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ARTICLE

Genome-wide uniparental diploidy of all paternal chromosomes in an 11-year-old girl with deafness and without malignancy

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Abstract

Approximately 20 cases of genome-wide uniparental disomy or diploidy (GWUPD) as mosaicism have previously been reported. We present the case of an 11-year-old deaf girl with a paternal uniparental diploidy or isodisomy with a genome-wide loss of heterozygosity (LOH). The patient was originally tested for non-syndromic deafness, and the novel variant p.V234I in the *ESRRB* gene was found in a homozygous state. Our female proband is the seventh patient diagnosed with GWUPD at a later age and is probably the least affected of the seven, as she has not yet presented any malignancy. Most, if not all, reported patients with GWUPD whose clinical details have been published have developed malignancy, and some of those patient developed malignancy several times. Therefore, our patient has a high risk of malignancy and is carefully monitored by a specific outpatient pediatric oncology program. This observation seems to be novel and unique in a GWUPD patient. Our study is also unique as it not only provides very detailed documentation of the genomic situations of various tissues but also reports differences in the mosaic ratios between the blood and saliva, as well as a normal biparental allelic situation in the skin and biliary duct. Additionally, we were able to demonstrate that the mosaic ratio in the blood remained stable even after 3 years and has not changed over a longer period.

Introduction

It is generally assumed that most uniparental disomies (UPDs), mainly isodisomies, result in no phenotypical anomalies when no pathogenic recessive mutations lie on the affected chromosome or chromosomal region and when no imprinting is present. However, UPD may lead to a disturbance of human gene expression through the manifestation of recessive diseases when the chromosome or chromosomal region of the parent who is a carrier of a recessive mutation is affected [1].

In early embryogenesis, there are three primary mechanisms by which UPD is explained, which are as follows: (a) trisomy rescue, in which there is a mitotic loss of one of the three copies of the trisomic chromosome; (b) monosomy duplication, in which the lone copy of a chromosome pair is duplicated via non-disjunction; and (c) gamete complementation, in which a gamete that is missing one chromosome unites with a gamete containing two copies of that chromosome by chance [2–4]. The mechanisms of genome-wide UPD mosaicism are well described by Kalish et al. [5].

UPD is not limited to the whole chromosome but is also common in chromosomal segments. The generation of a segmental UPD seems to occur because of a general somatic mutational mechanism rather than being functionally linked to aneuploidy rescue [6].

In exceptional cases, UPD may even affect not only a single chromosome or chromosomal segments but also all

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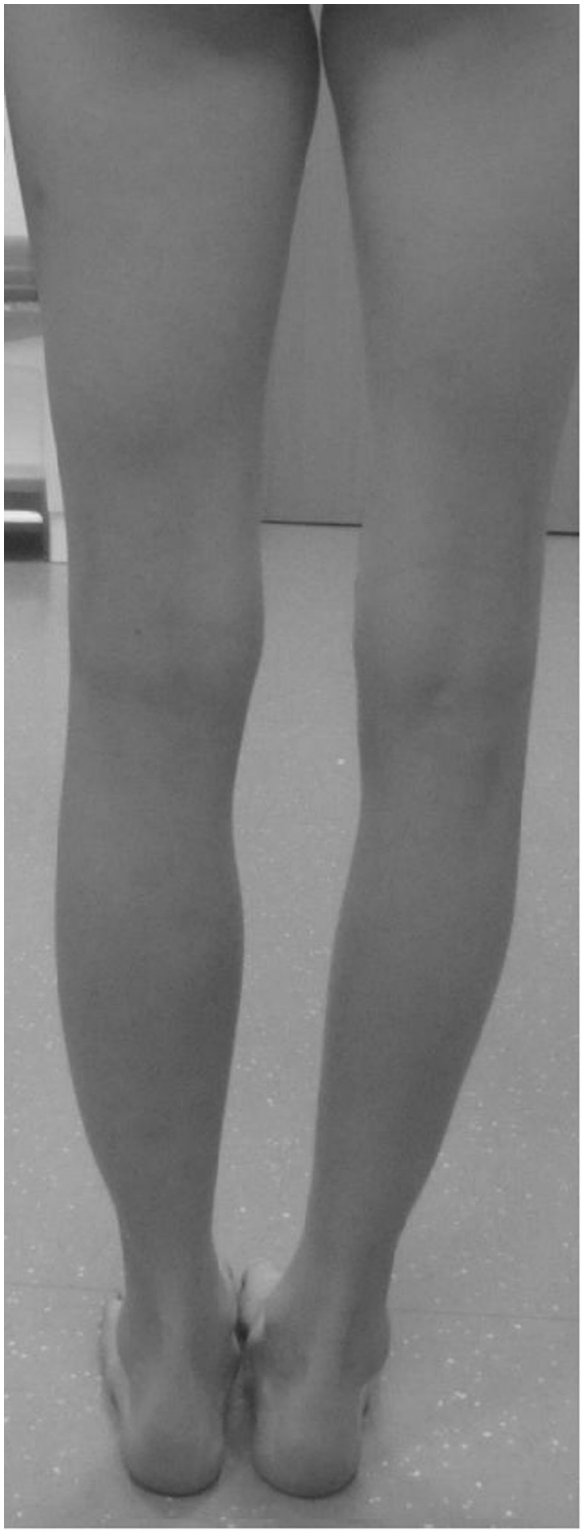

Fig. 1 The mild difference in leg length

23 chromosomes, i.e., the entire genome, and may be correctly called uniparental diploidy, but this term is not widely used. All the reported patients with UPD of all 23 chromosomes are females with somatic mosaicism. Mosaicism is characterized as two or more populations of cells with distinct genotypes that develop from a single fertilized egg/zygote within an individual [7]. This criterion of being formed from a single fertilized egg/zygote distinguishes mosaicism from chimerism, which describes an individual has multiple cell lineages derived from distinct fertilized eggs/zygotes [5].

Genome-wide UPD of all 23 paternal chromosomes, in the non-mosaic form, is known as mola hydatidosa (or hydatidiform mole or hydatid mole) [8]. The mechanism of a molar pregnancy occurs following fertilization by two sperms or a duplicated single sperm of an egg containing nuclear DNA (partial molar pregnancy) or without nuclear DNA (complete molar pregnancy) [9].

Several studies have presented clinical cases of UPD of specific chromosomes or chromosomal segments, but there are only 20 reports about exceptional cases of GWUPD. We report an unusual and very well documented case of a mosaic uniparental isodisomy/diploidy in an 11-year-old girl who is currently without malignancy or other severe disorders with the exception of prelingual sensorineural hearing loss. We report that the mosaic ratio in blood, which is a dynamic tissue, remained stable after even a 3-year period.

Materials and methods

Patient clinical data

The girl was born from the third uncomplicated pregnancy. The delivery was spontaneous but was preterm between the 35th and 36th weeks due to the preterm outflow of amniotic fluid, which was turbid. The birth weight was 2620 g (50th perc. for the 36th week of pregnancy), and the birth length was 46 cm (50th perc. for the 36th week of pregnancy); however, the birth was 4 weeks preterm. The percentile measurements of the birth weight and length were based on the growth charts of Fentom and Kim [10]. The mother further remembers that the placenta was abnormal, but no detailed report is available.

At the end of the pregnancy, a biliary duct cyst was detected by ultrasound examination of the fetus. She therefore underwent surgery 2 days after birth. At 2 months, she had surgery for a congenital umbilical hernia (Supplementary Material, Figure S1). Afterwards, a retroperitoneal cyst above the left kidney was detected by ultrasound examination and by subsequent computed tomography (CT), but, surprisingly, it disappeared spontaneously without surgery.

At ~3 months of age, the patient's parents noticed hearing impairment, and at 2 years of age, she received a cochlear implant. No mutations were detected in the *GJB2* or *SLC26A4* genes by Sanger sequencing of the entire coding

region, but subsequently, the novel homozygous variant p. V413I (c. 1237A>G), which was predicted to probably be benign, was found in the *ESRRB* gene by Sanger sequencing.

At the age of 11 years, the patient had a height of 148 cm (50th perc.) and a weight of 33 kg (25th perc.). Her growth and body weight were between the 10th and 50th percentiles as follows: at 1.5 years. 9.1 kg (10th perc.); 2 years. 10.6 kg (25th perc.)/82 cm (25th perc.); and 8 years. 25 kg (25–50th perc.)/127 cm (25–50th perc.). Slightly different lengths and circumferences of the legs were noted. The right leg was longer and mild hemihypertrophy was present on the left side (Fig. 1). Only one cafe au lait (CAL) spot on the left thigh with mild hemihypertrophy and tiny hyperpigmented spots on the left groin were present.

Methods

The examined family consisted of four family members, all of whom provided written informed consent for the elucidation of the deafness of the patient. In the case of children, informed consent was provided by their parents.

Genomic DNA from blood and saliva, cultivated skin fibroblasts and a paraffin-embedded sample of the biliary duct cyst were extracted using standard protocols. The patient´s blood samples were extracted at the ages of 8 and 11 years. Parentity was confirmed using a set of polymorphic short tandem repeat (STR) markers on chromosomes 2, 7, 13, 15, 16, 17, 18, 21, 22, X and Y. Fluorescently labeled primers were used for the amplification of the STR markers and analyzed on an ABI3130 Genetic Analyzer (Applied Biosystems) as described previously by Putzová et al. [11]. We also performed testing by multiplex ligation-dependent probe amplification (MLPA) from the Charcot- Marie-Tooth type 1A (CMT1A) regions on chromosome 17 to estimate the copy number of this region.

All coding exons of the *ESRRB* gene located on chromosome 14 from all family members were Sanger sequenced.

A single-nucleotide polymorphisms (SNPs) array that enabled whole-genome genotyping was provided on microarrays (Illumina) and allowed for the interrogation of over four million markers per sample. This array uses a combination of intensity and genotyping estimation that provides high-resolution detection of genomic copy number abnormalities.

Results

A GWUPD was found by chance in a girl who was examined for non-syndromic hearing loss at the age of 9 years. She was initially tested for a mutation in the *GJB2* gene by Sanger sequencing, and no pathogenic mutation was detected. Furthermore, Sanger sequencing of the *ESRRB* gene revealed the novel homozygous variant c. 1237A>G (p. V234I) in the proband, which was considered rather benign. Therefore, we explored the segregation in the family. The same variant was then found only in the proband's father and brother in a heterozygous state and, surprisingly, not in her mother (Supplementary Material, Figure S2).

Therefore, we performed a parentity test using DNA samples isolated from blood using polymorphic STR markers. We detected homozygosity for only one paternal allele of each microsatellite marker, and the maternal alleles were absent in the proband´s sample. The patient was homozygous for all the markers examined. Comparisons of the family DNA profiles are presented in Fig. 2. Initially, after the first test with a few STR markers from chromosome 17p, we suspected a deletion of a maternal chromosome 17 region, but MLPA from the CMT1A locus established the presence of two copies of this chromosomal region without any copy number change.

We continued testing with a set of 36 polymorphic STR markers from ten different chromosomes. Analyses of the STR markers revealed homozygosity for all markers; only the paternal alleles were present. Further, we used the SNP array, and it confirmed the biallelic results without copy number changes and genome-wide homozygosity (Fig. 3).

To test the situations in other tissues over a longer period of time with regard to the paternal uniparental diploidy/whole-genome paternal isodisomy resulting in mola hydatidosa, we repeated all of the above-mentioned testing with DNA samples isolated from other tissues of the patient, specifically from the saliva, cultivated skin fibroblasts and even from a paraffin-embedded sample of the biliary duct cyst that was extracted on the second day of life. The sample was found in the archive and still intact. Analyses of these tissues had not detected any abnormal results. No isodisomy or loss of heterozygosity was present. The biallelic pattern of alleles from each parent was detected, but in saliva and blood, the intensity of the paternal allele was much stronger. The comparisons of the tissues are presented in Fig. 4a.

Due to the paternal uniparental diploidy/whole-genome isodisomy and homozygosity in mosaicism, we evaluated the allelic ratio of somatic mosaicism in the proband´s blood and saliva via the relative quantification of fluorescently labeled PCR products of informative STR markers. The ratio between the two peaks (i.e., the paternal and maternal alleles) was calculated. The number of cells carrying the duplicated parental allele were established at 93% in the blood and 74% in the saliva. The SNP array confirmed this result; somatic mosaicism accounted for ~5% of the

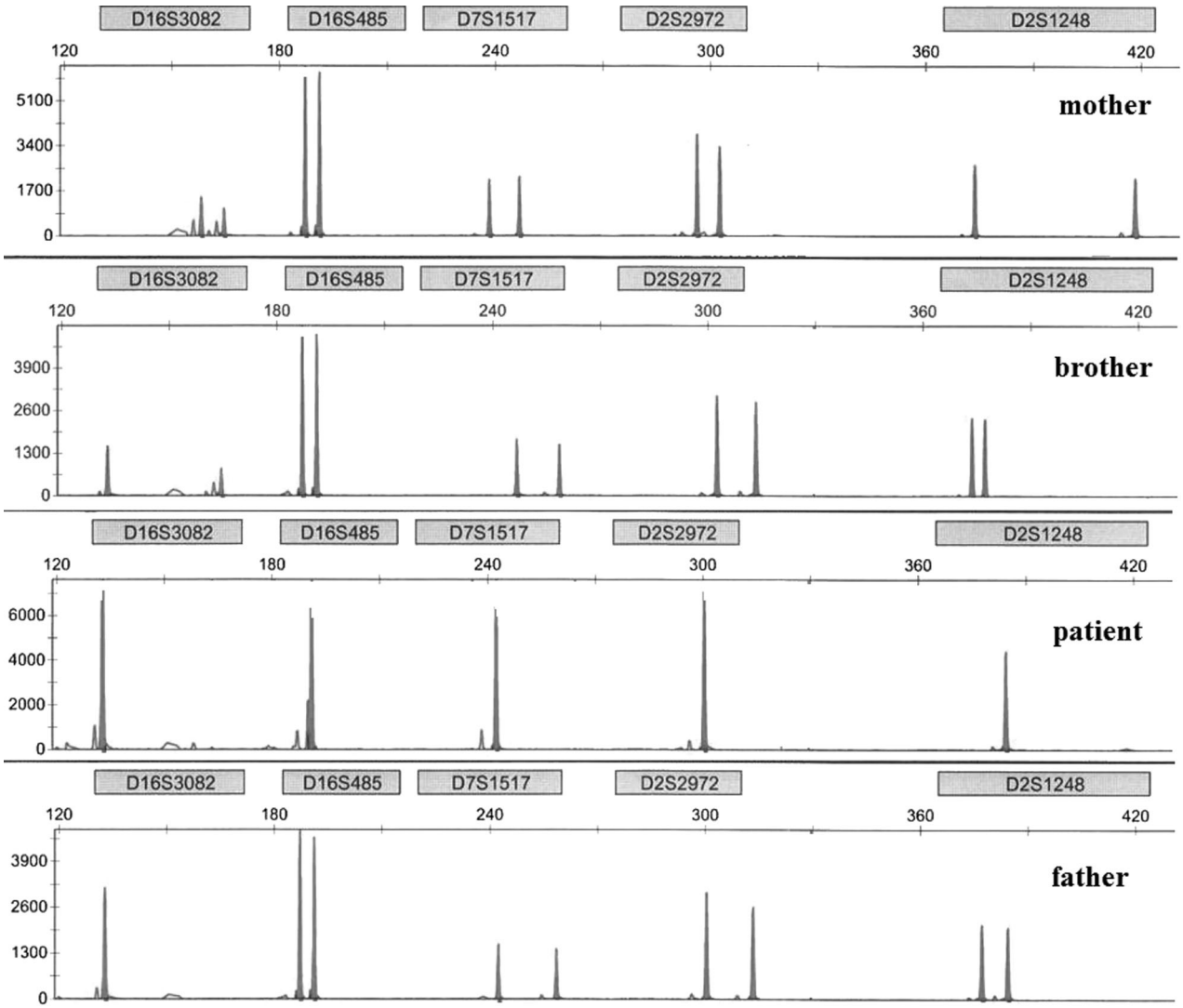

Fig. 2 Comparison of the DNA profiles obtained from all four family members

genomic DNA derived from the blood and ~25% of the genomic DNA isolated from the saliva.

Retesting the STR markers in the DNA from adolescent proband blood after a 3-year period revealed that the ratio of mosaicism was stable, and the results were identical to the DNA of the original blood sample. No detectable significant change in the ratio of paternal to maternal alleles was found. Sanger sequencing of the *ESRRB* gene with the variant p.V234I in the patient revealed a homozygous state in the blood, but in the skin fibroblasts, the variant was in a heterozygous state (Fig. 4b), which indicates that this variant was probably not causal for the hearing loss in this patient.

Biesecker and Spinner [6] reported differences between mosaicism and chimerism; these phenomena are distinguished by the extent of the genomic differences. In mosaicism, nearly all STR markers are identical in the different cell populations because all cells are derived from the same zygotic genotype; however, in chimerism, there are divergent genotypes across the genome. Finally, we concluded that it was probably a somatic mosaicism in our patient because the DNA from the blood and saliva samples was different only according to the allelic ratio between the paternal and maternal peaks compared with the normal biallelic ratio of the DNA derived from the skin and biliary duct cyst (Supplementary Material, Figure S3).

Although the girl is currently only affected by prelingual sensorineural deafness, due to the mosaic uniparental diploidy/uniparental isodisomy of all 23 paternal chromosomes in the blood, the prognosis is more severe in the future because of the increased risk of neoplasias that has been reported in other similar patients [12–15].

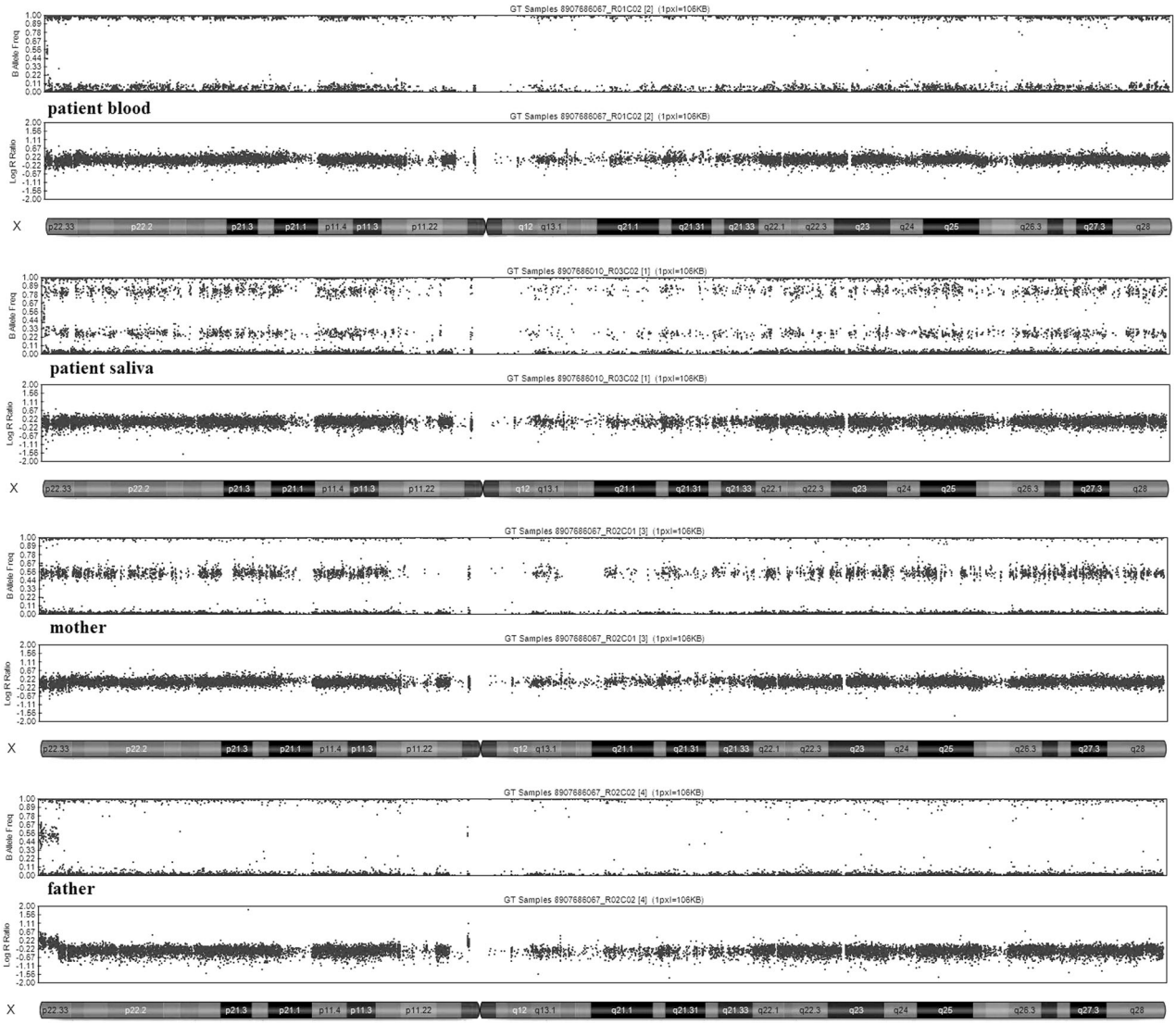

Fig. 3 Graphical output for the CNVs of chromosome X based on SNP arrays, demonstrating the juxtaposition of the female proband's DNA samples extracted from blood and buccal swabs compared to those of her mother and father

Discussion

Genome-wide uniparental isodisomy/diploidy (GWUPiD/GWUPD) has previously been reported [5, 12–26]. All of the authors of these publications use the terms uniparental disomy or isodisomy of all chromosomes. Most of the examined patients were diagnosed in early childhood, and only six cases with of GWUPD presented with probands older than 11 years [13, 14, 19, 20, 22, 26].

The clinical influence of the ESRRB variant p.V234I was unknown until recently; however, it is probably a benign variant, as it has been detected in only the heterozygous state in tissues other than blood, and there have been no variants on the opposite tested alleles. ESRRB variant p.V234I predicts a change in a weakly conserved amino acid that is described by Sorting intolerant from tolerant (SIFT) program as tolerated and by MutationTaster as a polymorphism. New data from population databases indicate that this variant has a relatively high population frequency (1.16–1.6%) among Europeans in Exome aggregation consortium (ExAC) and Exome variant server (EVS). This variant in now known by Single-nucleotide polymorphism database (dbSNP) as rs146351534 with a clinical significance that is benign and by ClinVar as RCV000038135.2 with a clinical significance that is also benign. Even if the variant is pathogenic, the homozygosity for this variant was only present in the blood and not in other tissues; therefore, we believe that this variant is not the cause of the deafness in this patient. The cause of the deafness remains unknown.

Uniparental disomy of a single chromosome or a chromosome segment occurs when two identical (isodisomy) or

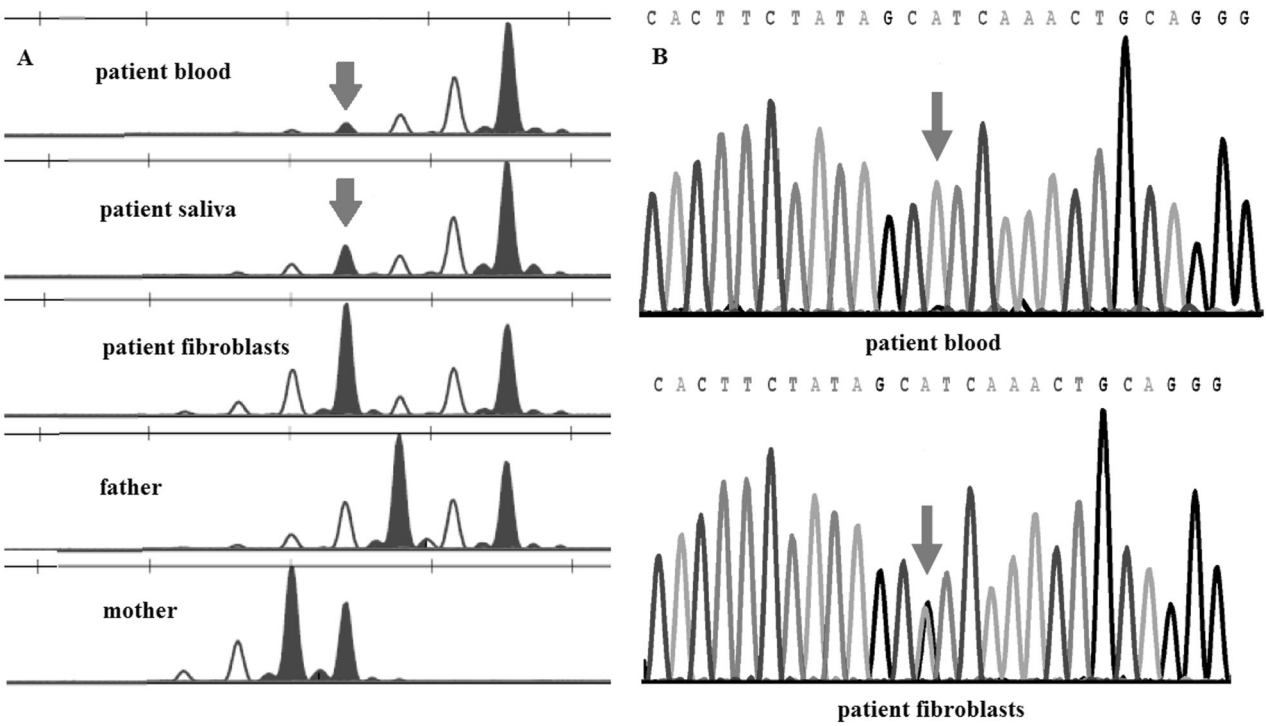

Fig. 4 Fragment analysis of three cell types from the female proband. The saliva and blood cells (ectodermal and mesodermal origins) exhibit a predominantly paternal homozygous state of alleles compared with the maternal alleles, in all polymorphic markers. The DNA from the skin fibroblasts (ectodermal origin) exhibits normal biallelic patterns in both parents that are frequently in the heterozygous state (**a**). The proband´s sequencing data of the *ESRRB* gene with the variant p.V234I were obtained from blood cells in a homozygous state and skin fibroblasts in a heterozygous state (**b**)

homologous (heterodisomy) chromosomes are inherited from the same parent [1, 27]. The mechanism of UPD is a random event during the formation of oocytes or sperm (prezygotic), or monosomic/trisomic rescue (postzygotic) [4, 6, 28]. In our patient, we believed that the origin of the mosaic uniparental diploidy/GWUPiD was due to a postzygotic mechanism because the presence of only one parental allele and the lack of a second allele in all examined STR markers excludes prezygotic formation. Gogiel et al. [13] and Kaiser-Roger et al. [29] suggested a period of postzygotic errors that arises during the replication of the maternal genome prior to the first cleavage. The same mechanism has been observed in 1–2% of human preimplantation embryos [30, 31].

Many publications dealing with the origin of uniparental and biparental mosaicism have agreed with this potential mechanism. However, the mechanism is predictive for only the female sex. Cases with XY karyotypes have also been documented; however, the formation process for the male thus far remained ambiguous. Cohen et al. [32] cited aneuploidy, whereas Surti et al. [33] and Strain et al. [34] proposed a chimerism resulting from the fusion of two independently fertilized zygotes. Another mechanism was proposed by Golubovsky [35] and involves the entry of two sperms into one normal egg.

The clinical phenotype resulting from somatic mosaicism varies depending on the mutation ratio or threshold in the specific tissue. The degree of somatic mosaicism is often variable in different tissues. Therefore, examinations of several different tissues may increase the chance of detect somatic mosaicism [36]. We analyzed DNA from the following four different tissues with different germinal layer origins: the saliva, which is a cell mixture from the salivary glands and the oral mucosa in which approximately one-third of cells are epithelial cells from the ectoderm [37], and two-thirds are leukocytes from the mesoderm; [38–40] the skin, which has an ectodermal origin; the blood, which is derived from the mesoderm; and the external surface of a biliary duct, which has additional endodermal epithelium. The presence of the somatic mosaicism was established in saliva (cell ratio 2.5:1); and in the blood (cell ratio 9:1), by fragment analysis and the SNP array. These findings could perhaps be associated with the mild symptoms observed in proband compared to other reported patients with mosaic uniparental diploidy/GWUPiD. Our patient has not fully expressed BWS with all the clinical symptoms (i.e., macroglosia and overgrowth), but she had some mild typical symptoms, such as an umbilical hernia, which was surgically addressed at the age of 3 months. She has a mild asymmetry of the lower extremities (the left leg/thigh is

thicker/wider), which is compatible with hemihypertrophy. Except for a biliary duct cyst, which was surgically removed on the first day of life, no organomegaly had yet been detected. Manifestations of BWS features (neonatal hypoglycemic, macrosomia, tumors, etc.) and a significant predisposition for cancer development have been observed in most patients with mosaic uniparental diploidy/GWUPiD, but deafness, as observed in our female proband, has not yet been reported. This proband either extends the spectrum of clinical symptoms of mosaic genome-wide UPD patients, or the deafness may have an independent cause.

Genome-wide UPD mosaicism can cause highly variable somatic phenotypes depending on tissue distribution and the level of mosaicism in the cell lineage. Additional studies dealing with uniparental diploidy/GWUPiD mosaicism can establish the unusual clinical symptoms of patients and determine the actual mechanism of the genomic error that arises during embryogenesis.

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Compliance with ethical standards

Ethical standards The experiments presented in this manuscript were conducted in accordance with law of the Czech Republic.

Conflict of interest The authors declare that they have no conflict of interest.

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