

# Association between glioma susceptibility loci and tumour pathology defines specific molecular etiologies

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**Background.** Genome-wide association studies have identified single-nucleotide polymorphisms (SNPs) at 7 loci influencing glioma risk: rs2736100 (*TERT*), rs11979158 and rs2252586 (*EGFR*), rs4295627 (*CCDC26*), rs4977756 (*CDKN2A/CDKN2B*), rs498872 (*PHLDB1*), and rs6010620 (*RTEL1*).

**Materials and methods.** We studied the relationship among these 7 glioma-risk SNPs and characteristics of tumors from 1374 patients, including grade, *IDH* (ie *IDH1* or *IDH2*) mutation, *EGFR* amplification, *CDKN2A-p16-INK4a* homozygous deletion, 9p and 10q loss, and 1p-19q codeletion.

**Results.** rs2736100 (*TERT*) and rs6010620 (*RTEL1*) risk alleles were associated with high-grade disease, *EGFR* amplification, *CDKN2A-p16-INK4a* homozygous deletion, and 9p and 10q deletion; rs4295627 (*CCDC26*) and rs498872 (*PHLDB1*) were associated with low-grade disease, *IDH* mutation, and 1p-19q codeletion. In contrast, rs4977756 (*CDKN2A/B*), rs11979158 (*EGFR*), and to a lesser extent, rs2252586 (*EGFR*) risk alleles were independent of tumor grade and genetic profile. Adjusting for tumor grade showed

a significant association between rs2736100 and *IDH* status ( $P = .01$ ), 10q loss ( $P = .02$ ); rs4295627 and 1p-19q codeletion ( $P = .04$ ), rs498872 and *IDH* ( $P = .02$ ), 9p loss ( $P = .04$ ), and 10q loss ( $P = .02$ ). Case-control analyses stratified into 4 molecular classes (defined by 1p-19q status, *IDH* mutation, and *EGFR* amplification) showed an association of rs4295627 and rs498872 with *IDH*-mutated gliomas ( $P < 10^{-3}$ ) and rs2736100 and rs6010620 with *IDH* wild-type gliomas ( $P < 10^{-3}$  and  $P = .03$ ).

**Conclusion.** The frequency of *EGFR* and *CDKN2A/B* risk alleles were largely independent of tumor genetic profile, whereas *TERT*, *RTEL1*, *CCDC26*, and *PHLDB1* variants were associated with different genetic profiles that annotate distinct molecular pathways. Our findings provide further insight into the biological basis of glioma etiology.

**Keywords:** etiology, glioma, pathology, SNP.

**G**liomas account for >30% of all primary brain tumors, and each year in the United States, >20,000 individuals receive a diagnosis of the disease.<sup>1</sup> Gliomas are heterogeneous and are typically classified according to tumor grade into pilocytic astrocytomas (World Health Organization [WHO] grade I), diffuse low-grade gliomas (WHO grade II), anaplastic gliomas (WHO grade III) and glioblastoma (GBM);

Received December 12, 2011; accepted October 2, 2012.

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WHO grade IV). Gliomas are also classified on the basis of cellular lineage: astrocytic, oligodendroglial, and mixed tumors.<sup>2</sup>

Over the past 10 years, specific tumor somatic aberrations have been shown to typify the various glioma subtypes, suggesting that different tumor genetic profiles result from different etiologic pathways. *IDH* (ie, *IDH1* or less frequently *IDH2*) mutation is involved in the development of low-grade glioma and progressive GBM.<sup>3,4</sup> The codeletion of chromosome 1p and 19q is highly correlated with oligodendroglial phenotype grade II and III and with *IDH* mutation. These molecular phenotypes are associated with good clinical outcome.<sup>5</sup> In contrast, loss of chromosome 9p and 10q, homozygous deletions of the oncosuppressor *CDKN2A-p16-INK4a*, and the amplification of the *EGFR* oncogene are associated with high-grade disease and, particularly, GBM.<sup>6</sup>

Although Li-Fraumeni, Turcot, and the melanoma/glioblastoma syndromes are associated with substantive risks of glioma, all are rare and collectively account for <5% of glioma cases. The hypothesis that common genetic variation is a determinant of glioma risk has recently been vindicated by genome-wide association studies (GWASs), which have identified single-nucleotide polymorphisms (SNPs) at 7 loci influencing glioma risk: rs2736100 (*TERT*), rs11979158 and rs2252586 (*EGFR*), rs4295627 (*CCDC26*), rs4977756 (*CDKN2A/B*), rs498872 (*PHLDB1*), rs6010620 (*RTEL1*).<sup>7-9</sup> Through an analysis of French and German patients, we previously showed that rs2736100 (*TERT*) and rs6010620 (*RTEL1*) risk variants are associated with high-grade disease, whereas the rs4295627 (*CCDC26*) and rs498872 (*PHLDB1*) risk variants are associated with low-grade disease.<sup>10</sup> Furthermore, rs11979158 and rs2252586 (*EGFR*) and rs4977756 (*CDKN2A/B*) risk variants appear to have a generic effect on tumor risk. This finding of a relationship between SNP genotype and tumor phenotype is supported by a recent study conducted by Jenkins et al.<sup>11</sup>

It is entirely possible that specific somatic genetic alterations may be associated with  $\geq 1$  of these polymorphisms, independent of tumor grade. To examine this proposition further, we investigated the association among the 7 glioma-risk SNPs and tumor histological and molecular genetic profile in a large French patient series that is part of the aforementioned study. Tumor genetic analyses included *EGFR* amplification, *IDH* mutation, *CDKN2A-p16-INK4a* homozygous deletion, and chromosomal loss on 9p, 10q, and 1p-19q.

## Materials and Methods

### Patients

Patients treated at the Pitié-Salpêtrière hospital were selected if they were part of a GWAS of gliomas previously reported<sup>7,8</sup> and tumor material or tumour DNA from the initial tumor were available.

Clinical data were retrieved from a prospectively maintained database: age at surgery, sex, and tumor

histology (astrocytoma grade II, oligoastrocytoma grade II, oligodendroglioma grade II, astrocytoma grade III, oligoastrocytoma grade III, oligodendroglioma grade III, GBM and glioblastoma with oligodendroglial component [GBMO] grade IV). Analyses were restricted to primary tumors. Pilocytic astrocytomas (WHO grade I) were excluded because of their peculiar histological, demographic, and biological characteristics, which differ from gliomagenesis for grades WHO II-IV. All tumor histologies were reviewed by 2 pathologists (V.D. and K.M.).

To calculate the risk of glioma by subtype, we made use of previously generated genotypes on 1190 controls.<sup>7</sup> Collection of blood samples and clinicopathological information was undertaken with informed consent and relevant ethical board approval in accordance with the tenets of the Declaration of Helsinki.

### SNP Genotyping

Genotyping of rs2736100, rs11979158, rs2252586, rs4295627, rs4977756, rs6010620, and rs498872 SNPs have previously been described.<sup>7,10</sup> In brief, DNA was extracted from samples using conventional methods and quantified using PicoGreen (Invitrogen). Genotyping was conducted using single-base primer extension chemistry matrix-assisted laser desorption/ionization time-of-flight mass spectrometry detection (Sequenom; <http://www.sequenom.com/>). Genotyping quality control was evaluated through inclusion of duplicate DNA samples in SNP assays. For all SNP assays, >99% concordant results were obtained. Samples having SNP call rates <90% were excluded from the analysis.

### Tumor Genotyping

Glioma samples were snap-frozen in liquid nitrogen. Tumor DNA was extracted from frozen tumors with use of the QIAmp DNA minikit, according to the manufacturer's instructions (Qiagen). DNA was analyzed by comparative genomic hybridization (CGH) array as previously described.<sup>12</sup> In the cases not analyzed by CGH array, 9p, 10q, 1p, and 19q status was determined by routine PCR microsatellite analysis, and *EGFR* amplification and *CDKN2A-p16-INK4a* homozygous deletion by quantitative PCR. R132 codon of *IDH1* and R172 codon of *IDH2* were analyzed by direct sequencing (IDH1f 5'-TGTGTTGAGATGGACGCCTATTTG, IDH1r 5'-ACTGAAC CAGCAACCACCGT, IDH2f 5'-GCCCCGGTCTGCCAC AAAGTC, and IDH2r 5'-TTGGCAGACTCCAGAGCC CA), as previously described.<sup>3</sup>

### Statistical Analyses

Statistical analyses were undertaken using R software ([www.r-project.org](http://www.r-project.org)). Differences in the distribution on categorical variables were analyzed using logistic regression. Odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated using unconditional

**Table 1.** Molecular glioma subtypes by histology

WHO Grade	Histological Subtype	Tumor Subgroup			
		1	2	3	4
	1p-19q codeletion	Yes	No	No	No
	IDH mutation	Yes	Yes	No	No
	EGFR amplification	No	No	No	Yes
II	Low grade astrocytoma	4/54 (7.40%)	35/54 (64.8%)	15/54 (27.7%)	0/54 (0.0%)
	Oligoastrocytoma	6/62 (9.7%)	27/62 (43.5%)	25/62 (40.3%)	4/62 (6.5%)
	Oligodendroglioma	69/203 (34.0%)	77/203 (37.9%)	55/203 (27.1%)	2/203 (1.0%)
	Total	79/319 (24.8%)	139/319 (43.6%)	95/319 (29.8%)	6/319 (1.9%)
III	Anaplastic astrocytoma	1/19 (5.3%)	7/19(36.8%)	8/19(42.1%)	3/19(15.8%)
	Anaplastic oligoastrocytoma	8/83 (9.6%)	31/83 (37.3%)	32/83 (38.6%)	12/83 (14.5%)
	Anaplastic oligodendroglioma	28/149 (18.8%)	30/149 (20.1%)	64/149 (43.0%)	27/149 (18.1%)
	Total	37/251 (14.7%)	68/251 (27.1%)	104/251 (41.4%)	42/251 (16.7%)
IV	Glioblastoma	1/221 (0.5%)	17/221 (7.7%)	143/221 (64.7%)	60/221 (27.1%)
	Glioblastoma with oligodendroglial component	1/76 (1.3%)	6/76 (7.9%)	43/76 (56.6%)	26/76 (34.2%)
	Total	2/297 (0.7%)	23/297 (7.7%)	186/297 (62.6%)	86/297 (29.0%)

logistic regression. In all analyses, we considered a *P* value of .05 (2-sided) as being statistically significant.

## Results

### Tumors Characteristics and Molecular Classification

One thousand three hundred seventy-two patients with glioma (511 WHO grade II, 410 grade III, and 451 grade IV) fulfilled the inclusion criteria (GBM is slightly under-represented, because unlike grade II and III, genomic analysis has not been performed routinely). The age at diagnosis was correlated with grade (median ages of 39, 50, and 57 years for II, III, and IV grade tumors, respectively). Median survival from diagnosis (50.1 months for the whole series) was strongly related to grade (133.3, 33.5, and 17.6 months for grade II, III, and IV tumors, respectively;  $P < .0001$ ). The 9p and 10q loss, *CDKN2A-p16-INK4a* homozygous deletion, and *EGFR* amplification were associated with high-grade disease, whereas *IDH* mutation was associated with low-grade disease and 1p-19q codeletion with oligodendroglial tumors (all  $P < .0001$ ; Supplementary material, Table S1).

Because a number of the molecular alterations in gliomas are highly correlated, we analyzed the association frequency of tumor genetic alterations and found *IDH* mutation, 1p-19q codeletion, and *EGFR* amplification showing the strongest association and exclusion scores (Supplementary material, Table S2). On the basis of this finding, we considered 4 mutually exclusive tumor classes:<sup>5,12</sup> (1) *IDH* mutation/1p-19q codeletion/*EGFR* normal status, (2) *IDH* mutation/1p-19q normal status/*EGFR* normal status, (3) *IDH* wild-type/1p-19q normal status/*EGFR* normal status, and (4) *IDH* wild-type/1p-19q normal status/*EGFR* amplification (Table 1). Survival was correlated to these 4 tumor classes: 211.2 months (95% CI, 139.3–Not Reached) for class 1, 103.9 months (95% CI, 82.1–115.8) for

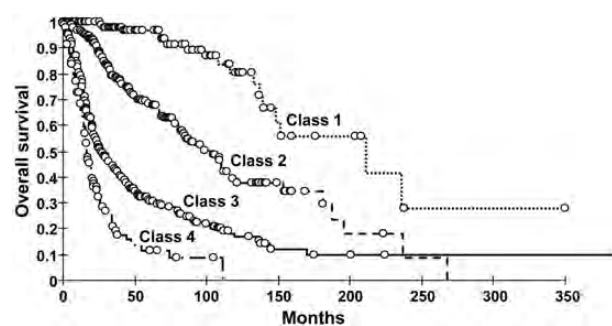


Fig. 1. Kaplan–Meier curves in all glioma population show significant overall survival difference between tumor class 1-*IDH* mut/1p-19q codelet/*EGFR* normal-(median OS 211.2 months), tumor class-2 *IDH* mut/1p-19q normal/*EGFR* normal-(median OS 103.9 months), tumor class 3-*IDH* wt/1p-19q normal/*EGFR* normal-(median OS 26.5 months), and tumor class 4-*IDH* wt/1p-19q normal/*EGFR* amplification-(median OS 16.6 months).

class 2, 26.5 months (95% CI, 22.9–33.5) for class 3, and 16.6 months (95% CI, 14.9–20.0) for class 4 ( $P < .0001$ ; Fig. 1).

### Association between SNP, Tumor Grades, and Tumor Genotypes

The frequency of the risk alleles did not differ by tumor grade for rs4977756 (*CDKN2A/B*) and rs11979158 (*EGFR*) but was higher in patients with GBM for rs2252586 (*EGFR*) (Supplementary material, Table S3) ( $P = .03$ ). rs11979158 and rs2252586 (*EGFR*) genotypes were not associated with amplification of *EGFR*, neither with *IDH* mutation, *CDKN2A-p16-INK4a* homozygous deletions, loss of chromosome 9p, loss of chromosome 10q, or 1p-19q codeletion (Supplementary material, Tables S4 and S5). rs4977756 (*CDKN2A/B*) genotype was not associated with homozygous *CDKN2A-p16-INK4a* deletion or loss of chromosome 9p. It was also independent of

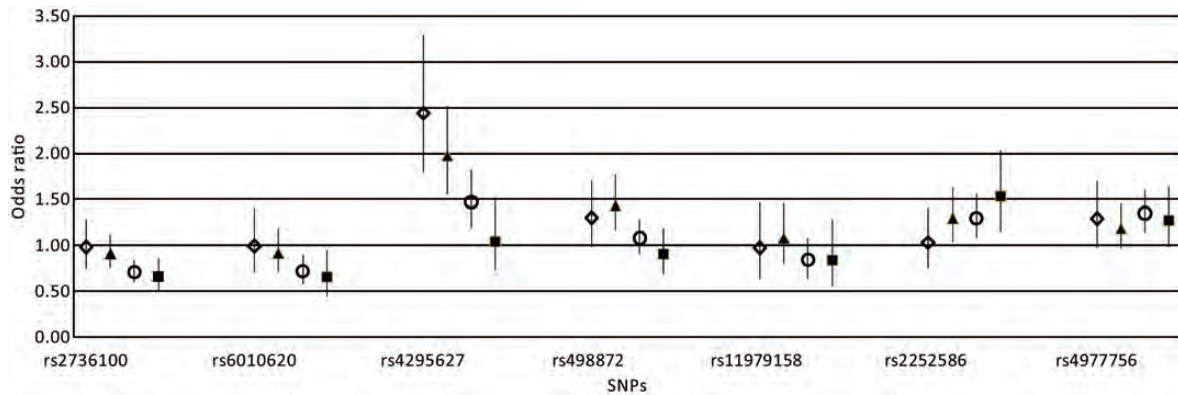


Fig. 2. Glioma risk, stratified by specific tumor class, is represented (OR and 95% CI) for each single SNP. The data correspond to the Supplementary material, Table S6. ◇ IDH mutation/1p-19q codeletion/EGFR normal status; ▲ IDH mutation/1p-19q normal status/EGFR normal status; ○ IDH wild-type/1p-19q normal status/EGFR normal status; ■ IDH wild-type/1p-19q normal status/EGFR amplification.

*EGFR* amplification, *IDH* mutation, loss of chromosome 10q, and 1p-19q codeletion (Supplementary material, Tables S4 and S5).

The carrier frequencies of the risk alleles for the rs6010620 (*RTEL1*) and rs2736100 (*TERT*) were both significantly correlated with a diagnosis of GBM ( $P = .02$  and  $P = .04$ , respectively), 10q loss ( $P = .005$  and  $P = .002$ , respectively), and absence of *IDH* mutation ( $P = .03$  and  $P = .0007$ , respectively) (Supplementary material, Tables S3–S5).

The carrier status for risk alleles of rs4295627 (*CCDC26*) and rs498872 (*PHLDB1*) were both correlated with the diagnosis of low-grade glioma ( $P < .0001$  and  $P = .007$ , respectively) (Supplementary material, Table S3). rs4295627 (*CCDC26*) risk allele was associated with *IDH* mutation ( $P = .0002$ ), 1p-19q codeletion ( $P = .0008$ ), absence of *EGFR* amplification ( $P = .03$ ), and absence of *CDKN2A-p16-INK4a* homozygous deletion ( $P = .01$ ) (Supplementary material, Table S4 and S5). Similarly, rs498872 (*PHLDB1*) risk allele was associated with *IDH* mutation ( $P = .001$ ), absence of *EGFR* amplification ( $P = .02$ ), and retention of chromosomes 9p ( $P = .01$ ) and 10q ( $P = .0007$ ) (Supplementary material, Tables S4 and S5).

We then conducted case-control analyses specific for tumor molecular classes. The relationship between SNP genotype and tumor class is detailed in Supplementary material, Table S6 and Fig. 2. Both rs4295627 (*CCDC26*) and rs498872 (*PHLDB1*) were associated with *IDH* mutation (tumor class 1 and 2), defining a less aggressive disease. The association was particularly strong between rs4295627 (*CCDC26*) and class 1 (1p-19q codeleted gliomas, OR = 2.44,  $P = 6.8 \times 10^{-9}$ ). Conversely, rs2736100 (*TERT*) and rs6010620 (*RTEL1*) genotypes were strongly associated with wild-type *IDH*, which define an aggressive disease (Fig. 2, Supplementary material, Table S6). A stronger impact of rs2252586 (*EGFR*) on wild-type *IDH* versus *IDH*-mutated tumor is also suggested, particularly on *EGFR*-amplified tumors.

### *TERT, CCDC26, and PHLDB1 SNPs Are Associated With Molecular Features Independently of Grade*

Because the somatic alterations seen in glioma are strongly related to tumor grade, we investigated whether any associations between SNP genotype and tumor molecular phenotype were independent of grade. Adjusting for tumor grade, we examined the relationship between SNP genotype and the molecular phenotype (Supplementary material, Table S7). Regression analysis adjusted for grade showed a significant association between carrier status for rs2736100 (*TERT*) and nonmutated *IDH* ( $P = .01$ ), 10q loss ( $P = .02$ ), between rs4295627 (*CCDC26*) and 1p-19q codeletion ( $P = .04$ ), between rs498872 (*PHLDB1*) and *IDH* mutation ( $P = .02$ ), retained chromosome 9p ( $P = .04$ ), and chromosome 10q ( $P = .025$ ). Adjusting for tumor grade, the rs6010620 (*RTEL1*) risk allele failed to show a significant association with any of the molecular features assayed in the tumors.

## Discussion

Because there is a high rate of interobserver discrepancy in defining glioma subtypes histologically,<sup>13</sup> we rather focused our analysis on the association between SNP genotype and molecular alterations. Using this approach, we have demonstrated a strong relationship among 4 of the 7 common risk variants for glioma and tumor phenotype and genotype.

It is particularly striking that GWAS has highlighted *CDKN2A/B* and *EGFR*, which are both among the most frequently altered genes in high-grade gliomas and especially GBM.<sup>6</sup> However, SNPs annotating these genes were not associated with somatic alterations or GBM phenotype, except for a possible link between rs2252586 and GBM, *IDH* wild-type, and *EGFR* amplification (Supplementary material, Table S3 and S6). These data are compatible with the impact of these



risk loci having a generic effect on the risk of developing glioma.

Both rs2736100 (*TERT*) and rs6010620 (*RTEL1*) were shown to predispose to the specific risk of developing high-grade gliomas and to 10q loss, a genetic alteration tightly related to GBM.<sup>14</sup> The *TERT* gene encodes the catalytic subunit of telomerase, a prerequisite for cellular immortalization, and is aberrantly reactivated in most malignancies, including GBM.<sup>15,16</sup> *RTEL1* is critical for telomere replication and the maintenance of genomic integrity by preventing homologous recombination.<sup>17</sup> Multivariate analysis demonstrated that the risk allele of rs2736100 (*TERT*) is associated with a nonmutated *IDH* and the loss of chromosome 10q independently of tumor grade. Of interest, telomerase activity is itself associated with the loss of chromosome 10, which contains on 10p15 a repressor of telomerase activity.<sup>18</sup>

In contrast, rs4295627 (*CCDC26*) and rs498872 (*PHLDB1*) risk alleles were associated with the risk of low-grade glioma, rs4295627 being particularly associated with oligodendroglioma. *CCDC26* encodes a retinoic acid-dependent regulator of cell differentiation and death.<sup>19</sup> The function of *PHLDB1* is currently unknown; however, the 11q23.3 region is commonly deleted in neuroblastoma,<sup>20</sup> and 11q loss is also reported in low-grade gliomas.<sup>21</sup> We found that both risk loci were associated to *IDH* mutation, which is more frequent in low-grade gliomas, and 1p-19q codeletion, which is tightly related to oligodendroglial phenotype. Independent of the grade, multivariate analysis found that rs4295627 (*CCDC26*) associated to 1p-19q codeletion and rs498872 (*PHLDB1*) associated with *IDH* mutation and retained 10q. The association between rs4295627 and 1p-19q codeletion is concordant with recently published results from a US study in which the *CCDC26* (8q24) region polymorphism rs4296627 was strongly associated with oligodendroglial tumor risk, especially with 1p-19q codeletion.<sup>11</sup> We found *CCDC26* SNP associated with oligodendroglial, but also mixed and astrocytic tumours, and not with GBM (Supplementary material, Table S3).<sup>10</sup> Taken together, these studies suggest that rs4295627 (*CCDC26*) is associated with a risk to develop progressive gliomas (oligodendroglial and astrocytic, mostly *IDH* mutated) and, particularly, oligodendrogliomas with 1p-19q codeletion.

We clustered our population into 4 subgroups of growing aggressiveness based on 1p-19q codeletion, *EGFR* amplification (strongly associated with glioblastoma phenotype), and *IDH* mutation status. *IDH* mutation is associated with low-grade gliomas and progressive glioblastomas, and it is a constant feature in 1p-19q codeleted gliomas.<sup>5</sup> By promoting DNA and

histone methylation, *IDH* mutation results in an hypermethylated phenotype with profound reorganization of gene expression and dysregulation of glial differentiation.<sup>22,23</sup> Therefore, it is not surprising that the most relevant and robust association, from our 4-class molecular clustering, was found with the *IDH* status: *IDH*-mutated gliomas (class 1–2) are associated with rs4295627 (*CCDC26*) and rs498872 (*PHLDB1*) risk alleles, whereas *IDH* wild type gliomas (class 3–4) are associated with rs2736100 (*TERT*) and rs6010620 (*RTEL1*) risk alleles.

In conclusion, we have shown heterogeneity in the risk profile of the different glioma pathways ascribable to common genetic susceptibility. Collectively, our data suggest that risk alleles in *TERT* and *RTEL1* predispose to an aggressive pathway involving loss of chromosome 10, whereas *CCDC26* and *PHLDB1* risk alleles predispose to lower grade disease involving *IDH* mutation and 1p-19q loss. Because this was an exploratory study, further studies are needed to replicate these results in independent populations. Although the impact of each of these SNPs on tumor biology is small and, thus, individually, they may not have immediate clinical application, the associations provide novel insights into the biological mechanism underlying glioma formation and development.

## Supplementary Material

Supplementary material is available at *Neuro-Oncology Journal* online (<http://neuro-oncology.oxfordjournals.org/>).

## Acknowledgments

We thank the patients for agreeing to participate in this study, Anne-Marie Lekieffre and Muriel Brandel for their assistance, the clinicians and nurses who contributed to data collection, and the Institut Hospitalier Universitaire de Neurosciences Translationnelles de Paris.

*Conflict of interest statement.* None declared.

## Funding

This work was supported by the Délégation à la Recherche Clinique (MUL03012), the Institut National du Cancer (INCa; PL046), the Ligue Nationale contre le Cancer, the program “Investissements d’avenir” ANR-10-IAIHU-06, and Cancer Research UK (C1298/A8362 supported by the Bobby Moore Fund to R. H.).

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