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Fumarate hydratase deficient renal cell carcinoma: Chromosomal numerical aberration analysis of 12 cases

Kristyna Pivovarcikova[a], Petr Martinek[a], Petr Grossmann[a], Kiril Trpkov[b], Reza Alaghehbandan[c], Cristina Magi-Galluzzi[d], Maria Pane Foix[e], Enric Condom Mundo[e], Daniel Berney[f], Anthony Gill[g], Boris Rychly[h], Kvetoslava Michalova[a], Joanna Rogala[i], Tomas Pitra[j], Tamas Micsik[k], Jiri Polivka[l], Milan Hora[j], Ozlem Tanas Isikci[m], Sarka Skalova[a], Jana Mareckova[a], Michal Michal[a], Ondrej Hes[a,*]

[a] Department of Pathology, Charles University in Prague, Faculty of Medicine in Plzeň, University Hospital Plzen, Pilsen, Czech Republic
[b] Calgary Laboratory Services and University of Calgary, Calgary, AB, Canada
[c] Department of Pathology, Faculty of Medicine, University of British Columbia, Royal Columbian Hospital, Vancouver, BC, Canada
[d] Department of Pathology, School of Medicine, University of Alabama, Birmingham, AL, USA
[e] Department of Pathology, Bellvitge Biomedical Research Institut (IDIBELL), Bellvitge University Hospital, University of Barcelona School of Medicine, L'Hospitalet de Llobregat, Barcelona, Spain"
[f] Bart's Cancer Center, London, United Kingdom
[g] Cancer Diagnosis and Pathology Group, Kolling Institute of Medical Research and University of Sydney, Sydney, NSW, Australia
[h] Department of Pathology, Cytopathos, Bratislava, Slovakia
[i] Department of Pathology Regional Specialist Hospital, Wroclaw, Poland
[j] Department of Urology, Charles University in Prague, Faculty of Medicine in Plzeň, Pilsen, Czech Republic
[k] 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary
[l] Department of Histology and Embryology, Charles University in Prague, Faculty of Medicine in Plzeň, Pilsen, Czech Republic
[m] Department of Pathology, Ankara Training and Research Hospital, Ankara, Turkey

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ABSTRACT

Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma (HLRCC)/fumarate hydratase deficient renal cell carcinoma (FHRCC) is defined by molecular genetic changes (mutation/LOH in fumarate hydratase (*FH*) gene). We investigated chromosomal numerical aberration pattern (CNV) in FHRCC/HLRCC using array comparative genomic hybridization analysis and low pass whole genome sequencing. Genetic analysis was successfully completed in 12 tumors. Most common chromosomal aberrations detected were a complete or partial loss of chromosome 4 (5/12 cases), chromosome 15 (4/12 cases), and chromosomes 9, 13, and 14 (each in 3/12 cases), as well as a complete or partial gain of chromosome 17 (in 4/12 cases). No chromosomal losses or gains were detected in 4 cases. Copy number variation pattern in FHRCC/HLRCC appears to be highly variable and does not provide a useful diagnostic tool in identifying these cases. Immunohistochemical staining and especially molecular genetic evaluation of *FH* gene mutations/LOH remain the gold standard in identifying FHRCC/HLRCC.

1. Introduction

Molecular genetic features have become an integral part of modern classifications of renal tumors. Chromosomal aberration status, mutations of particular genes, loss of heterozygosity (LOH), and hypermethylation are frequently utilized even in routine differential diagnostic processes. However, recently published data seem to confirm that chromosomal numerical aberration pattern in renal cell carcinomas (RCCs) is rather more complex and variable than initially thought.

Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma (HLRCC)/fumarate hydratase deficient renal cell carcinoma (FHRCC) is one of recently recognized tumors defined by a molecular genetic change. The diagnostic hallmark of HLRCC/FHRCC is the mutation/LOH of the fumarate hydratase (*FH*) gene. Although HLRCC/FHRCC has variable morphology, papillary/tubular

* Corresponding author at: Department of Pathology, Medical Faculty and Charles University Hospital Plzen, Alej Svobody 80, 304 60 Pilsen, Czech Republic.
E-mail address: hes@biopticka.cz (O. Hes).

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architectural pattern is the most frequently identified in the literature. The presence of large nuclei with prominent dark red nucleoli and perinucleolar clearing have been considered as helpful morphologic clue. However, even these morphologic features are not consistently present, and are not pathognomonic only for HLRCC/FHRCC [1]. In addition to the morphologic features, immunohistochemical stains including antibodies against fumarate hydratase (FH) and 2-succinocysteine (2SC) can also be helpful. It should be noted that there are several challenges concerning immunohistochemistry evaluation, given 2SC is not yet commercially available, and there are difficulties in the interpretation of these stains.

Two nomenclatures are used for renal tumors associated with impaired *FH* gene - hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma (HLRCC) and fumarate hydratase deficient renal cell carcinoma (FHRCC). The term HLRCC is used for syndromic patients - HLRCC is characterized by germline mutations of the *FH* gene, autosomal dominant heredity and concurrent presence of cutaneous and/or uterine leiomyomas. The onset of renal tumor, uterine/cutaneous leiomyomas can be seen within several years and synchronous presence of renal tumor together with leiomyomas is not seen frequently. This syndrome was first reported in two families from Finland in 2001 [2]. The term FHRCC is recommended for tumors with suggestive morphology, typical immunophenotype (FH negativity, 2-succinocysteine [2SC] positivity) in the setting of uncertain clinical and family history and unknown genetic status. FHRCC also allows designation of cases that might represent apparently sporadic forms, harbouring somatic (not germline) alterations in the *FH* gene [3-5]. In fact, with recent studies on molecular characteristics of FHRCC, it became apparent that the term FHRCC would be more appropriate, encompassing both sporadic (absence of features suggesting syndromic disease) and hereditary cases.

HLRCC/FHRCC was initially included in the WHO 2004 classification, not as separate entity but as a presumed familiar counterpart of papillary renal cell carcinoma (PRCC) type 2 [6]. Currently, HLRCC is recognized as a separate entity and variant of RCC in the 2012 International Society of Urological Pathology (ISUP) Vancouver Classification of renal tumors, and it was included in the most recent 2016 WHO classification [7,8]. In general, PRCC is believed to be characterized (in addition to other abnormalities) by trisomy/polysomy of chromosomes 7 and 17 and a loss of chromosome Y in male patients [8]. However, recently published papers showed much more variable genetic profile [9-31]. The aim of this study was to investigate the chromosomal numerical aberration pattern (CNV) in FHRCC/HLRCC, and to compare it with CNV pattern typically associated with PRCC. To the best of our knowledge, only one study dealing with CNV pattern in FHRCC/HLRCC has been previously published [32].

2. Material and methods

Fourteen cases of FHRCC were collected from 9 institutions: Medical Faculty and Charles University Hospital Plzen (Plzen, Czech Republic), Calgary Laboratory Services and University of Calgary (Calgary, Canada), Robert J. Tomsich Pathology and Laboratory Medicine Institute - Cleveland Clinic (Cleveland, USA), Bellvitge Biomedical Research Institute (Barcelona, Spain), Bart's Cancer Center (London, UK), Medical College Wisconsin (Milwaukee, USA), Royal North Shore Hospital - University of Sydney (Sydney, Australia), Cytopathos (Bratislava, Slovakia), and Semmelweis University (Budapest, Hungary).

All cases were confirmed FHRCC, with genetically detected mutation/LOH of the *FH* gene. We did not determine, if the *FH* gene mutation was germline or somatic, therefore the term FHRCC was used. The majority of cases were published in 2 previous studies; 9/14 cases were reported in a clinicopathologic, morphologic, immunohistochemical and molecular-genetic study, and 13/14 cases were included in a study examining PD1 and PDL1 expression [4,33]. The material for the latter study was available in 12 cases, and only these cases were included in the presented study.

2.1. DNA extraction

Tumor areas of the formalin-fixed paraffin-embedded (FFPE) samples were determined using hematoxylin-eosin stained slides and macro dissected. DNA from FFPE tumor tissue was extracted using QIAsymphony DNA Mini Kit (Qiagen, Hilden, Germany) on an automated extraction system (QIAsymphony SP; Qiagen) according to manufacturer's supplementary protocol for FFPE samples. Concentration and purity of isolated DNA were measured using NanoDrop ND-1000 and DNA integrity was examined by amplification of control genes in a multiplex polymerase chain reaction (PCR).

2.2. Low pass whole genome sequencing

SurePlex DNA amplification system (Illumina, San Diego, CA) was used to generate DNA template from tumor samples. Amplification is highly representative, which makes the resulting product suitable for copy number variation detection. The library of all samples was prepared using Nextera DNA Sample Prep Kit (Illumina, San Diego, CA) and was sequenced on MiSeq sequencer, copy-number variant analysis was performed using BlueFuse Multi software with the Veriseq plugin (Illumina, San Diego, CA). Following quality control filters for valid samples were set: minimum 1 million reads per sample, average quality score and average alignment score > 30, and overall noise < 0.3. Thresholds for CNV calling were set based on a group of samples with known CNVs, that were validated using array CGH and fluorecence in-situ hybridization. The percentage of tumor in the DNA sample was considered, when calling the lower frequency CNVs and thresholds for CNVs were set individually for each case typically the copy number was 1.5 for loss and 2.5 for gain. CNVs spanning less than the whole length of a chromosome arm were not called. FISH as described previously [34] was used for confirmation of cohort of 5 analyzed cases (results not shown). The more complex CNV changes are listed in the table. Aberrations on gonosomes were excluded from the results. CNV detection using low pass whole genome sequencing was proven to produce similar results as in fresh frozen tissue [35].

3. Results

Twelve tumors from 11 patients were included in this study (case 2 is a recurrence of patient/case 1). Clinical data were available for all 11 patients (and all 12 tumors) (Table 1). The study cohort included 8 males and 3 females, age range 24 to 65 years (median 51 years, mean 50.1 years). Tumor size ranged from 0.9 to 18 cm in greatest dimension (median 8 cm, mean 8.9 cm). Pathologic staging included pT1 in 2 cases, pT2 in 6, and pT3 in 3 cases. No information about stage was available in one case.

Follow-up data were available for all 11 patients (range 3 to192 months, mean 57.2 months, median 24 months). Five patients had metastatic disease. Five patients died of disease 3–24 months post-surgery. No records concerning aggressive behavior were found in 2 patients.

The morphologic characteristics are summarized in Table 1. Most of the tumors (8/12) showed papillary growth pattern (at least focally) (Fig. 1), while 4 did not demonstrate any papillary architecture (Fig. 2a). Papillary architecture was found to be mixed with other growth patterns (i.e., tubular, cribriform, cystic, tubulocystic, solid and sarcomatoid) in the majority of cases (Fig. 2B), only two cases were pure papillary. Macronucleoli were found in all 12 cases (at least focally) (Fig. 3).

Low pass whole genome sequencing was successful in all 12 tumors. There were 61 chromosomal aberrations detected. The CNV's included 31 gains and 30 individual losses of whole chromosomes or parts of

Table 1
Clinical data and histopathologic features of FHRCC.

Case	Age (years)	Sex	Size (cm)	Follow-up (months)	Current status	Stage (AJCC/ UICC2009)	Pattern
Case 1[a]	51	F	Multiple 1.4, 1.0, 1.6, 0.6	46	AWD (see case 2)	pT1a, M0	Papillary, tubulocystic
Case 2[a]	52	F	Multiple 0.9, 0.6, 0.3, 0.9, 0.2, 0.4	After 46 months, recurrent multiple lesions identified	Recurrence of case 1	pT1a, M0	Papillary
Case 3[a]	44	M	7	108	AWD	pT2a, M1	Tubulocystic
Case 4[a]	45	F	7	24	DOD	pT3a, M1	Papillary, tubular
Case 5[a]	42	M	10	18	DOD	pT2, M0	Papillary, tubular, cystic
Case 6[a]	65	M	18	3	DOD	pT3a, M1	Sarcomatoid, tubulocystic
Case 7[a]	60	M	8	114	AWD	pT2, M0	Papillary, cystic, tubulopapillary
Case 9[a]	60	M	8	7	AWD	pT2a, M0	Papillary, tubulocystic, cystic
Case 11[a]	54	M	14	96	ANED	pT2, M0	Papillary
Case 12[a]	61	M	12.5	12	DOD	pTx, M1	Papillary, solid, sarcomatoid
Case 13[a]	24	F	Multiple 2.3 and 13	192	ANED	pT2, M0	Solid, cribriform, cystic
Case 14	45	M	6.5	9	DOD	pT3a, M1	Tubulocystic

M male, *F* female, *NA* not available, *AWD* alive with the disease, *DOD* death of the disease, *ANED* alive and no evidence of disease.
[a] Cases already published [4,33].

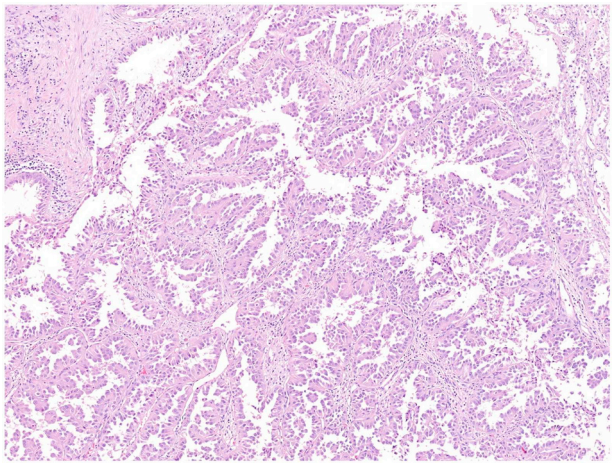

Fig. 1. FHRCC arranged in papillary pattern. Such cases were suggested to be familiar counterpart of so-called PRCC type 2 in previous WHO 2004 Classification of Genitourinary Tumors.

chromosomal arms (Table 2, Fig. 4). There were 42 unique changes. Most commonly detected chromosomal aberrations were a complete or partial loss of chromosomes 4 (found in 5/12 cases) loss of chromosome 15 (in 4/12 cases), and gain of chromosome 17 (4/12), followed by complete or partial loss of chromosome 9, 13, and 14 (in 3/12 cases). No chromosomal losses or gains were detected in 4 cases. The findings regarding losses and gains in individual cases are summarized in Table 3.

4. Discussion

HLRCC/FHRCC was recently defined as a tumor with variable architectural, cytological and clinical features. Historically, in earlier publications including the WHO 2004 classification, the tumor was described as displaying typically PRCC type 2 histology [2,6,32,36,37]. As the evidence accumulated in the literature, it became evident that the morphologic spectrum of these tumors is much wider than originally suggested. HLRCC/FHRCC includes tumors with predominantly papillary or tubulocystic architecture, usually mixed with other growing patterns representing multiplicity of patterns (cystic, tubular, tubulopapillary, tubulocystic, solid) [4,38-40]. Additionally, other RCC phenotypes have been described within the HLRCC/FHRCC entity, including collecting duct carcinoma [36,38,40-42], clear cell RCC [37,43,44], Wilms tumor [45], tubulocystic RCC [5], unclassified

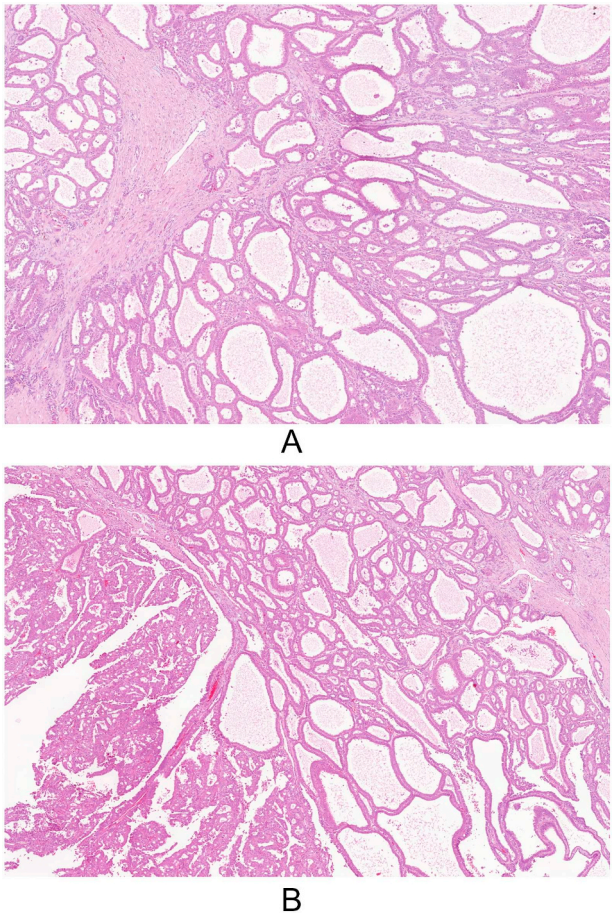

Fig. 2. Pure tubulocystic pattern is not frequently seen. Similar cases are always challenging (A). Mixed architecture is considered to be more characteristic (B).

oncocytic tumor [36,46], and even oncocytic type of RCC resembling SDH-deficient RCC [47]. In fact, HLRCC/FHRCC is a distinct histomolecular entity, which may have been previously labelled as unclassified high-grade RCC [4], PRCC type 2, tubulocystic with dedifferentiated foci, and collecting duct carcinoma. The most important histologic feature of these neoplasms seems to be the presence of a large nucleus with a prominent, inclusion-like eosinophilic nucleolus, surrounded by a clear halo [39]. However, with the current insight into the variable morphologic features associated with HLRCC/FHRCC, it is apparent

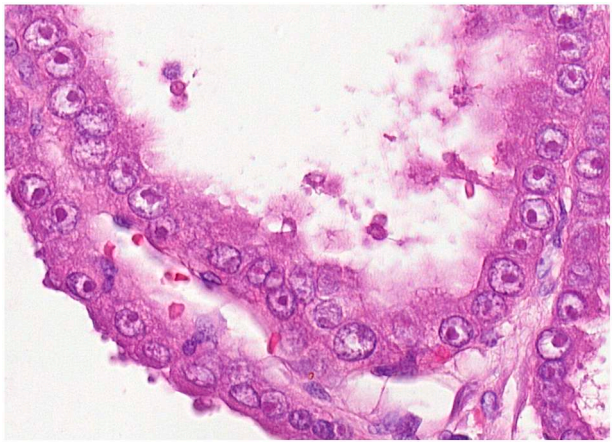

Fig. 3. Deep red macronucleoli with perinucleolar clearing were considered as specific for FHRCC, however they can be present in other renal cell carcinomas.

that the macronucleoli are not constant and specific morphologic feature of these tumors. A combined negative immunohistochemical staining for FH, and strong positive staining for 2SC is used as a useful ancillary tool, which strongly correlate with *FH* gene alterations and morphology compatible with HLRCC/FHRCC [1,4].

In this study, our tumors demonstrated a morphologically non-homogeneous spectrum. In fact, only two cases demonstrated pure papillary architectural growth pattern, while the majority (8 tumors) displayed mixed architectures, of which 6 cases exhibited only focal papillary areas, and 4 cases did not have any papillary foci.

The most frequent chromosomal gain in this study was the gain of chromosome 17 (4/12 cases). Only two cases demonstrated concurrent gains of chromosomes 7 and 17 (as typically seen in PRCC). A broad spectrum of individual gains was detected in the tumor cohort that included chromosomes 2, 3, 7, 10, 13, 15, 16, and 17 more than once. Losses of whole chromosomes or their parts were almost the same frequency as gains in our cohort (30 chromosomal losses, resp. 31 chromosomal gains). The most frequent loss was found in chromosome 4 (5/12 patients), followed by chromosome 15 (4/12 patients), and chromosomes 9, 13, 14 (each in 3/12 patients). Other less frequent individual chromosomal losses were recorded on chromosomes 1, 8, and 18 (each in 2/12 patients).

There was only one previous study that examined the CNV in FHRCC/HLRCC. Koski et al. studied 11 genetically confirmed HLRCCs and attempted to identify the specific chromosomal copy number changes characteristic of HLRCC. All tumors included in their study were morphologically defined as type 2 PRCC, according to the 2004 WHO classification. Array CGH analysis was successful in all 11 cases and showed that the most frequent changes were gains of chromosomes 2, 7, and 17 and losses in 13q12.3-q21.1, 14, 18, and X. They were able to confirm the gain of 17q and losses of 13q, 14q, 18p, and X at a frequency of 38% [32]. Copy number variation pattern in our study was also highly variable, which is similar to what was reported by Koski et al.

In light of the recent evidence, HLRCC/FHRCC is no longer considered part of the PRCC spectrum. PRCC represents a highly heterogeneous group of tumors with broad morphological spectrum and distinct immunohistochemical profile. In fact, CNV pattern of PRCC is much more complex than traditionally thought. Of all PRCC subtypes, PRCC type 1 seems to be the most genetically uniform group, while other types show different degrees of heterogeneity [48]. Nonetheless, the gains of chromosomes 7 and 17 are the most common findings even in PRCC type 2 (reported in 31%–69% for chromosome 7, and 50%–69% for chromosome 17). Other frequent chromosomal changes in PRCC type 2 include a polysomy of chromosomes 12, 16 and 20. Loss of gonosome Y was described in 64–90% male cases of PRCC type 2. Other chromosomal gains described with enormous variability in a small percentage of cases include gains of chromosomes 1, 2, 3, 4, 5, 6, 8, 9, 13, 18, 19 and 22, as well as losses of chromosomes 1, 2, 3, 4,5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 17, 18, 19, 20, 21, 22, and X [10,12,19,22,25,26,48].

On the basis of the current knowledge, we believe that CNV in HLRCC/FHRCC partially overlaps with the CNV described in PRCC. Considering the wide spectrum of numerical aberrations in PRCC, it is not surprising that there is a partial overlap of CNV in HLRCC/FHRCC and PRCC. Nonetheless, we were not able to identify a characteristic CNV associated with FHRCC/HLRCC, which may provide either diagnostic utility or clinical significance in routine practice.

5. Conclusions

Copy number variation pattern in FHRCC/HLRCC appears to be highly variable. The analyzable samples in this study showed complex copy number variations, affecting mainly chromosomes 4, 9, 13, 14, 15, and 17.

Our findings suggest that FHRCC/HLRCC is one of the most heterogeneous renal tumors from histologic and chromosomal perspectives. It demonstrates a variable morphology and the immunohistochemical evaluation can be challenging, CNV does not provide a useful diagnostic tool in identifying these cases. Immunohistochemical staining and especially molecular genetic evaluation of *FH* gene mutations/LOH remain the gold standard in identifying FHRCC/HLRCC.

Table 2
Molecular genetic analyses.

Case	FH mutation analysis	Low pass whole genome sequencing CNVs
Case 1	c.698G > A p.(Arg233His)	−1, −4, −13, −14, −15
Case 2	c.698G > A p.(Arg233His)	−1p, −14, +15
Case 3	c.911_917delCTTTTGT p.(Phe305Leufs*22)	−4, −9, −15, +17
Case 4	c.805delA p.(Ile269fs*15)	Neg.
Case 5	c.395_398delTAAAT p.(Leu132*)	Neg.
Case 6	c.1189G > A p.(Gly397Arg) + LOH	+3, −4, −8p, −9, −13, −15, −18q
Case 7	c.174_177dupTGAAA p.(Leu60*)	−4q, −6q, −8p, −9, −13, −14, −15, −17p, −18q, −20p, −22
Case 9	c.496G > T p.(Gly166*)	+2, −3q, +4, +7, +10q, −16, +17
Case 11	c.239dupA p.(Ile81Aspfs*14)	-4q, +13q, +16q, +17
Case 12	c.589A > T p.(Ile197Phe) + LOH	Neg.
Case 13	c.1118A > G p.Asn373Ser	Neg.
Case 14	c.[(698G > T(;)1098_1099insTT)]/p.[(Arg233Leu(;)Ile367LeufsTer7)]	+1q, +2, +3, +5p, +6, +7, +8, +9, +10, +11, +12, +13, +15, +16, +17, +18, +19, +20, +21, +22

Neg. no loss or gain detected.

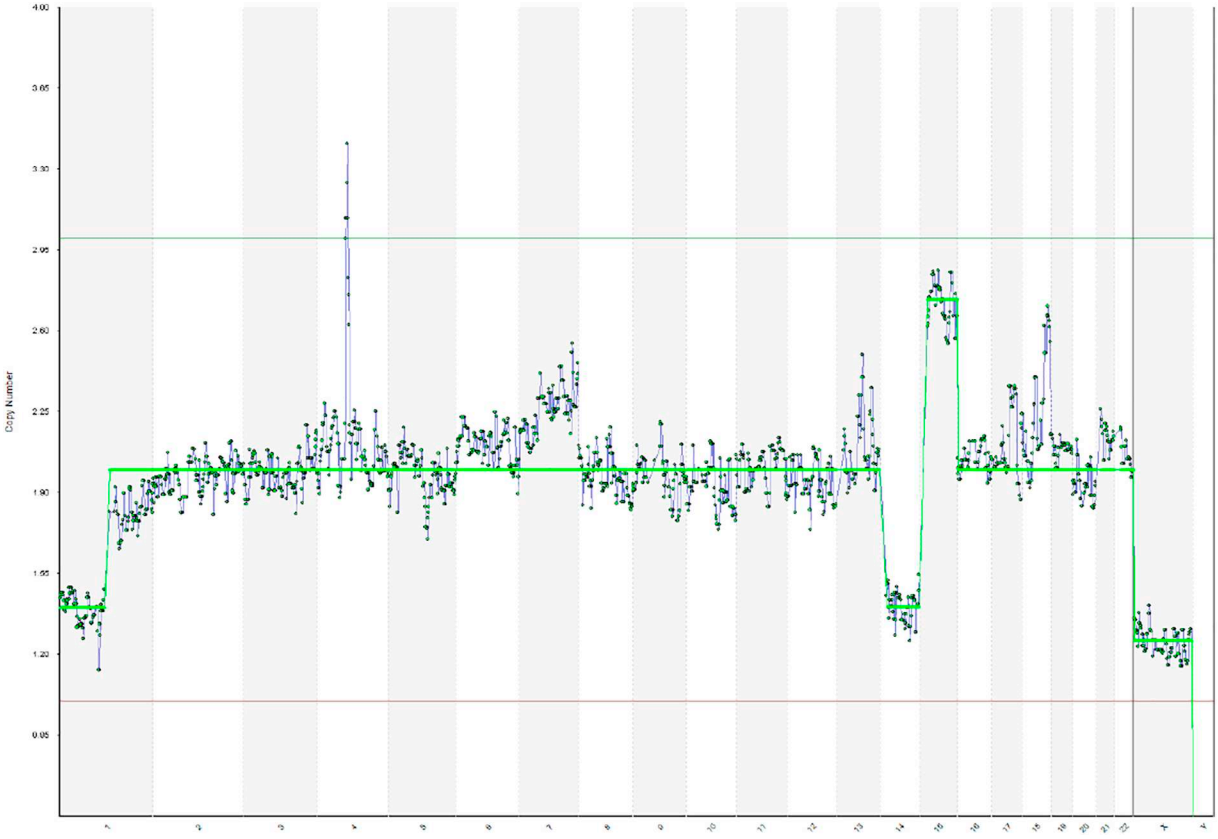

Fig. 4. Chromosomal numerical aberration pattern (CNV) chart of case 2. X axis - numbers of chromosomes, Y axis copy number.

Table 3
Summary of CNV pattern.

Case	Gains	Losses
Case 1	Neg.	−1, −4, −13, −14, −15
Case 2	+15	−1p, −14
Case 3	+17	−4, −9, −15
Case 4	Neg.	Neg.
Case 5	Neg.	Neg.
Case 6	+3	−4, −8p, −9, −13, −15, −18q
Case 7	Neg.	−4q, −6q, −8p, −9, −13, −14, −15, −17p, −18q, −20p, −22
Case 9	+2, +4, +7, +10q, +17	−3q, −16
Case 11	+13q, +16q, +17	−4q
Case 12	Neg.	Neg.
Case 13	Neg.	Neg.
Case 14	+1q, +2, +3, +5p, +6, +7, +8, +9, +10, +11, +12, +13, +15, +16, +17, +18, +19, +20, +21, +22	Neg.

Neg. - negative.

Disclosure of conflict of interest

All authors declare no conflict of interest.

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