molecular alteration associated with inactivation of tumour-suppressor genes or activation of oncogenes (for review, refer Tuna *et al*<sup>14</sup>) Han *et al*<sup>15</sup> recently suggested that the loss of *H19* expression is involved in the aetiology of WT. Leaned on the pathomechanism in WT, we hypothesise that genome-wide patUPD leads a decreased expression and thereby influences ovarian tumorigenesis in our patient,<sup>16</sup> as the ovary is one of the few tissues with *H19* expression, which is possibly related to steroid metabolism. On the other hand, it can be assumed that the genome-wide patUPD increases the expression of the paternally expressed insulin-like growth factor 2 (IGF2).<sup>17</sup> Additionally, the influence of other imprinted genes in ovarian tumorigenesis is conceivable.

The presence of only one paternal allele and the lack of a second paternal allele in all analysed markers excludes prezygotic mechanisms of mosaic genome-wide patUPD formation in our case. We therefore suggest a post-zygotic division error: In an early embryonic stage of a normal biparental diploid zygote, a replication error affecting the maternal DNA followed by endoreduplication of the paternal genome resulted in formation of a normal (biparental) and a uniparental cell line formation.<sup>10</sup>

The identification of mosaic genome-wide patUPD patients has an important impact on genetic counselling and clinical oncology. Considering the clinical course in our patient, we emphasise the importance of further molecular investigations in case of unusual BWS phenotypes. The current genetic BWS testing algorithms are focused on the 11p15 loci, and dependent on the informativity of the applied tests many mosaic genome-wide patUPD still remain undiagnosed. Furthermore, genome-wide UPD should also be considered in patients with genetic syndromes associated with tumours, as they have a high risk for further neoplasias. In case of BWS, it has been suggested to screen patients for abdominal tumours until the age of 8 years.<sup>18</sup> Our case now shows that general tumour surveillance is indicated for the whole life in the subgroup of BWS patients with genome-wide patUPD and unusual phenotypes. Furthermore, testing for genome-wide patUPD is generally indicated in BWS patients with upd(11p15)pat.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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