Supporting Data to

Molecular Characterization of an Embryonal Rhabdomyosarcoma Occurring in a Patient with Kabuki Syndrome.

Report and Literature Review in the Light of Tumor Predisposition Syndromes

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Supporting data

Supporting methods

Literature review The PubMed (ncbi.nlm.nih.gov/) based search included search terms “Kabuki and cancer", "Kabuki and malignancy", "Kabuki and tumor" as well as “*KMT2D* and cancer", "*KMT2D* and malignancy" and "*KMT2D* and tumor". In addition, the references in (case) reports of patients with Kabuki syndrome and a concomitant malignancy were screened for relevant publications. Also articles including the Supporting Data reporting on large series of patients with Kabuki syndrome were explored for patients with a malignancy. In the case no *KMT2D* or *KDM6A* variant was reported, the clinical features (photographs, clinical characteristics) were assessed for substantiation of the diagnosis of Kabuki syndrome by two investigators (S.M.A. and C.T.R.M.S.). With the Kabuki syndrome international consensus diagnostic criteria as guideline [1], the clinical diagnosis in those cases was scored as following: “(clinical features compatible with) Kabuki syndrome”, “clinical features not compatible with Kabuki syndrome” or “insufficient information for assessment of the diagnosis”. Only high-grade or intermediate-grade malignancies were included. E.g., patients with Kabuki syndrome and Becker naevus [2], pilomatrixoma [3, 4] or non-monoclonal lymphoproliferation [5] were excluded. In addition one recently published patient with Kabuki syndrome and multiple endocrine neoplasia type 2 A (MEN2A) caused by a pathogenic *RET* mutation who developed a pheochromocytoma was not included in the analysis (as if the pheochromocytoma was benign or malignant was not reported and most MEN2 related pheochromocytomas have a low risk for malignancy [6, 7]) [8]. Two patients with pheochromocytoma [9] and one with severe aplastic anaemia [10], who had constitutional missense *KMT2D* variants were not included as these patients either lacked any Kabuki-syndrome related features [9] or lacked a (clear) Kabuki phenotype (dysmorphism and intellectual disability were absent) [10]. Also patients with rare, non-truncating *KMT2D* germline variants and B-cell neoplasms were excluded [11]. Along the same lines, (pediatric) patients with Hodgkin lymphoma [12] and neuroblastoma [13] with

missense germline *KMT2D* variants but without any mentioning of Kabuki syndrome were not included. Subsequently we tried – based on the data presented in the individual manuscripts - to evaluate if the clinicopathologic and molecular features were typical for that malignancy type in the general population.

DNA-methylation : Analysis of the genome-wide methylation pattern was performed as previously described [14, 15]. In brief, ≈ 500 ng of genomic DNA isolated from fresh frozen tissue was subjected to bisulfite conversion using the EZ DNA Methylation kit (ZymoResearch, Irvine, CA, USA) according to manufacturers' instructions. Subsequently, the bisulfit converted DNA was hybridized on Infinium® MethylationEPIC (EPIC) BeadChip (Illumina Inc., San Diego USA) according to manufacturers' protocol. Raw methylation data was processed and normalised using the GenomeStudio software (v2011.1; methylation module 1.9.0; Illumina) applying the default settings. For data normalisation, the intrinsic controls present on the array were used. Subsequently, rs loci, loci on gonosomes and loci with a detection p value > 0.01 were excluded from further analysis. For molecular classification the "DKFZ sarcoma classifier" (version v12.2) available on www.molecularneuropathology.org/msp/ was applied [16]. DNA methylation data of five controls (blood), hybridized on the Human Methylation 450k BeadChip (450k array) and processed as already described in Bens et al., were used for comparison [17]. DNA methylation values corresponding to the imprinted regions H19 / imprinting center 1 (IC1) / differentially methylated region 1 (DMR1) and KCNQ1/KCNQ1OT1 imprinting center 2 (IC2) / differentially methylated region 2 (DMR2) were extracted from the 850k (n= 82 CpGs) and 450k (n=75 CpGs) data and visually compared. For copy number variant (CNV) analysis of the methylation data the R-package minfi (version 1.40.0) was used for normalisation and subsequently analysed with the package conumee (version 1.24.0)[18, 19].

Exome-sequencing (ES) : ES was performed on ≈ 50 ng of genomic DNA isolated from fresh frozen tissue using the NextSeq High Output Kit v2.5 (300 cycles; Illumina: Nextera™ Exome Kit) and sequenced on a NextSeq platform. Data was analysed with Varvis-Software Version 1.18.4 (Limbus Medical Technologies GmbH, Rostock). Genome build GRCh37/hg19 was

used. Exome data were filtered for a virtual panel of cancer predisposition genes with a total of 107 genes analyzed (according to the TruSightCancer Panel Illumina, San Diego, Ca., USA; 95 genes, Supporting Table S1). In addition *KMT2D*, *KDM6A* as well as 10 genes recurrently mutated in embryonal and/or fusion negative rhabdomyosarcoma were analysed [20–22].

Supporting references Table 1 and Supporting Table S4

The Supporting references for the common/general (clinical)presentation for the reported tumor entities include: embryonal rhabdomyosarcoma [23, 24], synovial sarcoma [25], low-grade fibromyxoid sarcoma [26, 27], giant cell fibroblastoma [28, 29], desmoid fibromatosis [29–32], Burkitt lymphoma [33, 34], Hodgkin lymphoma [35], pre-B-ALL [36], Wilms tumor / nephroblastoma [37, 38], neuroblastoma [37–39], hepatoblastoma [37, 38, 40], ependymoma [41], hepatocellular adenoma [42, 43] hepatocellular carcinoma [43, 44] and endometrial cancer [45].

Legends to Supporting Figures

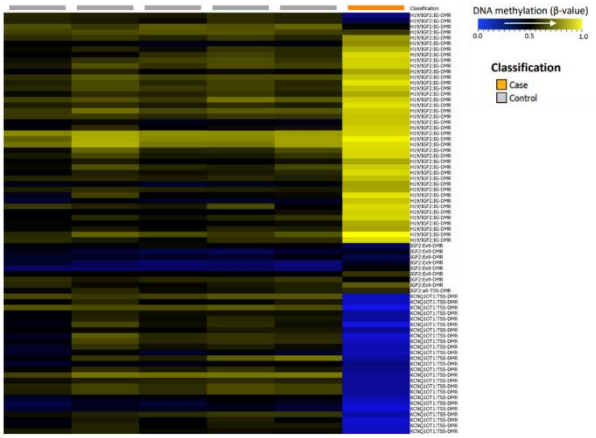
Supporting Figure S1

Heatmap of the Beckwith-Wiedemann imprinted locus on chromosome 11p15 showing methylation of the rhabdomyosarcoma of the patient (orange) compared to the 5 controls (blood) (grey). A DNA methylation value (Beta-value) of 0.5 was set as normal, a value of 0.0 indicates hypo- and 1.0 hypermethylation.

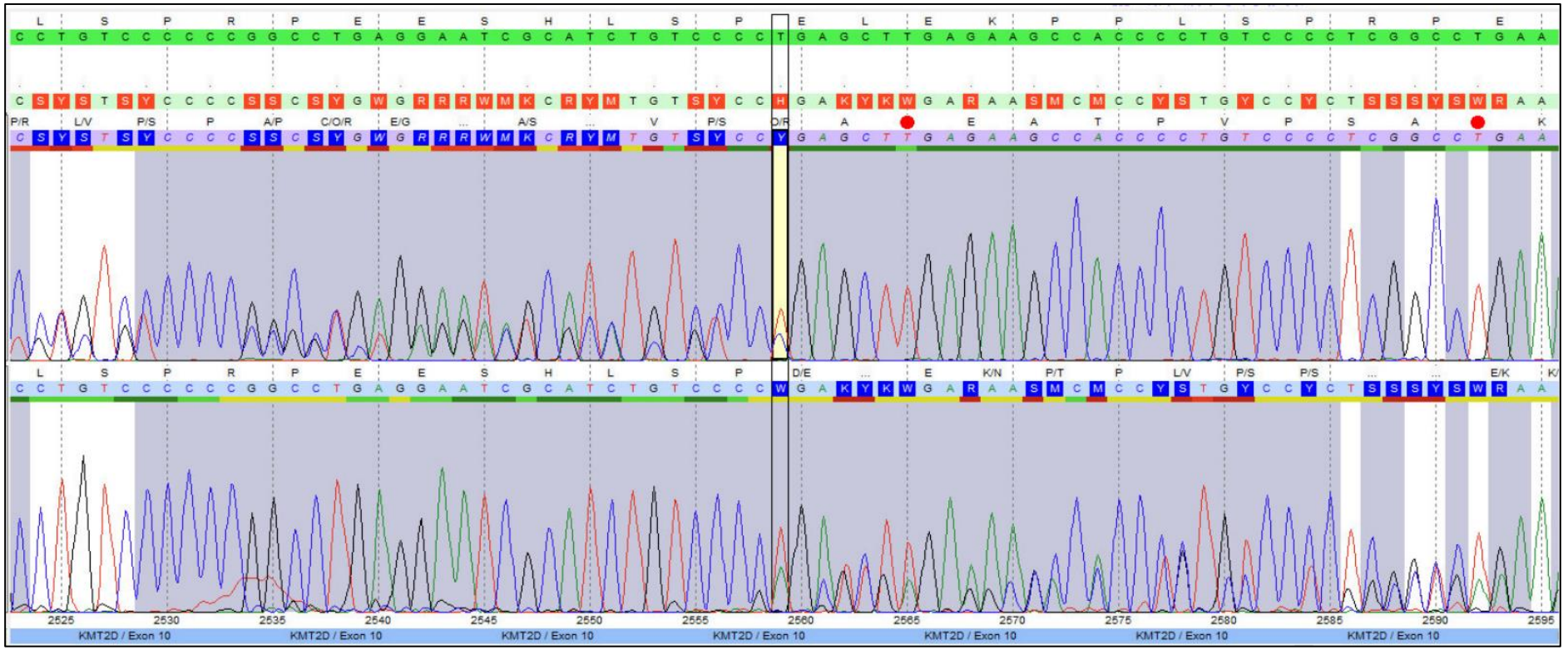
Supporting Figure S2

Screenshot from Integrative Genomics Viewer (IGV) of Sanger sequence of the position of the germline variant c.2558_2559delCT in Exon 10 in tumor material. Upper panel, reverse sequence and lower panel, forward sequence. Many of the nucleotide peaks are overlapping but in case two non-overlapping peaks are present at the same nucleotide position almost exclusively the wild-type sequence (depicted on top in green) has higher peaks compared to the mutated sequence which is suggestive of gain of the wild-type and not the mutated allele in the trisomy 12 (figure 1E).

Supporting Figure S1



Supporting Figure S2



Supporting Table S1

Gene list of the virtual panel including all 107 analysed tumor predisposition, Kabuki syndrome and sarcoma related genes.

AIP	*CDH1*	*ERCC3*	*FANCL*	*KRAS*	*PALB2*	*RECQL4*	*TMEM127*
ALK	*CDK4*	*ERCC4*	*FANCM*	*MAX*	*PHOX2B*	*RET*	*TP53*
APC	*CDKN1C*	*ERCC5*	*FBXW7*	*MEN1*	*PIK3CA*	*RHBDF2*	*TSC1*
ARID1A	*CDKN2A*	*EXT1*	*FGFR4*	*MET*	*PMS1*	*RUNX1*	*TSC2*
ATM	*CEBPA*	*EXT2*	*FH*	*MLH1*	*PMS2*	*SBDS*	*VHL*
BAP1	*CEP57*	*EZH2*	*FLCN*	*MSH2*	*PPM1D*	*SDHAF2*	*WRN*
BCOR	*CHEK2*	*FANCA*	*GAB1*	*MSH6*	*PRF1*	*SDHB*	*WT1*
BLM	*CYLD*	*FANCB*	*GATA2*	*MUTYH*	*PRKAR1A*	*SDHC*	*XPA*
BMPR1A	*DDB2*	*FANCC*	*GPC3*	*MYOD1*	*PTCH1*	*SDHD*	*XPC*
BRCA1	*DICER1*	*FANCD2*	*HNF1A*	*NBN*	*PTEN*	*SLX4*	
BRCA2	*DIS3L2*	*FANCE*	*HRAS*	*NF1*	*PTPN11*	*SMAD4*	
BRIP1	*EGFR*	*FANCF*	*KDM6A*	*NF2*	*RAD51C*	*SMARCB1*	
BUB1B	*EPCAM*	*FANCG*	*KIT*	*NRAS*	*RAD51D*	*STK11*	
CDC73	*ERCC2*	*FANCI*	*KMT2D*	*NSD1*	*RB1*	*SUFU*	

Supporting Table S2: primer sequences used for Sanger sequencing of the germline variant in tumor DNA.	
KMT2D_Ex_10_P1_F	**GTAGCGCGACGGCCAGTATTGAGGAATTGCACCTGTCC**
KMT2D_Ex_10_P1_R	**CAGGGCGCAGCGATGACGCAAAAGAAGGGCTCTTAGATTAGATG**

Supporting Table S3: Identified variants in the ERMS-tumor tissue by exome sequencing[a]										
								Variant predictions[b]		
Variant position and description	**Alt Func**	**Cov / VAF**	**Gene**	**Transcript**	**c.DNA**	**AA Change**	**COSMIC/ SOM**	**SIFT**	**PP**	**CADD**
Chr13(GRCh37):g.103510688C>G	MV	25/76	*ERCC5*	NM_000123.4	c.592C>G	p.(Pro198Ala)	No	T	PD	20.8
Chr17(GRCh37):g.7579472G>C	MV	50[d]	*TP53*	NM_000546.5	c.215C>G[d]	p.(Pro72Arg)	YES/YES	T	B	9.2
Variants in *KMT2D*										
Chr12(GRCh37):g.49444907_49444908del[c]	Fs	NA	*KMT2D*	ENST00000301067.7	c.2558_2559del	p.Pro853Argfs*3	NO	NA	NA	23.3
Chr12(GRCh37):g.49439659C>T	Intron	88[d]	*KMT2D*	ENST00000301067.7	c.4741+44G>A[d]	p.?	NO	NA	NA	NA
Chr12(GRCh37):g.49424534G>A	SYN	35/49	*KMT2D*	ENST00000301067.7	c.13689C>T	p.Pro4563(=)	YES/YES	NA	NA	NA
Variants in *KDM6A*										
ChrX(GRCh37):g.44938563G>A	SYN	56[d]	*KDM6A*	ENST00000377967.4	c.3111G>A[d]	p.Gln1037(=)	YES/YES	NA	NA	NA

AA, amino acid ; Alt, alteration/altered ; CADD, Combined Annotation Dependent Depletion score ; Chr, chromosome ; COSMIC, Catalogue Of Somatic Mutations In Cancer ; Cov, coverage at nucleotide position ; ERMS, embryonal rhabdomyosarcoma ; Fs, frameshift ; Func, function ; MV, missense variant ; NA, not applicable ; PP, Polymorphism Phenotyping ; SIFT, Sorting Intolerant from Tolerant ; SOM, somatic origin of the variant (once) confirmed in COSMIC-database ; SYN, synonymous variant ; VAF, variant allele frequency (%).

[a]missense variants are predicted to have moderate impact, truncating variants high-impact. Low-impact variants are not included. The variant in *ERCC5* is a class 3 variant, the truncating *KMT2D* variant class 5. All other variants probably benign/likely benign.

[b]For synonymous variants no variant predictions performed. For splice variants SIFT and PolyPhen predictions are not applicable.

[c]nucleotide position of germline variant insufficiently covered with exome sequencing, determined by Sanger-sequencing.

[d]Homozygous.

Supporting Table S4: Summary of literature review of patients with Kabuki syndrome and a malignancy with insufficient information

Pt	Sex, age	*KMT2D*/*KDM6A* variant	Clinical diagnosis (variant neg/ NA)[a]	Malignancy[b]	Histopathological features	Molecular tumor features	Typical (clinical) presentation (refs)?[c]	Predisposing factors?[s]	Reference case
Hematologic malignancies (n=2)									
S1	M (5)	NR	Insufficient information	Burkitt lymphoma	NR	NR	Yes. Typical age and gender.	No (potential) predisposing factors reported other than Kabuki syndrome.	[46]
S2[e]	NR, childhood	NR	Insufficient information	NHL	NR	NR	NA	NA	[47]
Embryonal tumours (n=1)									
S3[e]	NR	NR	(compatible with) Kabuki syndrome[f]	Neuroblastoma	NR	NR	NA	NA	[48]

M, male ; NA, not available ; NHL, non-Hodgkin lymphoma ; NR, not reported.
[a]Clinical diagnosis based on assessment of clinical features presented in the individual manuscripts by the author's of the present study, see the "supplementary materials and method's" section.
[b]Diagnosis, clinico- and histopathologic features as provided in the original manuscript. These may not fulfil the present World Health Organisation (WHO)-criteria for the respective tumors.
[c]References for common/general (clinical) presentation of individual tumor entities in Supporting References.
[d]Includes (other)potential predisposing (genetic) factors for the reported malignancy
[e]Insufficient information to include in literature review and/or discussion. Overlap with other published cases can not be excluded.
[f]Patients in the included manuscript have a clinical diagnosis (compatible with) Kabuki syndrome but for the individual patients, including the patient with neuroblastoma, no individual patient characteristics are provided. Due to the limited information provided for this patient this patient was excluded from the literature review.

Supporting Table S5: Summary of oncological characteristics, therapy and outcome of patients with Kabuki syndrome and a malignancy[a]							
Pt	**Sex, age**	**Malignancy[c]**	**Relapse, SMN, bilateral-/multifocal or meta-synchronous cancers?**	**Therapy**	**Excessive chemotherapy toxicity?**	**Outcome**	**Ref. case**
Bone- and soft-tissue tumors (n=5)							
1	F (10)	Embryonal rhabdomyosarcoma	No	Chemotherapy, surgery	Neutropenic sepsis[b]	Deceased after sepsis post-chemotherapy	*this study*
2	F (16)	Synovial sarcoma	Local relapse +4 Mo	Chemotherapy, surgery, radiotherapy	Not reported but no specific information regarding presence/absence of toxicity to chemotherapy.	Deceased within weeks after relapse due to progression	[49]
3	F (10)	Low-grade fibromyxoid sarcoma	No	Surgery	Not applicable (surgery)	No recurrence, +16 Mo after resection	[50]
4	F (10 & 12)	Giant cell fibroblastoma[d]	Recurrence +19 Mo after surgical resection	10 yrs: surgery 12 yrs: surgery	Not applicable (surgery)	No relapse at +6 Mo after resection of second tumor	[51]
5	F (10)	Aggressive desmoid fibromatosis	No	Surgery	Not applicable (surgery)	No (long term) follow-up reported	[52]
Hematologic malignancies (n=5)							
6	M (5)	Burkitt lymphoma	No	Surgery, chemotherapy	Not reported but no specific information regarding presence/absence of toxicity to chemotherapy	Complete remission, no evidence of disease +11.5 Yr	[53]
7	M (3)	Burkitt lymphoma	No	Chemotherapy	Not reported but no specific information regarding presence/absence of toxicity to chemotherapy	Complete remission followed by maintenance therapy, no relapse +3 Yr	[54]
8	M (3)	Burkitt lymphoma	NA	NA	NA	NA	[55]
9	M (≥32)	Hodgkin lymphoma	No[e]	Chemotherapy	Not reported but no specific information regarding toxicity response to chemotherapy	Complete remission	[56]
10	F (2)	Pre-B-ALL	No	Chemotherapy	Repetitive seizures[f]	Complete remission, +14 Mo after diagnosis (under maintenance therapy)	[57]

Pt	Sex, age	Malignancy[c]	Relapse, SMN, bilateral-/multifocal or meta-synchronous cancers?	Therapy	Excessive chemotherapy toxicity?	Outcome	Ref. case
Embryonal tumors (n=4)							
11	F (3)	Wilms tumor / nephroblastoma	No	Surgery, chemotherapy	Liver dysfunction (grade 3) and seizures (grade 2) requiring dose reductions and interval adjustments. No late effects after chemotherapy	Disease-free +18 Mo after diagnosis	[58]
12	F (0)	Neuroblastoma	No	Surgery	Not applicable (surgery)	Complete remission, +18 Mo after diagnosis	[59]
13	F (NR)	Neuroblastoma	NA	NA	NA	NA	[60]
14	M (6)	Fetal-type hepatoblastoma	No	Chemotherapy and surgery	No	Complete remission, +2 Yr after end of treatment	[59]
Other (n=4)							
15	F (23)	Ependymoma	No	Surgery	Not applicable (surgery)	Disease free, +14 Mo after diagnosis	[61]
16	F (15)	Hepatocellular carcinoma	No[g]	Surgery (liver transplantation)	Not applicable (surgery)	NA	[62]
17	F (16)	Carcinoma, unknown primary origin	No	Chemotherapy	Sepsis following febrile neutropenia[b] after chemotherapy	Progression. Deceased after sepsis, respiratory failure and cancerous lymphangiosis	[63]
18	F (≤31)[h]	Endometrial cancer	NA	NA	NA	NA	[64]

B-ALL, B-cell acute lymphoblastic leukemia ; F, female ; M, male ; Mo, months ; NA, not available ; NR, not reported ; Pt, patient ; SMN, second malignant neoplasms ; Yr, year.
[a]Patient S1 with Burkitt lymphoma with insufficient clinical information regarding Kabuki syndrome is not present in this table but is included in Supporting Table S4.
[b]Absolute neutrophil count not provided. [c]Diagnosis as provided in the original manuscript. This may not fulfil the present World Health Organisation (WHO) criteria for the respective tumor. [d]Initial tumor diagnosed as spindle cell hemangioma, 2nd tumor at same site as giant cell fibroblastoma. [e]Extensive lipomatosis, benign tumor. [f]State of consciousness during seizures and/or if medication was given for seizure control not provided. [g]Multifocal hepatic adenomas, single high-grade neoplasm (hepatocellular carcinoma). [h]Age at last examination.

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