Rosette-forming glioneuronal tumors share a distinct DNA methylation profile and mutations in *FGFR1*, with recurrent co-mutation of *PIK3CA* and *NF1*

Philipp Sievers[1,2], Romain Appay[3,4], Daniel Schrimpf[1,2], Damian Stichel[1,2], David E. Reuss[1,2], Annika K. Wefers[1,2], Annekathrin Reinhardt[1,2], Roland Coras[5], Viktoria Ruf[6], Karin de Stricker[7], Henning Boldt[8], Bjarne Winther Kristensen[8,9], Jeanette Krogh Petersen[8], Benedicte P. Ulhøi[10], Maria Gardberg[11], Eleonora Aronica[12,13], Martin Hasselblatt[14], Wolfgang Brück[15], Wolfgang Wick[16,17], Christel Herold-Mende[18], Daniel Hänggi[19], Sebastian Brandner[20,21], Felice Giangaspero[22,23], David Capper[24,25,26], Elisabeth Rushing[27], Pieter Wesseling[28,29], Stefan M. Pfister[30,31,32], Dominique Figarella-Branger[3,4], Andreas von Deimling[1,2], Felix Sahm[1,2,30*], David T. W. Jones[30,33*]

[1]Department of Neuropathology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany

[2]Clinical Cooperation Unit Neuropathology, German Consortium for Translational Cancer Research (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

[3]APHM, Hôpital de la Timone, Service d'Anatomie Pathologique et de Neuropathologie, Marseille, France

[4]Aix-Marseille Univ, CNRS, INP, Inst Neurophysiopathol, Marseille, France

[5]Department of Neuropathology, University of Erlangen-Nürnberg, Erlangen, Germany

[6]Department of Neuropathology, Ludwig-Maximilian University, Munich, Germany

[7]Department of Pathology, Rigshospitalet, Copenhagen, Denmark

[8]Department of Pathology, Odense University Hospital, Odense, Denmark

[9]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[10]Department of Pathology, Aarhus University Hospital, Aarhus, Denmark

[11]Department of Pathology University of Turku and Turku University Hospital, Turku, Finland

[12]Department of (Neuro)Pathology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[13]Stichting Epilepsie Instellingen Nederland (SEIN), Zwolle, The Netherlands

[14]Institute of Neuropathology, University Hospital Münster, Münster, Germany

[15]Institute of Neuropathology, University Medical Center, Göttingen, Germany

[16]Clinical Cooperation Unit Neurooncology, German Consortium for Translational Cancer Research (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

[17]Department of Neurology and Neurooncology Program, National Center for Tumor Diseases, Heidelberg University Hospital, Heidelberg, Germany

[18]Division of Experimental Neurosurgery, Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany

[19]Department of Neurosurgery, University Medical Centre Mannheim, University of Heidelberg, Mannheim, Germany

[20]Division of Neuropathology, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, Queen Square, London, UK

[21]Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, Queen Square, London, UK

[22]Department of Radiological Sciences, Oncology and Anatomical Pathology, Sapienza University Rome, Rome, Italy

[23]IRCCS Neuromed, Pozzilli, Italy

[24]Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany

[25]Institute of Neuropathology, Berlin Institute of Health, Berlin, Germany

[26]German Cancer Consortium (DKTK), Partner Site Berlin, Berlin, Germany

[27]Institute of Neuropathology, University Hospital Zurich, Zurich, Switzerland

[28]Department of Pathology, VU University Medical Center/Brain Tumor Center Amsterdam, Amsterdam, The Netherlands

[29]Department of Pathology, Princess Máxima Center for Pediatric Oncology and University Medical Center Utrecht, Utrecht, The Netherlands

[30]Hopp Children’s Cancer Center at the NCT Heidelberg (KiTZ), Heidelberg, Germany

[31]Division of Pediatric Neurooncology, German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

[32]Department of Pediatric Oncology, Hematology, Immunology and Pulmonology, University Hospital Heidelberg, Heidelberg, Germany

[33]Pediatric Glioma Research Group, German Consortium for Translational Cancer Research (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

* These authors share senior authorship

Corresponding authors:

Felix Sahm

felix.sahm@med.uni-heidelberg.de

David T. W. Jones

david.jones@kitz-heidelberg.de

Abstract

Rosette-forming glioneuronal tumor (RGNT) is a rare brain neoplasm that primarily affects young adults. Although alterations affecting the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signaling pathway have been associated with this low-grade glioneuronal entity, comprehensive molecular investigations of RGNT in larger series have not been performed to date, and an integrated view of their genetic and epigenetic profiles is still lacking. Here we describe a genome-wide DNA methylation and targeted sequencing-based characterization of a molecularly distinct class of tumors (n = 30), initially identified through genome-wide DNA methylation screening amongst a cohort of > 30,000 tumors, of which most were diagnosed histologically as RGNT. *FGFR1* hotspot mutations were observed in all tumors analyzed, with co-occurrence of *PIK3CA* mutations in about two thirds of the cases (63%). Additional loss-of-function mutations in the tumor suppressor gene *NF1* were detected in a subset of cases (33%). Notably, in contrast to most other low-grade gliomas, these tumors often displayed co-occurrence of two or even all three of these mutations. Our data highlight that molecularly defined RGNTs are characterized by combined genetic alterations affecting both MAPK and PI3K signaling pathways. Thus, these two pathways appear to synergistically interact in the formation of RGNT, and offer potential therapeutic targets for this disease.

Keywords: Rosette-forming glioneuronal tumor, RGNT, Brain tumor, DNA methylation profile, Molecular classification, MAPK, PI3K, *FGFR1*, *PIK3CA*, *NF1*

Introduction

Rosette-forming glioneuronal tumor (RGNT) is an uncommon central nervous system (CNS) neoplasm that primarily affects young adults [17]. It typically arises in the midline, usually occupying a substantial fraction of the fourth ventricle. In the World Health Organization (WHO) classification of brain tumors 2007, RGNT was therefore per definition associated with the fourth ventricle. However, more recent reports have shown that it can also affect other sites [1,2,17,25,29]. Thus, the extension “of the fourth ventricle” was abandoned in the current update of the classification [17].

Histologically, RGNT is characterized by a biphasic histologic architecture consisting of well-differentiated neurocytic cells forming rosettes or perivascular pseudorosettes and a glial component resembling pilocytic astrocytoma [9,14,19,23]. While large-scale genomic and epigenomic analyses over the past decade have immensely contributed to our understanding of molecular mechanisms underlying many primary brain tumors, current knowledge on the molecular background of RGNT is based mainly on individual case reports or small series. Targeted molecular analyses revealed absence of *KIAA1549-BRAF* fusions or activating *BRAF* mutations [6] which are a hallmark of pilocytic astrocytoma [10,11] and can also be found in other low-grade glial and glioneuronal tumors [30]. In contrast, activating mutations in *FGFR1* [7,16] and/or *PIK3CA* [3,5,16,28] have been described in a subset of RGNTs.

We here performed a combined (epi)genomic analysis of genome-wide DNA methylation profiling and targeted next-generation DNA sequencing data from 30 tumors in order to evaluate the underlying molecular background and to identify new diagnostic biomarkers as well as potentially targetable alterations.

Materials and methods

Study population and sample collection

Tumor samples and retrospectively determined clinical data from 30 patients were obtained from multiple international collaborating centers and collected at the Department of Neuropathology of the University Hospital Heidelberg (Heidelberg, Germany). Case selection was based on unsupervised hierarchical clustering of genome-wide DNA methylation data in a cohort of > 30,000 tumors that revealed a molecularly distinct group of tumors comprising 30 samples, of which the majority was diagnosed histologically as RGNT. Tissue was available for 24 cases thereof. Additionally, DNA methylation data of numerous well characterized reference samples representing CNS tumors of known histological and/or molecular subtype were used for comparative analyses [4]. Detailed descriptions of the reference methylation classes are outlined under https://www.molecularneuropathology.org. Tissue sample collection and processing, data collection, and use were performed in accordance with local ethics regulations and approvals. Clinical patient details are listed in Fig. 2 and Supplementary Table 1.

Histology and immunohistochemistry

All samples with available tissue (n = 24/30) were histopathologically re-assessed according to the WHO 2016 classification of tumors of the central nervous system. Formalin-fixed, paraffin-embedded (FFPE) tissue samples were stained with hematoxylin and eosin (H&E) according to standard protocols. For all cases with sufficient material, immunohistochemistry was performed on a Ventana BenchMark ULTRA Immunostainer using either the OptiView DAB IHC Detection Kit or the ultraView Universal DAB Detection Kit (Ventana Medical Systems, Tucson, Arizona, USA). Antibodies were directed against: glial fibrillary acid protein (GFAP; Z0334, rabbit polyclonal, 1:1000 dilution, Dako Agilent, Santa Clara, CA, USA), Olig2 (clone EPR2673, rabbit monoclonal, 1:100 dilution, Abcam, Cambridge, UK), Synaptophysin (clone MRQ-40, rabbit monoclonal, 1:160 dilution, Cell Marque Corp., Rocklin, CA, USA), NeuN (clone A60, mouse monoclonal, 1:100 dilution, Millipore, Burlington, MA, USA), CD34 (clone QBEnd/10, mouse monoclonal, Ventana Medical Systems), Ki-67 (clone MIB-1, mouse monoclonal, 1:100 dilution, Dako Agilent).

DNA extraction

Representative tumor tissue with highest available tumor cell content (~50-90%) was histologically identified and selected for nucleic acid extraction. Genomic DNA was extracted from fresh-frozen or formalin-fixed and paraffin-embedded (FFPE) tissue samples using the automated Maxwell system with the Maxwell 16 Tissue DNA Purification Kit or the Maxwell 16 FFPE Plus LEV DNA Purification Kit (Promega, Madison, WI, USA), according to the manufacturer’s instructions.

DNA methylation array processing and copy number profiling

The Infinium HumanMethylation450 (450k) BeadChip or Infinium MethylationEPIC (850k) BeadChip array (Illumina, San Diego, CA, USA) were used to obtain genome-wide DNA methylation profiles of tumor samples according to the manufacturer’s instructions at the Genomics and Proteomics Core Facility of the German Cancer Research Center (DKFZ; Heidelberg, Germany). DNA methylation data were generated from both fresh-frozen and FFPE tissue samples. On-chip quality metrics of all samples were carefully controlled. Processing of DNA methylation data was performed with custom approaches as previously described [8,27]. Copy number profiles were generated using the ‘conumee’ package for the “R” environment (http://bioconductor.org/packages/release/bioc/html/conumee.html). All samples were checked for duplicates by pairwise correlation of the genotyping probes on the 450k/850k array.

Targeted next-generation DNA sequencing and mutational analysis

Targeted exon capture and next-generation sequencing covering the coding regions of 130 genes of particular relevance in brain tumors was performed on a NextSeq 500 sequencer (Illumina) as previously described [24] for all tumor samples (n = 30). Fusion discovery was done based on panel sequencing data using deFuse [18] and arriba (https://github.com/suhrig/arriba/).

Statistical analysis

DNA methylation array data were processed with the R/Bioconductor package minfi (version 1.20). For unsupervised hierarchical clustering of samples, the 20,000 most variably methylated probes by median absolute deviation across the dataset were selected. Samples were hierarchically clustered using Euclidean distance and Ward’s linkage method. DNA methylation probes were reordered using Euclidian distance and complete linkage. For unsupervised 2D representation of pairwise sample correlations, dimensionality reduction by t-distributed stochastic neighbor embedding (t-SNE) was performed using the 20,000 most variable CpG sites according to standard deviation, a perplexity value of 10 and 3000 iterations. Survival data were analyzed by Kaplan-Meier analysis and compared by log-rank test using GraphPad Prism 8 (GraphPad Software, La Jolla, CA, USA). P values < 0.05 were considered significant.

Results

DNA methylation profiling highlights a distinct epigenetic signature of RGNT

Based on an unsupervised analysis of genome-wide DNA methylation data in a cohort of >30,000 tumors, we identified a molecularly distinct group of tumors forming a cluster separate from other established entities. The majority of these were diagnosed histologically as RGNT (Supplementary Table 1 and Fig. 2). A subsequent focused unsupervised hierarchical clustering and t-distributed stochastic neighbor embedding (t-SNE) analysis of DNA methylation patterns of these cases, alongside 106 well-characterized CNS neoplasms encompassing other low-grade glial/glioneuronal tumor entities and control tissue (white matter), consistently confirmed the distinct nature of this class (Fig. 1). This unique pattern supports the consideration of RGNT as a distinct molecular tumor type. Analysis of copy number variations (CNVs) calculated from the DNA methylation array data revealed a flat (=balanced) profile in most of the cases. Only single cases showed a small number of copy number alterations, with no obvious recurrent patterns.

RGNTs are characterized by alterations affecting MAPK and PI3K signaling pathways

To investigate the mutational landscape in RGNT, we performed targeted next-generation sequencing on genomic DNA isolated from 30 tumors (Fig. 2 and Supplementary Table 1). In all analyzed tumors, a missense mutation within the kinase domain of *FGFR1* was identified – resulting in either a p.N546K (n = 22) or p.K656E (n = 8) substitution (details are listed in Supplementary Table 2). Both result in activating alterations within the kinase domain of FGFR1 and were previously reported in other glioneuronal tumors [21]. Additionally, 19 of 30 (63%) of the *FGFR1*-mutant tumors harbored a concomitant mutation in *PIK3CA* which acts as an integral part of the PI3K pathway, including 14 with a p.H1047R, two with a p.E545K, and one each with a p.E542K, p.H1047L or p.G1049R substitution. The mutant allele frequency for the *FGFR1* and *PIK3CA* variants ranged from 23 to 58% / 23 to 48%, consistent with a heterozygous somatic mutation on the background of ~50-90% tumor purity (Supplementary Table 2).

Besides activating *FGFR1* and *PIK3CA* mutations, missense or damaging mutations in *NF1* were identified in 10 of the cases. Allele frequencies (13-55%) were consistent with being heterozygous somatic variants. No indication for a loss of heterozygosity was found by copy number analysis. Notably, seven of the tumors (23%) had a combined triple alteration of *FGFR1*, *PIK3CA* and *NF1* - indicating a cooperative role in tumorigenesis.

Two of the *FGFR1*-mutant tumors also harbored a *PTPN11* variant, typically altered in patients with Noonan syndrome. The *PTPN11* variants could not be verified as being in the germline because analysis was performed without matched normal tissue sample. In one of the cases, however, a Noonan syndrome was clinically known.

Clinical characteristics and morphological features within the molecularly defined RGNT cohort

All cases were located infratentorially, preferentially in the posterior fossa occupying the 4th ventricle and the cerebellum. However, in line with other studies, the molecularly-defined

RGNTs described here also arose in mesencephalic or diencephalic regions [1,2,17,25,29]. Median age of the patients at the time of diagnosis was 32 years (range 10–69) and the sex distribution was balanced (male:female ratio 1.0). Basic clinical characteristics of the cases are summarized in Figure 2 and Supplementary Table 1. Outcome data were available for only ten patients. Analysis of overall survival (OS) of RGNT patients in comparison to reference glioma groups supports classification of the molecularly-rendered RGNT as WHO grade I, in line with the so far histologically-defined entity (Supplementary Fig. 1).

Histologically, all tumors were characterized by a moderate cellularity of neuroepithelial tumor cells. While a glial component consisting of spindle to stellate-shaped astrocytic cells with oval or elongated nuclei in a dense fibrillary background were seen in all tumors, populations of uniform neurocytic cells arranged in rosettes and perivascular pseudorosettes could be observed in only 20 of the 24 cases (Fig. 3). Neurocytic cells typically showed round nuclei with fine stippled chromatin dispersed in a mucoid or fibrillary matrix. In seven of the cases an oligodendroglioma-like cytology was seen focally. Some of the tumors demonstrated eosinophilic granular bodies (n = 9) or Rosenthal fibers (n = 8). Calcification were seen in a small number of tumors (n = 5). Hyalinized vessels and focal reactive vascular proliferation were observed in nine cases. Necrosis was uniformly absent. Mitotic activity was very low to absent. Immunoreactivity for synaptophysin was present in the neurocytic component (Fig. 3), whereas the glial component exhibited strong positivity for GFAP. The tumor cells were Olig2 positive and NeuN and CD34 negative. Proliferation index (Ki67) ranged from 1 to 3% in 22 of the cases, only two of the cases showed a slightly elevated proliferation index of up to 7 or 10%. Notably, all cases were histologically compatible with the diagnosis RGNT, although some cases would more likely have been favored as a typical differential diagnosis of RGNT.

Discussion

Using genome-wide DNA methylation profiling, we have confirmed a highly distinct epigenetic signature of RGNT and shown that tumors within this group share recurrent alterations within the MAPK and PI3K/AKT/mTOR signaling pathways.

As alterations within the kinase domain of *FGFR1* were detected in all tumors analyzed, it seems that RGNTs are primarily driven by mutations leading to constitutive activation of FGFR signaling. Genetic alterations within the FGFR signaling pathway are also common in other low-grade glial and glioneuronal tumors, with missense mutations in *FGFR1*, internal tandem duplication of the kinase domain, and *FGFR1-TACC1* fusions being observed [10,20,21,26,30]. In contrast to those other tumor types, however, RGNT showed further recurrent mutations in the oncogene *PIK3CA*, which acts as an integral part of the PI3K pathway, and in the *NF1* tumor suppressor. Although these genes are each mutated in several other primary brain tumors, concomitant mutations (in such a high frequency as observed here) seem to be extremely uncommon, particularly in low-grade glioneuronal tumors. However, combined activation of MAPK and PI3K/AKT/mTOR signaling pathways has been previously reported in single cases of RGNT [7,16] and therefore appears to be highly characteristic of this molecular class. While *FGFR* alterations are also common in dysembryoplastic neuroepithelial tumor, another low-grade glioneuronal tumor with histological overlap to RGNT, no mutations of *PIK3CA* and only one concomitant *NF1* mutation were found in 32 analyzed cases.

Although there is no certain association with hereditary syndromes, RGNT has been described in patients with neurofibromatosis type 1 [13], as well as Noonan syndrome [12,16]. None of the *NF1* mutations in our cohort could be confirmed as being present in the germline, although only very few cases had germline material available. Two of the *FGFR1*-mutant tumors also displayed a *PTPN11* variant, typically altered in patients with Noonan syndrome. Although matched normal tissue samples were unfortunately not available for these cases, in one of them a Noonan syndrome had already been clinically diagnosed.

In comparison to the vast majority of other low-grade glial and glioneuronal tumors that have alterations exclusively within a single molecular pathway [20,30], RGNT seem to be a multiple-pathway disease, a fact that is more characteristic for high-grade tumors. Furthermore, PI3K/AKT/mTOR pathway alterations have been associated with clinical and histologic aggressiveness in LGG [22] as well as poor outcome in patients with RGNT [7]. However, clinical follow-up data of our series appear in line with the current WHO grade I designation.

Our findings also have important implications for treatment management of patients with subtotally resected or recurrent tumors. Highly potent inhibitors of *FGFR1*, several of which are currently in various phases of clinical development [15], may be valuable treatments for these patients. Similarly, mutations in *PIK3CA* and *NF1* might also be targeted with specific inhibitors of the PI3K and MAPK pathways. However, this will need confirmation in clinical trials.

In conclusion, our findings provide new insight into the molecular genetic background of RGNT and suggest that RGNTs are highly linked to combined MAPK and PI3K/AKT/mTOR signaling pathway activation via concomitant mutations in *FGFR1* and *PIK3CA*, thereby offering options for targeted therapies.

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Figure legends

Fig. 1 Rosette-forming glioneuronal tumor (RGNT) by DNA Methylation Profiling. Unsupervised hierarchical clustering of DNA methylation profiles of 30 rosette-forming glioneuronal tumors alongside 106 well-characterized CNS neoplasms encompassing other low-grade glial/glioneuronal tumor entities and control tissue. Shown in a two-dimensional representation of pairwise sample correlations using the 20,000 most variant probes by t-distributed stochastic neighbor embedding (t-SNE) dimensionality reduction. Reference methylation classes: IDH-mutant astrocytoma (A IDH), IDH-mutant oligodendroglioma (O IDH), posterior fossa pilocytic astrocytoma (LGG, PA PF), ganglioglioma (LGG, GG), midline pilocytic astrocytoma (LGG, PA MID), supratentorial/hemispheric pilocytic astrocytoma and ganglioglioma (LGG, PA/GG), diffuse leptomeningeal glioneuronal tumor subgroup 1 (DLGNT_1), diffuse leptomeningeal glioneuronal tumor subgroup 2 (DLGNT_2), extraventricular neurocytoma (EVN), dysembryoplastic neuroepithelial tumor (LGG, DNT), rosette-forming glioneuronal tumor (LGG, RGNT) and control tissue white matter (CONTROL).

Fig 2 Clinicopathological characteristics and recurrent genetic alterations in rosette-forming glioneuronal tumors examined by DNA methylation profiling and targeted next-generation sequencing. M, male; F, female; RGNT, rosette-forming glioneuronal tumor; LGG/LGGNT, low-grade glial/glioneuronal tumor; PA, pilocytic astrocytoma

Fig. 3 Morphological and immunohistochemical features of rosette-forming glioneuronal tumors. Typical histomorphological features of RGNT showing well-differentiated neurocytic cells forming rosettes and perivascular pseudorosettes (a) with immunoreactivity for synaptophysin (b).

Supplementary Table 1 Summary of clinicopathological characteristics and key genetic alterations identified in the RGNT cohort.

Supplementary Table 2 Single nucleotide variants (SNVs), small insertions/deletions/substitutions and splice site variants detected in the RGNT cohort.

Supplementary Fig. 1 Kaplan–Meier curves for overall survival of methylation class RGNT patients in comparison to reference glioma group patients (pilocytic astrocytoma WHO grade I; diffuse astrocytoma, IDH-mutant, WHO grade II).

Supplementary Fig. 2 Unsupervised hierarchical clustering of DNA methylation profiles of 30 rosette-forming glioneuronal tumors alongside 106 well-characterized CNS neoplasms encompassing other low-grade glial/glioneuronal tumor entities and control tissue.

Supplementary Table 1 - Summary of clinicopathological characteristics and key genetic alterations identified in the RGNT cohort

Case #	Age (years)	Sex	Tumor location	Diagnosis	*FGFR1*	*PIK3CA*	*NF1*	*PTPN11*	Copy number variations
1	12	m	4th ventricle	LGGNT	p.N546K	p.H1047R		p.N58H	balanced
2	23	m	4th ventricle	RGNT	p.N546K	p.H1047R	splicing		balanced
3	25	f	Cerebellum	PA	p.N546K	p.H1047R	p.M1149V		balanced
4	43	m	Pineal region	RGNT	p.K656E				gain of chr 7, 12
5	39	m	4th ventricle	LGG	p.K656E				loss of chr 4, 19, 21q
6	28	f	Tectum	PA	p.N546K				balanced
7	69	f	3th ventricle	LGG/LGGNT	p.K656E		p.R1276X and p.N1259S		balanced
8	67	f	Cerebellum	PA	p.N546K				balanced
9	20	f	Cerebellum	LGG	p.N546K	p.H1047R	p.E1790X		balanced
10	31	m	4th ventricle	RGNT	p.N546K	p.H1047R			balanced
11	34	m	4th ventricle	RGNT	p.N546K	p.G1049R			loss of chr 8p, 20p
12	36	f	Thalamus, brainsteam	RGNT	p.N546K	p.H1047R	p.W1831X		balanced
13	44	m	3th ventricle	RGNT	p.K656E				balanced
14	55	f	4th ventricle	RGNT	p.N546K				balanced
15	43	m	Cerebellum	PA	p.N546K				gain of chr 5, 6, 7, 8, 11, 12, 20
16	14	f	4th ventricle	RGNT	p.N546K	p.H1047R		p.P491H	balanced
17	24	f	Pineal region	PA	p.N546K	p.H1047R	p.R2637X		balanced
18	21	m	4th ventricle	RGNT	p.N546K	p.E545K			balanced
19	59	m	Cerebellum	PA	p.N546K		p.R897W and p.H647R		gain of chr 6p, segmnetal gain of 2q, 7q, 12q
20	40	m	4th ventricle	RGNT	p.N546K				balanced
21	50	m	Cerebellum	RGNT	p.K656E	p.E542K			balanced
22	10	f	Cerebellum	PA	p.K656E	p.H1047R			balanced
23	20	m	4th ventricle	RGNT	p.K656E	p.H1047R	splicing		balanced
24	38	f	4th ventricle	RGNT	p.N546K	p.H1047R			balanced
25	21	f	Cerebellum	PA	p.N546K	p.H1047R			balanced
26	18	f	4th ventricle	RGNT	p.N546K	p.H1047R	p.R416X		balanced
27	28	f	4th ventricle	RGNT	p.N546K	p.H1047R			balanced
28	41	f	4th ventricle	RGNT	p.K656E		p.E1264G and p. L1161V		balanced
29	25	m	Cerebellum	RGNT	p.N546K	p.H1047L			balanced
30	21	m	Cerebellum	RGNT	p.N546K	p.E545K			balanced

Abbreviations: m, male; f, female; RGNT I, rosette-forming glioneuronal tumor WHO grade I; PA I, pilocytic astrocytoma WHO grade I; LGG, low-grade glioma; LGGNT, low-grade glioneuronal tumor; chr, chromosome

Supplementary Table 2 - Single nucleotide variants (SNVs), small insertions/deletions/substitutions and splice site variants detected in the RGNT cohort

Case #	Chromosome	Position (hg19)	Reference Allele	Alternative Allele	Mutant Allele Fraction	Gene Symbol	Class	RefSeq ID	CDS Change	Amino Acid Change	Annovar Output	Function
1	chr12	112888156	A	C	0,51	PTPN11	nonsynonymous SNV	NM_080601	c.A172C	p.N58H	PTPN11:NM_080601:exon3:c.A172C:p.N58H	exonic
1	chr8	38274849	G	T	0,29	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
1	chr4	55984939	G	T	0,50	KDR	nonsynonymous SNV	NM_002253	c.C190A	p.P64T	KDR:NM_002253:exon3:c.C190A:p.P64T	exonic
1	chr3	178952085	A	G	0,23	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
2	chr3	178952085	A	G	0,48	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
2	chr8	38274849	G	T	0,43	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
2	chr17	29528504	-	T		NF1	splicing	NA	NA	p.NA	NA	splicing
3	chr3	178952085	A	G	0,24	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
3	chr17	29559848	A	G	0,29	NF1	nonsynonymous SNV	NM_001042492	c.A3445G	p.M1149V	NF1:NM_001042492:exon26:c.A3445G:p.M1149V	exonic
3	chr8	38274849	G	T	0,36	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
3	chr12	18719885	T	G	0,51	PIK3C2G	nonsynonymous SNV	NM_001288772	c.T3905G	p.F1302C	PIK3C2G:NM_001288772:exon29:c.T3905G:p.F1302C	exonic
4	chr8	38274857	T	C	0,39	FGFR1	nonsynonymous SNV	NM_023105	c.A1363G	p.I455V	FGFR1:NM_023105:exon11:c.A1363G:p.I455V	exonic
4	chr8	38272308	T	C	0,38	FGFR1	nonsynonymous SNV	NM_023105	c.A1699G	p.K567E	FGFR1:NM_023105:exon13:c.A1699G:p.K567E	exonic
5	chr8	38272308	T	C	0,38	FGFR1	nonsynonymous SNV	NM_023105	c.A1699G	p.K567E	FGFR1:NM_023105:exon13:c.A1699G:p.K567E	exonic
5	chr6	36169331	A	G	0,45	BRPF3	nonsynonymous SNV	NM_015695	c.A1232G	p.E411G	BRPF3:NM_015695:exon2:c.A1232G:p.E411G	exonic
6	chr2	211179766	T	-	0,37	MYL1	frameshift deletion	NM_079420	c.1delA	p.M1fs	MYL1:NM_079420:exon1:c.1delA:p.M1fs	exonic
6	chr5	67589597	ACT	-	0,40	PIK3R1	nonframeshift deletion	NM_181504	c.550_552del	p.184_184del	PIK3R1:NM_181504:exon5:c.550_552del:p.184_184del	exonic
6	chr17	41243509	T	C	0,44	BRCA1	nonsynonymous SNV	NM_007294	c.A4039G	p.R1347G	BRCA1:NM_007294:exon10:c.A4039G:p.R1347G	exonic
6	chr9	5022130	G	A	0,45	JAK2	nonsynonymous SNV	NM_004972	c.G143A	p.G48E	JAK2:NM_004972:exon3:c.G143A:p.G48E	exonic
6	chr5	1282733	C	A	0,52	TERT	nonsynonymous SNV	NM_198253	c.G1580T	p.G527V	TERT:NM_198253:exon3:c.G1580T:p.G527V	exonic
6	chr8	39872972	G	T	0,47	IDO2	nonsynonymous SNV	NM_194294	c.G1114T	p.A372S	IDO2:NM_194294:exon11:c.G1114T:p.A372S	exonic
6	chr12	25398281	C	T	0,36	KRAS	nonsynonymous SNV	NM_033360	c.G38A	p.G13D	KRAS:NM_033360:exon2:c.G38A:p.G13D	exonic
6	chr8	38274849	G	T	0,43	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
7	chr8	38272321	G	C	0,42	FGFR1	nonsynonymous SNV	NM_023105	c.C1686G	p.I562M	FGFR1:NM_023105:exon13:c.C1686G:p.I562M	exonic
7	chr8	38272308	T	C	0,40	FGFR1	nonsynonymous SNV	NM_023105	c.A1699G	p.K567E	FGFR1:NM_023105:exon13:c.A1699G:p.K567E	exonic
7	chr3	47162897	T	C	0,52	SETD2	nonsynonymous SNV	NM_014159	c.A3229G	p.T1077A	SETD2:NM_014159:exon3:c.A3229G:p.T1077A	exonic
7	chr3	10183605	C	T	0,51	VHL	nonsynonymous SNV	NM_198156	c.C74T	p.P25L	VHL:NM_198156:exon1:c.C74T:p.P25L	exonic
7	chr1	120548095	C	A	0,25	NOTCH2	nonsynonymous SNV	NM_024408	c.G272T	p.R91L	NOTCH2:NM_024408:exon3:c.G272T:p.R91L	exonic
7	chr17	29562696	A	G	0,43	NF1	nonsynonymous SNV	NM_001042492	c.A3776G	p.N1259S	NF1:NM_001042492:exon28:c.A3776G:p.N1259S	exonic
7	chr11	108139154	G	T	0,48	ATM	nonsynonymous SNV	NM_000051	c.G2656T	p.A886S	ATM:NM_000051:exon18:c.G2656T:p.A886S	exonic
7	chr17	29562746	C	T	0,43	NF1	stopgain SNV	NM_001042492	c.C3826T	p.R1276X	NF1:NM_001042492:exon28:c.C3826T:p.R1276X	exonic
8	chr8	38274849	G	C	0,35	FGFR1	nonsynonymous SNV	NM_023105	c.C1371G	p.N457K	FGFR1:NM_023105:exon11:c.C1371G:p.N457K	exonic
9	chr2	29416250	T	G	0,49	ALK	nonsynonymous SNV	NM_004304	c.A4703C	p.E1568A	ALK:NM_004304:exon29:c.A4703C:p.E1568A	exonic
9	chr3	178952085	A	G	0,36	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
9	chr5	67575523	C	T	0,47	PIK3R1	nonsynonymous SNV	NM_181523	c.C596T	p.P199L	PIK3R1:NM_181523:exon5:c.C596T:p.P199L	exonic
9	chr7	55238037	C	A	0,52	EGFR	nonsynonymous SNV	NM_201284	c.C1918A	p.L640I	EGFR:NM_201284:exon16:c.C1918A:p.L640I	exonic
9	chr8	38274849	G	C	0,35	FGFR1	nonsynonymous SNV	NM_023105	c.C1371G	p.N457K	FGFR1:NM_023105:exon11:c.C1371G:p.N457K	exonic
9	chr17	29654616	G	T	0,36	NF1	stopgain SNV	NM_001042492	c.G5368T	p.E1790X	NF1:NM_001042492:exon38:c.G5368T:p.E1790X	exonic
9	chr17	41245466	GCTGTC	ACTGTT	0,44	BRCA1	nonframeshift substitution	NM_007294	c.2077_2082AACAGT	p.NA	BRCA1:NM_007294:exon10:c.2077_2082AACAGT	exonic
10	chr3	178952085	A	G	0,44	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
10	chr13	32915313	G	T	0,43	BRCA2	nonsynonymous SNV	NM_000059	c.G6821T	p.G2274V	BRCA2:NM_000059:exon11:c.G6821T:p.G2274V	exonic
10	chr12	25368405	A	T	0,44	KRAS	stopgain SNV	NM_033360	c.T540A	p.C180X	KRAS:NM_033360:exon5:c.T540A:p.C180X	exonic
10	chr7	55259460	G	A	0,49	EGFR	nonsynonymous SNV	NM_005228	c.G2518A	p.A840T	EGFR:NM_005228:exon21:c.G2518A:p.A840T	exonic
10	chr3	47061329	G	A	0,44	SETD2	nonsynonymous SNV	NM_014159	c.C7352T	p.A2451V	SETD2:NM_014159:exon19:c.C7352T:p.A2451V	exonic
10	chr1	27023483	G	A	0,49	ARID1A	nonsynonymous SNV	NM_139135	c.G589A	p.G197R	ARID1A:NM_139135:exon1:c.G589A:p.G197R	exonic
10	chr8	38274849	G	T	0,37	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
11	chr9	139405209	C	T	0,50	NOTCH1	nonsynonymous SNV	NM_017617	c.G2636A	p.R879Q	NOTCH1:NM_017617:exon17:c.G2636A:p.R879Q	exonic
11	chr9	5126715	A	G	0,46	JAK2	nonsynonymous SNV	NM_004972	c.A3323G	p.N1108S	JAK2:NM_004972:exon25:c.A3323G:p.N1108S	exonic
11	chr8	38274849	G	T	0,58	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
11	chr4	55980379	C	A	0,43	KDR	nonsynonymous SNV	NM_002253	c.G712T	p.V238F	KDR:NM_002253:exon6:c.G712T:p.V238F	exonic
11	chr3	178952090	G	C	0,40	PIK3CA	nonsynonymous SNV	NM_006218	c.G3145C	p.G1049R	PIK3CA:NM_006218:exon21:c.G3145C:p.G1049R	exonic
11	chr16	3824628	C	A	0,50	CREBBP	nonsynonymous SNV	NM_004380	c.G2225T	p.R742L	CREBBP:NM_004380:exon12:c.G2225T:p.R742L	exonic
11	chr20	57429775	C	A	0,43	GNAS	nonsynonymous SNV	NM_001077490	c.C1268A	p.P423H	GNAS:NM_001077490:exon1:c.C1268A:p.P423H	exonic
11	chr1	120479948	T	C	0,50	NOTCH2	nonsynonymous SNV	NM_024408	c.A3479G	p.H1160R	NOTCH2:NM_024408:exon21:c.A3479G:p.H1160R	exonic
11	chr1	51439754	T	G	0,48	CDKN2C	nonsynonymous SNV	NM_001262	c.T319G	p.L107V	CDKN2C:NM_001262:exon3:c.T319G:p.L107V	exonic
12	chr8	38274849	G	T	0,35	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
12	chr17	29654741	G	A	0,13	NF1	stopgain SNV	NM_001042492	c.G5493A	p.W1831X	NF1:NM_001042492:exon38:c.G5493A:p.W1831X	exonic
12	chr3	178952085	A	G	0,28	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
12	chr5	131915022	G	A	0,48	RAD50	nonsynonymous SNV	NM_005732	c.G379A	p.V127I	RAD50:NM_005732:exon4:c.G379A:p.V127I	exonic
13	chr8	38272308	T	C	0,39	FGFR1	nonsynonymous SNV	NM_023105	c.A1699G	p.K567E	FGFR1:NM_023105:exon13:c.A1699G:p.K567E	exonic
13	chr5	67589588	GAA	-	0,34	PIK3R1	nonframeshift deletion	NM_181504	c.541_543del	p.181_181del	PIK3R1:NM_181504:exon5:c.541_543del:p.181_181del	exonic
14	chr8	38274849	G	T	0,35	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
13	chr9	133759575	C	A	0,23	ABL1	nonsynonymous SNV	NM_007313	c.C1955A	p.A652D	ABL1:NM_007313:exon11:c.C1955A:p.A652D	exonic
13	chr14	105242084	C	A	0,52	AKT1	stopgain SNV	NM_005163	c.G340T	p.E114X	AKT1:NM_005163:exon5:c.G340T:p.E114X	exonic
13	chr19	40771132	G	A	0,14	AKT2	nonsynonymous SNV	NM_001626	c.C43T	p.R15C	AKT2:NM_001626:exon2:c.C43T:p.R15C	exonic
13	chr2	29443583	G	T	0,29	ALK	nonsynonymous SNV	NM_004304	c.C3634A	p.R1212S	ALK:NM_004304:exon23:c.C3634A:p.R1212S	exonic
13	chr13	53418870	C	T	0,19	PCDH8	nonsynonymous SNV	NM_032949	c.G2747A	p.G916E	PCDH8:NM_032949:exon3:c.G2747A:p.G916E	exonic
15	chr16	3789606	C	A	0,29	CREBBP	nonsynonymous SNV	NM_004380	c.G4253T	p.G1418V	CREBBP:NM_004380:exon25:c.G4253T:p.G1418V	exonic
15	chr17	7579717	G	A	0,53	TP53	nonsynonymous SNV	NM_001126112	c.C79T	p.P27S	TP53:NM_001126112:exon3:c.C79T:p.P27S	exonic
15	chr11	94192659	T	G	0,42	MRE11A	nonsynonymous SNV	NM_005591	c.A1415C	p.E472A	MRE11A:NM_005591:exon13:c.A1415C:p.E472A	exonic
15	chr8	38274849	G	T	0,26	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
15	chr3	142272098	A	G	0,43	ATR	nonsynonymous SNV	NM_001184	c.T2776C	p.F926L	ATR:NM_001184:exon13:c.T2776C:p.F926L	exonic
15	chr19	42797203	G	A	0,46	CIC	nonsynonymous SNV	NM_015125	c.G3565A	p.V1189M	CIC:NM_015125:exon15:c.G3565A:p.V1189M	exonic
16	chr5	1293676	TCC	-	0,34	TERT	nonframeshift deletion	NM_198253	c.1323_1325del	p.441_442del	TERT:NM_198253:exon2:c.1323_1325del:p.441_442del	exonic
16	chr3	142212087	T	C	0,52	ATR	nonsynonymous SNV	NM_001184	c.A5965G	p.T1989A	ATR:NM_001184:exon35:c.A5965G:p.T1989A	exonic
16	chr3	178952085	A	G	0,39	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
16	chr6	33286923	G	A	0,44	DAXX	nonsynonymous SNV	NM_001141969	c.C2014T	p.P672S	DAXX:NM_001141969:exon7:c.C2014T:p.P672S	exonic
16	chr8	38274849	G	T	0,47	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
16	chr12	112926852	C	A	0,50	PTPN11	nonsynonymous SNV	NM_002834	c.C1472A	p.P491H	PTPN11:NM_002834:exon13:c.C1472A:p.P491H	exonic
16	chr13	53420063	C	G	0,47	PCDH8	nonsynonymous SNV	NM_002590	c.G2509C	p.A837P	PCDH8:NM_002590:exon1:c.G2509C:p.A837P	exonic
16	chr14	21488110	G	A	0,52	NDRG2	nonsynonymous SNV	NM_001282216	c.C401T	p.P134L	NDRG2:NM_001282216:exon8:c.C401T:p.P134L	exonic

Suppl. Table 2

16	chr19	11096912	C	G	0,49	SMARCA4	nonsynonymous SNV	NM_001128846	c.C403G	p.P135A	SMARCA4:NM_001128846:exon3:c.C403G:p.P135A	exonic
17	chr3	178952085	A	G	0,26	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
17	chr8	38274849	G	C	0,23	FGFR1	nonsynonymous SNV	NM_023105	c.C1371G	p.N457K	FGFR1:NM_023105:exon11:c.C1371G:p.N457K	exonic
17	chr13	53419568	A	G	0,45	PCDH8	nonsynonymous SNV	NM_032949	c.T2540C	p.M847T	PCDH8:NM_032949:exon2:c.T2540C:p.M847T	exonic
17	chr17	29684326	C	T	0,21	NF1	stopgain SNV	NM_001042492	c.C7909T	p.R2637X	NF1:NM_001042492:exon54:c.C7909T:p.R2637X	exonic
18	chr3	178936091	G	A	0,31	PIK3CA	nonsynonymous SNV	NM_006218	c.G1633A	p.E545K	PIK3CA:NM_006218:exon10:c.G1633A:p.E545K	exonic
18	chr3	9782480	A	G	0,50	BRPF1	nonsynonymous SNV	NM_004634	c.A1577G	p.N526S	BRPF1:NM_004634:exon4:c.A1577G:p.N526S	exonic
18	chr2	29446388	C	A	0,54	ALK	nonsynonymous SNV	NM_004304	c.G3179T	p.R1060L	ALK:NM_004304:exon20:c.G3179T:p.R1060L	exonic
18	chr8	38274849	G	C	0,31	FGFR1	nonsynonymous SNV	NM_023105	c.C1371G	p.N457K	FGFR1:NM_023105:exon11:c.C1371G:p.N457K	exonic
19	chr11	108203572	T	A	0,53	ATM	stopgain SNV	NM_000051	c.T7872A	p.C2624X	ATM:NM_000051:exon53:c.T7872A:p.C2624X	exonic
19	chr7	140624404	CGGCGC	-		BRAF	nonframeshift deletion	NM_004333	c.95_100del	p.32_34del	BRAF:NM_004333:exon1:c.95_100del:p.32_34del	exonic
19	chr5	131924421	G	A	0,47	RAD50	nonsynonymous SNV	NM_005732	c.G1094A	p.R365Q	RAD50:NM_005732:exon8:c.G1094A:p.R365Q	exonic
19	chr8	38274849	G	T	0,39	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
19	chr17	29556322	C	T	0,37	NF1	nonsynonymous SNV	NM_001042492	c.C2689T	p.R897W	NF1:NM_001042492:exon21:c.C2689T:p.R897W	exonic
19	chrX	76874309	G	C	0,75	ATRX	nonsynonymous SNV	NM_000489	c.C5413G	p.H1805D	ATRX:NM_000489:exon21:c.C5413G:p.H1805D	exonic
19	chr5	67589599	TCAGTT	-		PIK3R1	nonframeshift deletion	NM_181504	c.552_557del	p.184_186del	PIK3R1:NM_181504:exon5:c.552_557del:p.184_186del	exonic
19	chr17	29552207	A	G	0,55	NF1	nonsynonymous SNV	NM_001042492	c.A1940G	p.H647R	NF1:NM_001042492:exon17:c.A1940G:p.H647R	exonic
20	chr6	36181882	G	A	0,58	BRPF3	nonsynonymous SNV	NM_015695	c.G2708A	p.G903D	BRPF3:NM_015695:exon8:c.G2708A:p.G903D	exonic
20	chr8	38274849	G	T	0,29	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
20	chr13	32968951	C	T	0,42	BRCA2	stopgain SNV	NM_000059	c.C9382T	p.R3128X	BRCA2:NM_000059:exon25:c.C9382T:p.R3128X	exonic
21	chr8	38272310	T	A	0,40	FGFR1	nonsynonymous SNV	NM_023105	c.A1697T	p.K566I	FGFR1:NM_023105:exon13:c.A1697T:p.K566I	exonic
21	chr8	38272308	T	C	0,40	FGFR1	nonsynonymous SNV	NM_023105	c.A1699G	p.K567E	FGFR1:NM_023105:exon13:c.A1699G:p.K567E	exonic
21	chr3	178936082	G	A	0,36	PIK3CA	nonsynonymous SNV	NM_006218	c.G1624A	p.E542K	PIK3CA:NM_006218:exon10:c.G1624A:p.E542K	exonic
21	chr8	38272308	TTT	CTA	0,42	FGFR1	nonframeshift substitution	NM_023105	c.1697_1699TAG	p.NA	FGFR1:NM_023105:exon13:c.1697_1699TAG	exonic
22	chr8	38272308	T	C	0,34	FGFR1	nonsynonymous SNV	NM_023105	c.A1699G	p.K567E	FGFR1:NM_023105:exon13:c.A1699G:p.K567E	exonic
22	chr8	38272306	CTT	GTC	0,34	FGFR1	nonframeshift substitution	NM_023105	c.1699_1701GAC	p.NA	FGFR1:NM_023105:exon13:c.1699_1701GAC	exonic
22	chr1	27099302	G	C	0,47	ARID1A	spiling	NA	NA	p.NA	NA	splicing
22	chr3	178952085	A	G	0,26	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
22	chr8	38272306	C	G	0,33	FGFR1	nonsynonymous SNV	NM_023105	c.G1701C	p.K567N	FGFR1:NM_023105:exon13:c.G1701C:p.K567N	exonic
22	chr12	49443634	G	A	0,53	KMT2D	nonsynonymous SNV	NM_003482	c.C3737T	p.T1246M	KMT2D:NM_003482:exon11:c.C3737T:p.T1246M	exonic
22	chr16	2120559	G	A	0,49	TSC2	nonsynonymous SNV	NM_001077183	c.G1819A	p.A607T	TSC2:NM_001077183:exon17:c.G1819A:p.A607T	exonic
22	chr16	68846048	C	T	0,46	CDH1	nonsynonymous SNV	NM_004360	c.C1019T	p.T340M	CDH1:NM_004360:exon8:c.C1019T:p.T340M	exonic
22	chr4	55972049	G	A	0,49	KDR	nonsynonymous SNV	NM_002253	c.C1595T	p.A532V	KDR:NM_002253:exon12:c.C1595T:p.A532V	exonic
23	chr9	133760871	C	T	0,49	ABL1	nonsynonymous SNV	NM_007313	c.C3251T	p.T1084M	ABL1:NM_007313:exon11:c.C3251T:p.T1084M	exonic
23	chr9	139413909	G	A	0,44	NOTCH1	nonsynonymous SNV	NM_017617	c.C851T	p.P284L	NOTCH1:NM_017617:exon5:c.C851T:p.P284L	exonic
23	chr16	3779329	C	T	0,43	CREBBP	nonsynonymous SNV	NM_004380	c.G5719A	p.A1907T	CREBBP:NM_004380:exon31:c.G5719A:p.A1907T	exonic
23	chr17	29684388	GTAA	-		NF1	splicing	NA	NA	p.NA	NA	splicing
23	chr8	38272308	T	C	0,32	FGFR1	nonsynonymous SNV	NM_023105	c.A1699G	p.K567E	FGFR1:NM_023105:exon13:c.A1699G:p.K567E	exonic
23	chr3	178952085	A	G	0,30	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
23	chr5	112174802	C	T	0,47	APC	nonsynonymous SNV	NM_000038	c.C3511T	p.R1171C	APC:NM_000038:exon16:c.C3511T:p.R1171C	exonic
23	chr8	38274849	G	T	0,39	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
23	chr3	178952085	A	G	0,30	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
23	chr5	67591132	GAC	-		PIK3R1	nonframeshift deletion	NM_181504	c.915_917del	p.305_306del	PIK3R1:NM_181504:exon7:c.915_917del:p.305_306del	exonic
25	chr13	53420536	T	A	0,46	PCDH8	nonsynonymous SNV	NM_032949	c.A2036T	p.Q679L	PCDH8:NM_032949:exon1:c.A2036T:p.Q679L	exonic
25	chr11	108170506	A	C	0,47	ATM	nonsynonymous SNV	NM_000051	c.A5071C	p.S1691R	ATM:NM_000051:exon34:c.A5071C:p.S1691R	exonic
25	chr8	38274849	G	T	0,23	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
25	chr5	112179179	G	A	0,49	APC	nonsynonymous SNV	NM_000038	c.G7888A	p.V2630I	APC:NM_000038:exon16:c.G7888A:p.V2630I	exonic
25	chr3	178952085	A	G	0,26	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
25	chr3	10191545	A	G	0,44	VHL	nonsynonymous SNV	NM_000551	c.A538G	p.I180V	VHL:NM_000551:exon3:c.A538G:p.I180V	exonic
26	chr3	178952085	A	G	0,41	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
26	chr7	128843395	C	T	0,48	SMO	nonsynonymous SNV	NM_005631	c.C502T	p.R168C	SMO:NM_005631:exon2:c.C502T:p.R168C	exonic
26	chr8	38274849	G	C	0,30	FGFR1	nonsynonymous SNV	NM_023105	c.C1371G	p.N457K	FGFR1:NM_023105:exon11:c.C1371G:p.N457K	exonic
26	chr13	53420063	C	G	0,49	PCDH8	nonsynonymous SNV	NM_002590	c.G2509C	p.A837P	PCDH8:NM_002590:exon1:c.G2509C:p.A837P	exonic
26	chr17	29528489	C	T	0,31	NF1	stopgain SNV	NM_001042492	c.C1246T	p.R416X	NF1:NM_001042492:exon11:c.C1246T:p.R416X	exonic
26	chr9	2191388	G	A	0,50	SMARCA2	nonsynonymous SNV	NM_001289399	c.G775A	p.D259N	SMARCA2:NM_001289399:exon7:c.G775A:p.D259N	exonic
27	chr12	18499770	GGTGAGTCGT	-	0,91	PIK3C2G	frameshift deletion	NM_001288774	c.959_959del	p.320_320del	PIK3C2G:NM_001288774:exon11:c.959_959del:p.320_320del	exonic
27	chr16	85695351	G	A	0,52	GSE1	nonsynonymous SNV	NM_001278184	c.G2021A	p.R674Q	GSE1:NM_001278184:exon8:c.G2021A:p.R674Q	exonic
27	chr8	38274849	G	C	0,30	FGFR1	nonsynonymous SNV	NM_023105	c.C1371G	p.N457K	FGFR1:NM_023105:exon11:c.C1371G:p.N457K	exonic
27	chr3	178952085	A	G	0,41	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047R	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047R	exonic
27	chr12	18499769	AGGTGAGTCGT	AGGTGAGTGGT	0,91	PIK3C2G	nonframeshift substitution	NM_001288774	c.958_959AGGTGAGTGGT	p.958_959AGGTGAGTGGT	PIK3C2G:NM_001288774:exon11:c.958_959AGGTGAGTGGT	exonic
28	chr8	38272308	T	C	0,36	FGFR1	nonsynonymous SNV	NM_023105	c.A1699G	p.K567E	FGFR1:NM_023105:exon13:c.A1699G:p.K567E	exonic
28	chr6	114262250	G	T	0,54	HDAC2	nonsynonymous SNV	NM_001527	c.C1439A	p.T480N	HDAC2:NM_001527:exon14:c.C1439A:p.T480N	exonic
28	chr17	29559883	TC	GG	0,28	NF1	nonframeshift substitution	NM_001042492	c.3480_3481GG		NF1:NM_001042492:exon26:c.3480_3481GG	exonic
28	chr17	29562711	A	G	0,30	NF1	nonsynonymous SNV	NM_001042492	c.A3791G	p.E1264G	NF1:NM_001042492:exon28:c.A3791G:p.E1264G	exonic
28	chr17	29559884	C	G	0,29	NF1	nonsynonymous SNV	NM_001042492	c.C3481G	p.L1161V	NF1:NM_001042492:exon26:c.C3481G:p.L1161V	exonic
29	chr17	41245466	GCTGTC	ACTGTT	0,62	BRCA1	nonframeshift substitution	NM_007294	c.2077_2082AACAGT		BRCA1:NM_007294:exon10:c.2077_2082AACAGT	exonic
29	chr8	38274849	G	T	0,37	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
29	chr4	55561723	C	T	0,42	KIT	nonsynonymous SNV	NM_001093772	c.C113T	p.S38F	KIT:NM_001093772:exon2:c.C113T:p.S38F	exonic
29	chr3	178952085	A	G	0,41	PIK3CA	nonsynonymous SNV	NM_006218	c.A3140G	p.H1047L	PIK3CA:NM_006218:exon21:c.A3140G:p.H1047L	exonic
30	chr8	38274849	G	T	0,37	FGFR1	nonsynonymous SNV	NM_023105	c.C1371A	p.N457K	FGFR1:NM_023105:exon11:c.C1371A:p.N457K	exonic
30	chr3	178936091	G	A	0,31	PIK3CA	nonsynonymous SNV	NM_006218	c.G1633A	p.E545K	PIK3CA:NM_006218:exon10:c.G1633A:p.E545K	exonic