A susceptibility locus for classical Hodgkin lymphoma at 8q24 near *MYC*/*PVT1* predicts patient outcome in two independent cohorts

Hervé Ghesquières[1,2,3], Beth R. Larrabee[3], Olivier Casasnovas[4], Matthew J. Maurer[3], James D. McKay[5], Stephen M. Ansell[6], Dorothy Montgomery[7], Yan W. Asmann[3], Katrina Farrell[7], Aurélie Verney[2], Susan L. Slager[3], Cristine Allmer[3], Aurore Perrot[8], Richard Delarue[9], Thomas M. Habermann[6], Jehan Dupuis[10], Brian K. Link[11], Danielle Canioni[12], Ahmet Dogan[13], Wendy Cozen[14], Ruth F. Jarrett[7], James R. Cerhan[3*] and Gilles Salles[1,2*]

[1]Department of Hematology, Centre Hospitalier Lyon Sud, Pierre-Bénite, France

[2]Centre de Recherche en Cancérologie de Lyon - INSERM U 1052/CNRS UMR 5286/Centre Léon Bérard, Lyon, France

[3]Health Sciences Research, Mayo Clinic, Rochester, MN, USA

[4]Department of Hematology, Hôpital Le Bocage–CHU Dijon, Dijon, France

[5]International Agency for Research on Cancer (IARC), Lyon, France

[6]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

[7]MRC-University of Glasgow Centre for Virus Research, Glasgow, UK

[8]Department of Hematology, CHU Nancy-Brabois, Vandoeuvre, France

[9]Department of Hematology, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Necker, Paris, France

[10]Lymphoid Malignancies Unit, Hôpital Henri Mondor, Assistance Publique-Hôpitaux de Paris (AP-HP) and University Paris Est, Créteil, France

[11]University of Iowa, Holden Comprehensive Cancer Center, Iowa City, IA, USA

[12]Department of Pathology, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Necker, Paris, France

[13]Department of Laboratory Medicine and Pathology, Memorial Sloan-Kettering Cancer Center, NY, USA

[14]USC Keck School of Medicine, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA

*James R. Cerhan and Gilles Salles should be considered as co-senior authors

Corresponding author: Hervé Ghesquières, Service d'Hématologie, Centre Hospitalier Lyon Sud, 165, chemin du Grand Revoyet, 69495 Pierre-Bénite Cedex, France. Phone: +33 4 78 86 43 02; fax: +33 4 78 86 43 54; E-mail: herve.ghesquieres@chu-lyon.fr

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The role of the HLA system in Hodgkin lymphoma (HL) susceptibility has been known for many years. Large genome-wide association studies (GWAS) also identified genetic variants outside of the HLA region, including 2p16.1 (near *REL*, rs1432295), 8q24.21 (near *MYC*/*PVT1*, rs2608053 and rs2019960), 10p14 (near *GATA3*, rs501764 and rs485411) and 19p13.3 (intron 2 of *TCF3*, rs1860661) (Enciso-Mora *et al* 2010; Cozen *et al*, 2014). *REL*, which encodes c-rel, a member of the NFkB pathway is activated in classical HL (cHL) and *GATA3* is aberrantly expressed in cHL. *PVT1*, which is downstream of the *MYC* locus, encodes five non-coding microRNAs (miR-1204, 1205, 1206, 1207, 1208), with suspected oncogenic properties (Barsotti *et al*, 2012). *TCF3*, a crucial gene for lymphoid progenitor commitment in B-cell and T-cell lineages, is disturbed in cHL (Renne *et al*, 2006). We investigated whether single nucleotide polymorphisms (SNPs) at 6p21 (*HLA-DRA*), 2p16 (*REL*), 8q24 (*MYC*/*PVT1*), 10p14 (*GATA3*) and 19p13.3 (*TCF3*) associated with HL susceptibility were also associated with outcome in two independent prospective cohorts.

The first cohort consisted of 342 cHL patients enrolled in a prospective biologic study of the Lymphoma Study Association (LYSA) and the second cohort consisted of 239 cHL patients prospectively enrolled in the University of Iowa/Mayo Clinic Specialized Program of Research Excellence (SPORE) Molecular Epidemiology Resource (Casasnovas *et al*, 2007; Thompson *et al*, 2011). The clinical characteristics of these patients are presented in Table S1. Patients were mainly treated with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) in LYSA (85%) and SPORE (90%). After a median follow-up of 5 years (range 0.04-9.75), the 5-year progression-free survival (PFS) and overall survival (OS) were 83% and 92% for the LYSA patients, respectively. After a median follow-up of 7.8 years (range 0.45-11.03), the PFS and OS for the SPORE cohort were 76% and 86%, respectively.

A peripheral blood sample for DNA analysis was collected from all patients. Details of DNA extraction and genotyping are presented in the Supporting Information. The seven SNPs genotyped from 2p16 (*REL*, rs1432295), 6p21 (*HLA-DRA*, rs6903608), 8q24 (*MYC*/*PVT1*, rs2608053 and rs2019960), 10p14 (*GATA3*, rs501764 and rs485411) and 19p13.3 (*TCF3*, rs1860661) had a similar minor allele frequency (MAF) between the two study cohorts (Table S2) and frequencies were consistent with prior studies (Enciso-Mora *et al*, 2010; Cozen *et al*, 2014). No significant correlation between the seven SNPs and the international prognostic score (IPS) was showed (Table S3 and S4).

Correlation between the seven SNPs and outcome is presented in Table I. In LYSA, *GATA3* (rs501767) was associated with PFS (HR=1.86; 95%CI, 1.11-3.12; *P*=0.02). There were suggestive associations for *MYC*/*PVT1* (rs2608053) (HR=1.76; 95%CI, 0.95-3.26; *P*=0.07) and *REL* (rs1432295) (HR=0.63; 95%CI 0.37-1.06; *P*=0.08). In SPORE, only *MYC*/*PVT1* (rs2608053) was associated with PFS (HR=2.22; 95%CI, 1.09-4.54; *P*=0.03). In a meta-analysis of the two studies, *MYC*/*PVT1* (rs2608053) was significantly associated with PFS (HR=1.94; 95%CI, 1.22-3.10; *P*=0.01), and adjustment for IPS did not alter the results (HR=1.83; 95%CI, 1.13-2.96; *P*=0.03). In SPORE, *MYC*/*PVT1* (rs2608053) was also associated with OS (HR=2.52; 95%CI, 1.06-6.00; *P*=0.04), while in LYSA the HR was attenuated (HR=1.38; 95%CI, 0.65-2.96; *P*=0.40). The number of deaths was lower in the LYSA cohort, limiting the power to detect a statistically significant difference for OS. In a meta-analysis of OS in the two studies, the pooled estimate for *MYC*/*PVT1* (rs2608053) was statistically significant in univariate analysis (HR=1.80; 95%CI, 1.01-3.18; *P*=0.04), but not after IPS adjustment (HR=1.60; 95%CI, 0.89-2.85; *P*=0.11). Survival curves comparing patients with *MYC*/*PVT1* (rs2608053) GG vs AG+AA genotypes are presented in Fig 1. The second SNP in the *MYC*/*PVT1* locus (rs2019960) was

associated with OS in only the SPORE cohort (HR=0.49; 95%CI, 0.26-0.93; *P*=0.03). In an exploratory analysis, associations of *MYC*/*PVT1* (rs2608053) with PFS were stronger for older age (≥45 years), male sex, nodular sclerosis subtype, and stage I-II disease (Table S5).

We conducted exploratory analyses assessing these SNPs with PFS stratified by EBV status (Table S6). The only significant association was observed for the *HLA-DRA* SNP (rs6903608) with PFS in EBV^- cHL from the SPORE cohort (HR=0.35; 95%CI, 0.13-0.94; *P*=0.04); a much weaker association was observed in the LYSA cohort (HR=0.67; 95%CI, 0.30-1.51) (*P*=0.33). These suggestive results could parallel the findings of risk studies in which the HLA class II SNP rs6903608 was mainly linked to EBV^- cHL susceptibility (Enciso-Mora *et al*, 2010; Urayama *et al*, 2012).

In this study, we observed that one risk SNP (rs2608053) for cHL at 8q24 near the *MYC*/*PVT1* locus was associated with patient outcome. The function of miR-1204, 1205, 1206, 1207 and 1208 in cHL pathogenesis is currently unknown. The prognostic association of *MYC*/*PVT1* rs2608053, a non-coding SNP, could be related to miRs or *MYC* deregulation. We found 14 SNPs in linkage disequilibrium (LD) with rs2608053 at r^2>0.50 (Table S7). None of these SNPs was in strong LD with SNPs within the miR genes in or near *MYC*. One of these SNPs, rs2720660 (r^2=0.52), was localized at -156 bp 5' of pre-miR-1207 in an active regulatory region (Fig S1). A previous study showed that *PVT1* transcripts including miR-1207 are induced by daunorubicin in a P53 dependent manner leading to cell cycle alterations and apoptosis (Barsotti *et al*, 2012). In a gastric cancer model, miR-1207-5p reduced *in vitro* proliferation by targeting the telomerase reverse transcriptase, in favour of an anti-oncogenic function (Chen *et al*, 2014). Recently, miR-217 overexpression was found to promote B-cell lymphoma by the

suppression of DNA damage response and the stabilization of *BCL6* that induces germinal center reaction (de Yebenes *et al*, 2014). Our bioinformatics research (Fig S2) showed that miR-1207-5p could also negatively regulate *BCL6* via the *heparin binding epidermal growth factor gene* (*HBEGF*) and that *HBEGF* is expressed in lymph nodes (Fig S3). One model in CFHR5 nephropathy confirmed that miR-1207-5p is effectively a target of *HBEGF* (Papagregoriou *et al*, 2012).

In conclusion, the cHL susceptibility locus rs2608053 at 8q24 was associated with PFS in two independent cohorts of cHL. Whether some polymorphisms at 8q24 locus could influence the functionality of translated miRs of this region and consequently cHL development and tumor sensitivity to cHL treatment need additional studies.

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Authorship Contributions

H.G. designed the research, performed the research, analyzed the data, and wrote the manuscript; G.S., J.R.C. designed the research, analyzed the data and reviewed the manuscript; R.F.J. analyzed the data and reviewed the manuscript; B.R.L., M.J.M., S.L.S. performed statistical research and analyzed the data; Y.W.A. performed bioinformatic research; A.V. performed the research; D.C., A.D. performed pathological review; H.G., B.R.L., K.F., O.C., M.J.M., S.M.A., D.M., Y.W.A., A.V., S.L.S., A.P., R.D., T.M.H., J.D., B.K.L., D.C., A.D., R.F.J., J.R.C., G.S. provided study materials or patients, collected and assembled data; H.G., B.R.L., K.F., O.C., M.J.M., S.M.A., D.M., Y.W.A., A.V., S.L.S., A.P., R.D., T.M.H., J.D., B.K.L., D.C., A.D., R.F.J., J.R.C., G.S. approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Genotyping conditions

Data S2. Statistics

Table S1. Clinical, biologic characteristics and treatment of classical Hodgkin lymphoma patients

Table S2. Genotyping of the seven SNPs in the two cohorts

Table S3. P-value (Chi-square test) evaluating the correlation between clinical characteristics and the genotyping of the seven studied SNPs in the LYSA cohort

Table S4. P-value (Chi-square test) evaluating the correlation between clinical characteristics and the genotyping of the seven studied SNPs in the SPORE cohort

Table S5. Univariate analysis of *MYC*/*PVT1* rs2608053 (dominant model) with progression-free survival by classical Hodgkin lymphoma subgroup in LYSA and SPORE cohorts

Table S6. Univariate associations of SNPs (dominant model) with progression-free survival in classical Hodgkin lymphoma stratified by EBV tumor status

Table S7. Single nucleotide polymorphisms in linkage disequilibrium with *MYC*/*PVT1* rs2608053 on chromosome 8 according to 1000 Genomes Project

Fig S1. *MYC*/*PVT1* rs2608053 is located in epigenetic regulatory domain with high PhastCons and PolyP conservation scores across Mammal and Vertebrates according to UCSC GoldenPath Database

Fig S2. MetaCore Regulatory Network Analyses of miR-1207-5p targets using the Auto-Expand algorithm

Fig S3. Expression of *HBEGF* in lymph nodes and other tissues based on Microarray (left panel), RNAseq (center panel), and Serial Analysis of Gene Expression (SAGE, right panel) data from GTEx, BioGPS, Illumina Human BodyMap, and SAGE. The image of the expression profile is compiled by GeneCards (http://www.genecards.org/)

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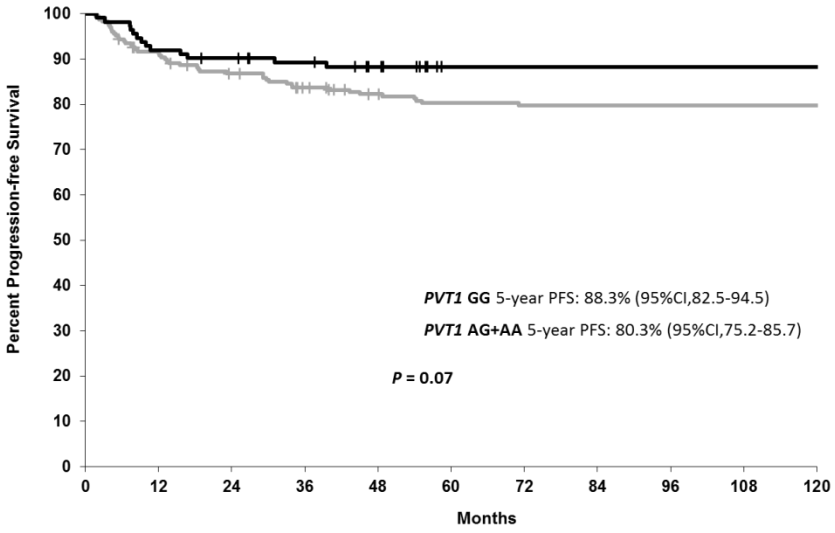
Fig 1. Outcome of classical Hodgkin lymphoma patients according to *MYC*/*PVT1* (rs2608053) genotype. Progression-free survival in LYSA (1A) and in the SPORE cohorts (1B). Overall survival in LYSA (1C) and in the SPORE (1D). Progression-free survival was measured from the date of initiation of therapy (LYSA) or the date of diagnosis (SPORE) to the date of first relapse, progression, retreatment, or death (any cause). Overall survival was evaluated from the date of initiation of therapy (LYSA) or the date of diagnosis (SPORE) to the date of death from any cause. Survival was estimated by the Kaplan-Meier product limit method and compared using the log-rank test.

1A



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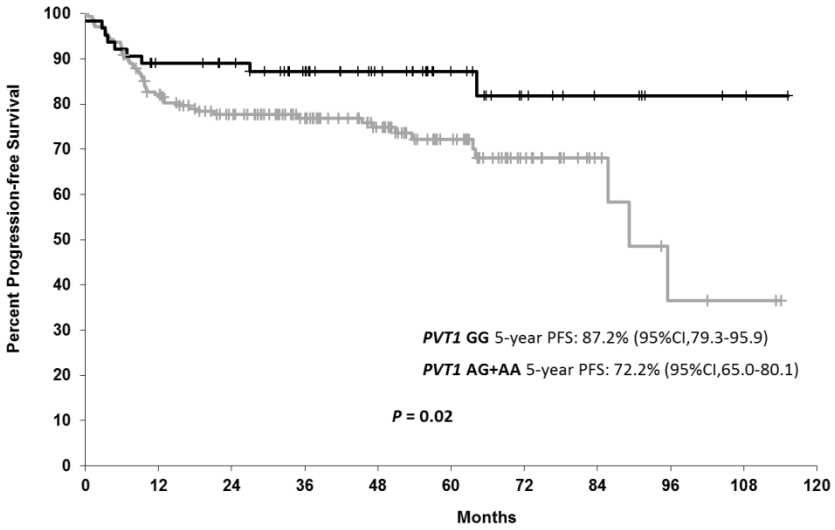
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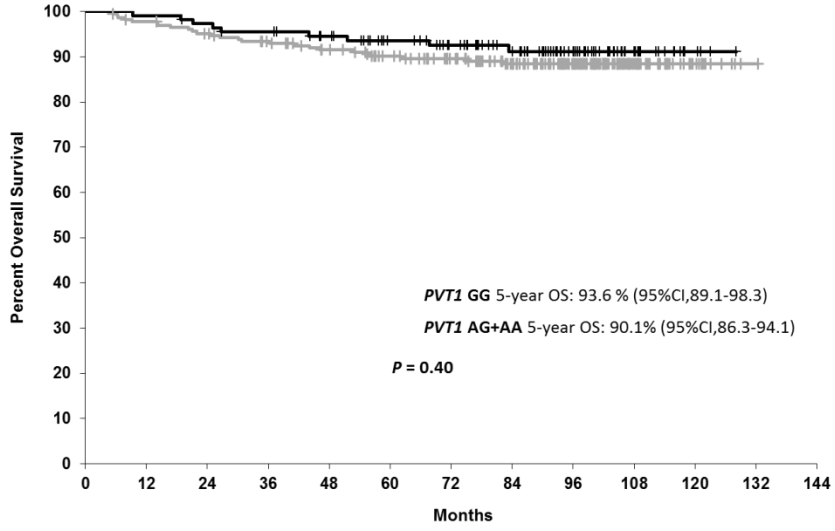
80
70
60
50
40
30
20
10
0
0
12
24
36
48
60
72
84
96
108
120
Months
PVT1 GG 5-year PFS: 87.2% (95%CI,79.3-95.9)
PVT1 AG+AA 5-year PFS: 72.2% (95%CI,65.0-80.1)
P = 0.02

1C


Percent Overall Survival
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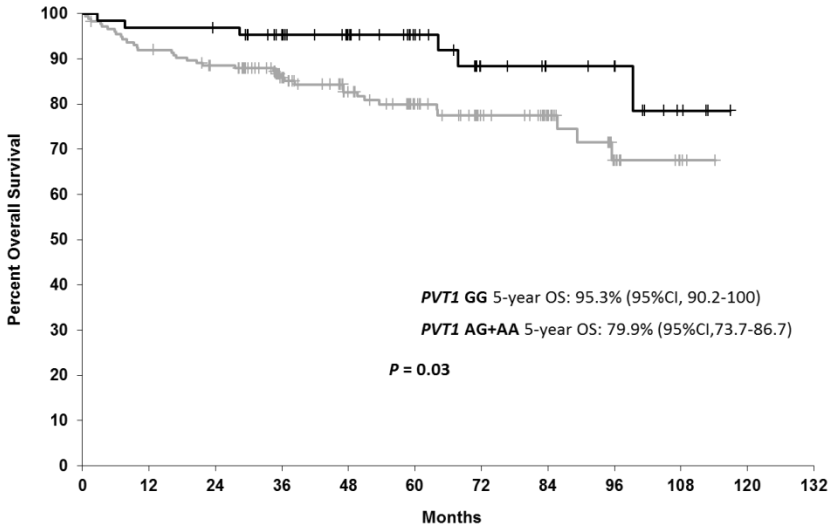
80
70
60
50
40
30
20
10
0
0
12
24
36
48
60
72
84
96
108
120
132
144
Months
PVT1 GG 5-year OS: 93.6 % (95%CI,89.1-98.3)
PVT1 AG+AA 5-year OS: 90.1% (95%CI,86.3-94.1)
P = 0.40

1D


Percent Overall Survival
100
90
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10
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24
36
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60
72
84
96
108
120
132
Months
PVT1 GG 5-year OS: 95.3% (95%CI, 90.2-100)
PVT1 AG+AA 5-year OS: 79.9% (95%CI,73.7-86.7)
P = 0.03

Table I. Univariate associations of SNPs (dominant model) with progression-free and overall survival in classical Hodgkin lymphoma

	Progression-Free Survival						Overall Survival					
	LYSA		SPORE		Combined analysis		LYSA		SPORE		Combined analysis	
Gene and SNP	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
REL, rs1432295	0.63 (0.37-1.06)	0.08	1.01 (0.57-1.76)	0.99	0.78 (0.53-1.15)	0.21	0.52 (0.27-1.03)	0.06	1.36 (0.68-2.71)	0.38	0.84 (0.52-1.36)	0.47
HLA-DRA, rs6903608	0.95 (0.54-1.68)	0.87	0.70 (0.41-1.18)	0.18	0.81 (0.55-1.18)	0.27	0.83 (0.40-1.70)	0.61	0.80 (0.43-1.48)	0.48	0.81 (0.51-1.30)	0.38
MYC/PVT1, rs2608053	1.76 (0.95-3.26)	0.07	2.22 (1.09-4.54)	0.03	1.94 (1.22-3.10)	0.01	1.38 (0.65-2.96)	0.40	2.52 (1.06-6.00)	0.04	1.80 (1.01-3.18)	0.04
MYC/PVT1, rs2019960	1.16 (0.69-1.94)	0.57	0.71 (0.42-1.21)	0.21	0.91 (0.63-1.32)	0.64	0.93 (0.47-1.83)	0.84	0.49 (0.26-0.93)	0.03	0.67 (0.42-1.06)	0.09
GATA3, rs501764	1.86 (1.11-3.12)	0.02	0.71 (0.41-1.23)	0.23	1.18 (0.81-1.72)	0.38	1.06 (0.54-2.10)	0.86	0.75 (0.40-1.41)	0.37	0.88 (0.55-1.40)	0.59
GATA3, rs485411	1.43 (0.85-2.39)	0.18	1.10 (0.65-1.86)	0.72	1.25 (0.87-1.81)	0.23	0.77 (0.39-1.52)	0.45	1.05 (0.57-1.92)	0.88	0.91 (0.58-1.44)	0.70
TCF3, rs1860661	1.10 (0.61-1.98)	0.74	1.42 (0.78-2.59)	0.25	1.25 (0.82-1.90)	0.30	1.45 (0.64-3.28)	0.37	1.40 (0.71-2.73)	0.33	1.42 (0.84-2.38)	0.19

Abbreviations: HR, hazard ratio; CI, confidence interval; SNP, single nucleotide polymorphism.

Supporting information

Data S1: Genotyping conditions

A peripheral blood sample for DNA was collected from all patients in the two studies. These studies were approved by the ethics committees from Dijon and Lyon University Hospitals (LYSA) and Mayo Clinic and the University of Iowa Institutional Review Boards (SPORE). All patients provided written consent for participation. DNA for genotyping was extracted using standard protocols. In the LYSA, SNPs at 6p21 (*HLA-DRA*, rs6903608), 8q24 (*MYC*/*PVT1* rs2608053 and rs2019960), 10p14 (*GATA3*, rs501764) and rs485411) were analyzed using a complete commercially available assay (Applied Biosystems, Foster City, California, USA) that contains primers, probes and TaqMan Genotyping Master Mix. Real-time PCR analysis was performed on an ABI Prism 7000 Sequence Detection System (Applied Biosystems). The *REL* polymorphism was genotyped by using a PCR-based restriction fragment length polymorphism (PCR-RFLP). The amplified fragments of 401 bp were obtained with the use of upstream (5'-CTTTACACCTAAATTGTTGTCTTGTG) and downstream (5'-AGTGCTGGGACTACAGGTATGA) primers. PCR amplification was performed with a first step at 94°C for 10 minutes, followed by 35 cycles of 45 s at 95°C, 45 s at 60°C, 1 minute at 72°C, followed by a final extension step at 72°C for 10 minutes, in a final volume of 50 µL. The PCR-amplified products (10 µL) were digested 1 hour at 37°C with 1 unit of Alw26I (Fermentas, ThermoScientific). The digested PCR-products were separated by electrophoresis on agarose gel. Ten percent of the LYSA samples were duplicates, with 100% concordance of genotyping results.

In the SPORE, all but one of the candidate SNPs (*TCF3* at 19p13.3) were genotyped as part of a larger project using a custom Illumina Infinium array (Illumina, San Diego, CA) (Charbonneau *et al*, 2013). Standard genotyping quality control procedures were performed and

included duplicate genotyping, dropping samples or SNPs with call rates<95%, and testing for Hardy-Weinberg equilibrium (HWE). We found >99.9% genotyping concordance among the 3502 samples with duplicates.

The genotyping of *TCF3* SNP (rs1860661) of the LYSA and the SPORE cohorts was performed in the context of a GWAS meta-analysis (Cozen *et al*, 2014) for HL susceptibility of three previous HL GWAS (Cozen *et al*, 2012; Urayama *et al*, 2012; Best *et al*, 2011). Genotyping of the LYSA cases was performed by the IARC, and the SPORE series was performed by the Molecular Genomics Core of USC (Norris Comprehensive Cancer Center, Los Angeles, CA) using TaqMan Pre-Designed SNP Genotyping Assays (Applied Biosystems, Carlsbad, CA). A TaqMan Pre-Designed SNP Genotyping Assay Mix (containing probes and primers) was used for this SNP (Applied Biosystems assay-on-demand order code C__11969900_10 for rs1860661).

Data S2. Statistics

Progression free survival (PFS) was measured from the date of initiation of therapy (LYSA series) or the date of diagnosis (SPORE series) to the date of first relapse, progression, retreatment, or death (any cause). Overall survival (OS) was measured from the date of initiation of therapy (LYSA series) or the date of diagnosis (SPORE series) to the date of death (any cause). Patients without an event were censored at date of last follow-up. Kaplan-Meier curves and Cox proportional hazards models were used to assess the association of each genotype (dominant model) with PFS and OS in both a univariate fashion and after adjusting for the international prognostic score (IPS). Analyses were done independently for the two cohorts and then to increase power, a meta-analysis approach was used to combine results. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and R (http://www.r-project.org/).

Table S1. Clinical, biologic characteristics and treatment of classical Hodgkin lymphoma patients

	LYSA	SPORE	
	N=342 (%)	N=239 (%)	P-value
Median age (range)	32 (15-93)	38 (18-89)	<0.0001
Age≥45 years	71 (21)	92 (39)	<0.0001
Male	196 (57)	124 (52)	0.20
Ethnicity			
Caucasian	-	202 (85)	
Non-Caucasian	-	6 (2)	
Unknown	-[a]	31 (13)	
ECOG PS			
0-1	295 (97)	205 (86)	<0.0001
2-4	9 (3)	34 (14)	
Histological subtype			
Nodular sclerosis	288 (84)	161 (67)	<0.0001[c]
Mixed cellularity	30 (9)	27 (11)	
Lymphocyte rich	2 (<1)	12 (5)	
Lymphocyte depletion	1 (<1)	0 (0)	
Unclassified	21 (6)	39 (16)	
EBV status of tumor[b]			
EBV positive	40 (22)	23 (22)	
EBV negative	140 (78)	81 (78)	
Ann Arbor Stage			
I-II	247 (72)	122 (51)	<0.0001
III-IV	95 (28)	113 (47)	
B symptoms	154 (45)	92 (38)	0.12
Hemoglobin level<10.5g/dl	44 (13)	32 (13)	0.77
ESR≥50	146 (43)	50 (21)	0.03
White-cell count≥15,000/mm^3	71 (21)	30 (13)	0.01
Lymphocyte count<600/mm^3	25 (7)	29 (12)	0.02
Albumin level<40g/l	145 (42)	103 (43)	0.32
IPS			
0-2	229 (73)	120 (50)	<0.0001
3-7	84 (27)	119 (50)	
Treatment			
ABVD	206 (60)	214 (90)	<0.0001[d]
EBVP	76 (22)	-	
BEACOPP	41 (12)	-	
Other regimens	19 (6)	10 (4)	
Stanford V	-	12 (5)	
MOPP	-	3 (1)	

Table S1. Clinical, biologic characteristics and treatment of classical Hodgkin lymphoma patients

	LYSA	SPORE	
	N=342 (%)	N=239 (%)	P-value

Abbreviations: EBV, Epstein - Barr virus; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ESR, erythrocyte sedimentation rate; IPS, international prognostic score; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; EBVP, epirubicin, bleomycin, cyclophosphamide, vincristine, prednisone; BEACOPP, bleomycin, etoposide, doxorubin, cyclophosphamide, vincristin, procarbazine, prednisone; MOPP, caryolysine, vincristine, vinblastine, procarbazine.

[a]In accordance with French law, race or ethnicity could not be collected. This cohort likely reflects the genetic heterogeneity of the French population, which is dominated by Western-European ancestry given the national scope of this prospective study.

[b]EBV status was obtained in 180 (53%) and 104 (48%) patients in LYSA and SPORE cohorts, respectively. In the LYSA, EBV status was obtained by immunohistochemical detection of latent membrane protein-1 (LMP-1) in 134 patients (75%), by EBER in situ hybridization in 37 patients (21%) or by other techniques in the remaining 7 patients (4%). In the SPORE EBV status was performed by EBER in situ hybridization.

[c]P-value compared nodular-sclerosis versus other.

[d]P-value compared ABVD versus other.

Table S2. Genotyping of the seven SNPs in the two cohorts

		LYSA		SPORE		GWAS[a]	
		n=342		n=239		Cases	Controls
		N (%)	MAF	N (%)	MAF	MAF	
2p16 (*REL*)	AA	104 (30)	0.44	75 (31)	0.46	0.48	0.40
rs1432295	AG	173 (51)		110 (46)			
	GG	65 (19)		54 (23)			
6p21 (*HLA-DRA*)	AA	95 (28)	0.50	85 (36)	0.42	0.40	0.27
rs6903608	AG	155 (45)		108 (45)			
	GG	92 (27)		46 (19)			
8q24 (*MYC/PVT1*)	GG	112 (33)	0.43	64 (27)	0.46	0.41	0.48
rs2608053	GA	168 (49)		128 (54)			
	AA	62 (18)		47 (20)			
8q24 (*MYC/PVT1*)	AA	176 (51)	0.29	125 (52)	0.29	0.29	0.23
rs2019960	AG	135 (40)		91 (38)			
	GG	31 (9)		23 (10)			
10p14 (*GATA3*)	AA	206 (60)	0.22	137 (57)	0.24	0.25	0.19
rs501764	AG	121 (36)		87 (36)			
	GG	14 (4)		15 (6)			
10p14 (*GATA3*)	GG	181 (53)	0.28	113 (47)	0.31	0.31	0.25
rs485411	GA	133 (39)		106 (44)			
	AA	28 (8)		20 (8)			
19p13.3 (*TCF3*)	AA	107 (35)	0.42	79 (39)	0.39	0.35[b]	0.41[b]
rs1860661	AG	140 (46)		87 (43)			
	GG	56 (18)		35 (17)			

Abbreviations: MAF, minor allele frequency; GWAS, genome wide-association study.

[a]Data for the GWAS from Enciso-Mora *et al* (2010), except for *TCF3*.

[b]Data from the discovery phase of the meta-analysis GWAS from Cozen *et al* (2014). Of note, our cases were analyzed as part of the validation phase of this study.

Table S3. P-value (Chi-square test) evaluating the correlation between clinical characteristics and the genotyping of the seven studied SNPs in the LYSA cohort

	REL rs1432295	*HLA-DRA* rs6903608	*MYC/PVT1* rs2608053	*MYC/PVT1* rs2019960	*GATA3* rs501764	*GATA3* rs485411	*TCF3* rs1860661
Age ≥45 years	0.09	0.23	0.80	0.25	0.25	0.50	0.91
Male	0.74	0.43	0.75	0.69	0.76	0.85	0.29
Stage III/IV	1.00	0.79	0.23	0.27	0.86	0.94	0.91
Nodular sclerosis vs other	0.73	0.25	0.98	0.17	0.21	0.14	0.49
ECOG PS	0.58	0.89	**0.001**[a]	0.48	0.77	0.66	0.09
B Symptoms	0.53	0.06	0.93	0.32	0.41	0.26	0.41
Hemoglobin level<10.5g/dl	0.81	0.53	0.24	0.85	0.69	0.58	0.29
White-cell count≥15,000/mm^3	0.52	0.12	0.23	0.95	0.69	0.52	0.29
ESR<50	0.18	0.15	0.49	0.66	0.85	0.78	0.50
Lymphocyte Count<600/mm^3	0.68	0.47	0.14	0.99	0.21	0.42	0.82
Albumin<40g/l	0.26	0.20	0.55	0.72	0.90	0.94	0.33
IPS	0.52	0.64	0.59	0.20	0.44	0.60	0.95

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; ESR, erythrocyte sedimentation rate; IPS, international prognostic score.

[a]PS 0-2: GG: 94 (84%), AG: 150 (89%), GG: 51 (82%)
PS 2-4: GG: 1 (1%), AG: 2 (1%), GG: 6 (10%)

Table S4. P-value (Chi-square test) evaluating the correlation between clinical characteristics and the genotyping of the seven studied SNPs in the SPORE cohort

	REL rs1432295	*HLA-DRA* rs6903608	*MYC/PVT1* rs2608053	*MYC/PVT1* rs2019960	*GATA3* rs501764	*GATA3* rs485411	*TCF3* rs1860661
Age ≥45 years	0.05	**0.03**[a]	0.23	0.21	0.61	0.31	0.12
Male	0.43	0.32	0.41	0.83	0.73	0.46	0.47
Ann Arbor stage III/IV	0.59	0.62	0.55	0.62	0.95	0.36	**0.02**[b]
Nodular sclerosis vs. other	0.66	0.20	0.49	0.89	0.38	**0.05**[c]	0.09
ECOG PS	0.55	0.77	0.56	0.55	0.22	0.84	0.65
B Symptoms	0.86	**0.002**[d]	0.61	0.43	0.81	0.92	0.16
Hemoglobin level <10.5g/dl	0.29	0.09	0.29	0.88	0.22	0.13	0.06
White-cell count≥15,000/mm^3	0.63	0.79	0.88	0.55	0.44	0.88	0.67
ESR < 50	0.46	0.73	0.30	0.63	0.31	0.48	0.69
Lymphocyte Count<600/mm^3	0.79	0.69	**0.04**[e]	0.76	0.33	0.22	0.45
Albumin<40g/l	0.63	0.87	0.28	0.77	0.92	0.41	0.90
IPS	0.99	0.30	0.22	0.87	0.19	0.23	0.38

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; ESR, erythrocyte sedimentation rate; IPS, international prognostic score.

[a] Age <45: GG (n=50, 59%), AG (n=61, 56%), AA (n=36, 78%)
Age ≥45: GG (n=35, 41%), AG (n=47, 44%), AA (n=19, 22%)

[b] Stage I-II: AA (n=44, 57%), AG (n=49, 56%), GG (n=10, 29%)
Stage III-IV: AA (n=35, 43%), AG (n=36, 41%), GG (n=24, 69%)

[c] Nodular sclerosis: AA (n=82, 73%), AG (n=70, 66%), GG (n=9, 45%)
Other: AA (n=31, 27%), AG (n=36, 34%), GG (n=11, 55%)

[d] B symptoms: GG (n=43, 51%), AG (n=40, 27%), AA (n=9, 20%)
No B symptoms: GG (n=42, 49%), AG (n=68, 63%), AA (n=37, 80%)

[e] Lymphocyte Count<600/mm^3: GG (n=4, 6%), AG (n=15, 12%), AA (n=10, 21%)
Lymphocyte Count≥600/mm^3: GG (n=55, 86%), AG (n=103, 80%), AA (n=31, 66%)

Table S5. Univariate analysis of *MYC/PVT1* rs2608053 (dominant model) with progression-free survival by classical Hodgkin lymphoma subgroup in LYSA and SPORE cohorts

	LYSA				SPORE			
Subgroup	N	Events	HR (95%CI)	P	N	Events	HR (95%CI)	P
All patients	342	58	1.76 (0.95-3.26)	0.07	238	57	2.22 (1.09-4.54)	0.03
Nodular Sclerosis	288	49	2.02 (1.01-4.05)	0.05	161	35	2.65 (1.03-6.85)	0.04
Other cHL subtypes	54	9	0.89 (0.22-3.58)	0.87	77	22	1.38 (0.46-4.12)	0.56
<45 years old	271	37	1.40 (0.68-2.90)	0.36	147	27	2.20 (0.76-6.38)	0.15
≥45 years old	71	21	2.75 (0.81-9.35)	0.10	91	30	2.23 (0.85-5.85)	0.10
Males	196	38	2.73 (1.14-6.53)	0.02	124	35	1.42 (0.52-3.85)	0.02
Females	146	20	0.93 (0.37-2.33)	0.88	114	22	6.47 (0.86-49.0)	0.49
Ann Arbor Stage I-II	247	33	2.15 (0.93-4.96)	0.07	122	18	2.05 (0.90-4.66)	0.07
Ann Arbor Stage III-IV	95	25	1.08 (0.43-2.72)	0.86	112	38	2.22 (1.09-4.54)	0.09

Abbreviations: HR, hazard ratio; CI, confidence interval, cHL, classical Hodgkin lymphoma; EBV, Epstein-Barr Virus.

Table S6. Univariate associations of SNPs (dominant model) with progression-free survival in classical Hodgkin lymphoma stratified by EBV tumor status.

	EBV$^-$ cHL								EBV$^+$ cHL							
	LYSA				SPORE				LYSA				SPORE			
Gene and SNP	N, Events		HR (95%CI)	*P*	N, Events		HR (95%CI)	*P*	N, Events		HR (95%CI)	*P*	N, Events		HR (95%CI)	*P*
REL, rs1432295	140	26	0.93 (0.40-2.14)	0.86	81	16	2.38 (0.54-10.5)	0.25	40	8	0.44 (0.11-1.77)	0.25	23	11	3.47 (0.89-13.6)	0.07
HLA-DRA, rs6903608	140	26	0.67 (0.30-1.51)	0.33	81	16	0.35 (0.13-0.94)	0.04	40	8	0.91 (0.22-3.80)	0.90	23	11	1.62 (0.46-5.74)	0.46
MYC/PVT1, rs2608053	140	26	1.72 (0.65-4.55)	0.28	81	16	2.38 (0.67-8.40)	0.18	40	8	1.40 (0.28-6.93)	0.68	23	11	0.96 (0.20-4.66)	0.96
MYC/PVT1, rs2019960	140	26	1.01 (0.47-2.18)	0.98	81	16	0.72 (0.27-1.92)	0.51	40	8	0.90 (0.22-3.77)	0.89	23	11	0.64 (0.16-2.48)	0.52
GATA3, rs501764	140	26	1.58 (0.73-3.42)	0.24	81	16	0.69 (0.25-1.89)	0.47	40	8	2.17 (0.54-8.67)	0.27	23	11	0.92 (0.23-3.69)	0.91
GATA3, rs485411	140	26	1.41 (0.65-3.07)	0.38	81	16	0.98 (0.36-2.62)	0.96	40	8	1.67 (0.42-6.70)	0.47	23	11	1.62 (0.43-6.05)	0.47
TCF3, rs1860661	121	21	1.48 (0.60-3.67)	0.40	72	16	0.91 (0.34-2.45)	0.85	35	6	0.42 (0.08-2.10)	0.29	19	8	0.77 (0.14-4.24)	0.77

Abbreviations: cHL, classical Hodgkin lymphoma; EBV, Epstein-Barr Virus; HR, hazard ratio; CI, confidence interval.

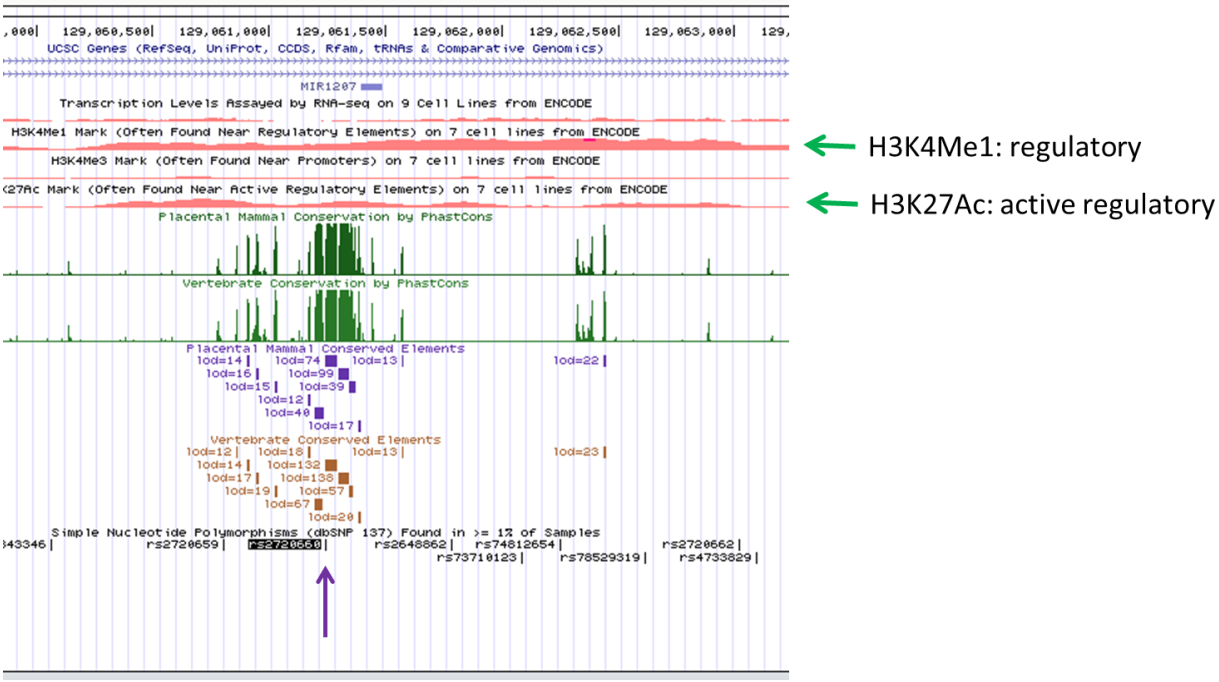
Table S7. Single nucleotide polymorphisms in linkage disequilibrium with *MYC*/*PVT1* rs2608053 on chromosome 8 according to 1000 Genomes Project[a]

SNP[a]	*Position*[b]	r^2
rs2720665	129076509	0.87
rs2608052	129076284	0.72
rs1499363	129074902	0.66
rs2720658	129059423	0.65
rs2648861	129059568	0.65
rs12547679	129053040	0.64
rs11775301	129059110	0.61
rs2648879	129073712	0.58
rs58467928	129074450	0.55
rs2720660	129061242	0.52
rs2648876	129072966	0.52
rs13250078	129070428	0.52
rs13248311	129070559	0.52
rs35916594	129069820	0.51

[a]Abecacis *et al*, 2012

[b]The research of the SNPs was performed from 112076290 and 146075832 position that convers *PVT1* and *MYC* loci

Fig S1. *MYC*/*PVT1* rs2608053 is located in epigenetic regulatory domain with high PhastCons and PolyP conservation scores across Mammal and Vertebrates according to UCSC GoldenPath Database



We investigated the potential functional roles of rs2608053 and the 14 SNPs in LD with rs2608053 (Table S7) using data from the Encode Project[a] and UCSC GoldenPath Database[b]. Since neither rs2608053 nor other SNPs in LD with rs2608053 are located in exons, we hypothesized that rs2608053 is a regulatory SNP or is in LD with a regulatory SNP. Among the 15 SNPs investigated including rs2608053, only rs2720660 is located in an evolutionarily conserved region. As shown in the Figure above, rs2720660 (r^2 = 0.52) is in elements conserved across both vertebrates and placental mammals, as calculated using two methods (phastCons and pyloP) from the PHAST package[c]. Further evidence of rs2720660 as a regulatory SNP comes from the ENCODE epi-genetic marker profiling data of cell lines. The figure above only displays the data from GM12878, a lymphoblastoid cell line. Specifically, rs2720660 was found in the H3K4Me1 mark which is often found near regulatory elements, as well as the H3K27Ac mark which is usually near "active" regulatory elements.

[a]The ENCODE (ENCyclopedia Of DNA Elements) Project. *Science* 2004; **306**: 636-640. http://genome.ucsc.edu/ENCODE/ [Accessed April 09, 2013].

[b]UCSC GoldenPath database. http://genome.ucsc.edu/ [Accessed April 09, 2013].

[c]PHAST package: http://compgen.bscb.cornell.edu/phast/ [Accessed April 09, 2013].

Fig S2. MetaCore Regulatory Network Analyses of miR-1207-5p targets using the Auto-Expand algorithm

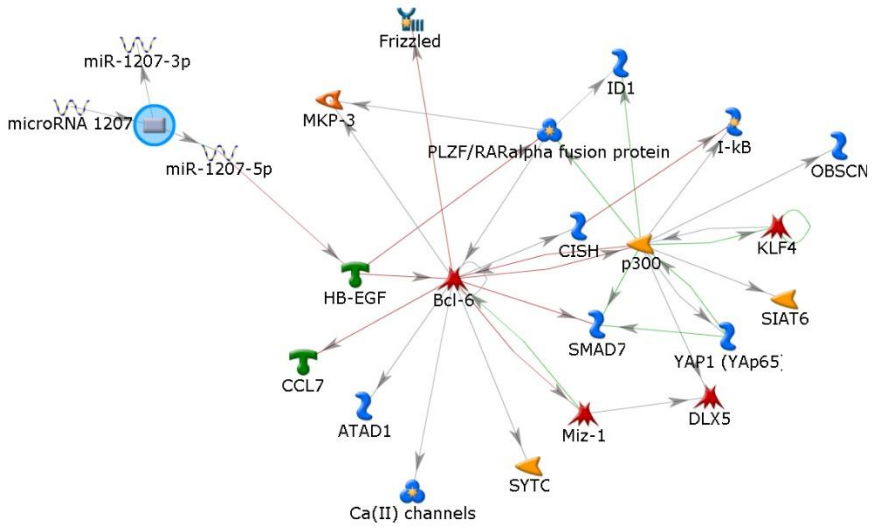
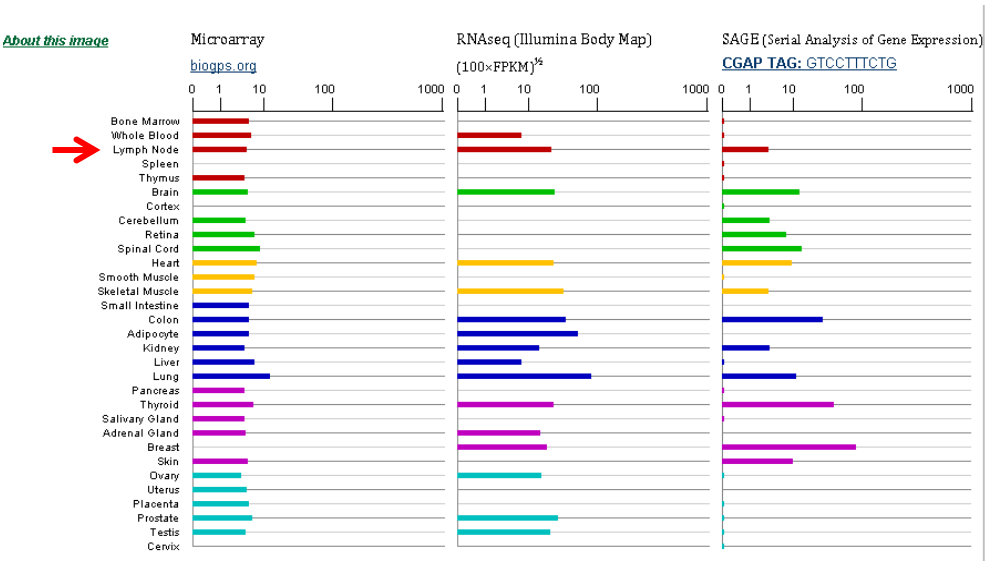


Fig S3. Expression of *HBEGF* in lymph nodes and other tissues based on Microarray (left panel), RNAseq (center panel), and Serial Analysis of Gene Expression (SAGE, right panel) data from GTEx, BioGPS, Illumina Human BodyMap, and SAGE. The image of the expression profile is compiled by GeneCards (http://www.genecards.org/)



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