Sequence variant on 8q24 confers susceptibility to urinary bladder cancer

Lambertus A. Kiemeney[2,3,4,*,#], Steinunn Thorlacius[1,*], Patrick Sulem[1], Frank Geller[1], Katja K.H. Aben[2,4], Simon N. Stacey[1], Julius Gudmundsson[1], Margret Jakobsdottir[1], Jon T. Bergthorsson[1], Asgeir Sigurdsson[1], Thorarinn Blondal[1], J. Alfred Witjes[3], Sita H. Vermeulen[2], Christina A. Hulsbergen-van de Kaa[5], Dorine W. Swinkels[6], Martine Ploeg[3], Erik B. Cornel[7], Henk Vergunst[8], Thorgeir E. Thorgeirsson[1], Daniel Gudbjartsson[1], Sigurjon A. Gudjonsson[1], Gudmar Thorleifsson[1], Kari T. Kristinsson[1], Magali Mouy[1], Steinunn Snorradottir [1], Donatella Placidi[9], Marcello Campagna[9], Cecilia Arici[9], Kvetoslava Koppova[10], Eugene Gurzau[11], Peter Rudnai[12], Eliane Kellen[13,14], Silvia Polidoro[15,16], Simonetta Guarrera[15,16], Carlotta Sacerdote[17], Manuel Sanchez[18], Berta Saez[19], Gabriel Valdivia[20], Charlotta Ryk[21], Petra de Verdier[21], Annika Lindblom[21], Klaus Golka[22], D. Timothy Bishop[23], Margaret A. Knowles[24], Sigfus Nikulasson[25], Vigdis Petursdottir[25], Eirikur Jonsson[26], Gudmundur Geirsson[26], Baldvin Kristjansson[26], Jose I. Mayordomo[27,28], Gunnar Steineck[29,30], Stefano Porru[9], Frank Buntinx[13,31], Maurice P. Zeegers[32,33], Tony Fletcher[34], Rajiv Kumar[35], Giuseppe Matullo[15,16], Paolo Vineis[15,36], Anne E. Kiltie[24], Jeffrey R. Gulcher[1], Unnur Thorsteinsdottir[1,37], Augustine Kong[1], Thorunn Rafnar[1], Kari Stefansson[1,37,#].

[1]deCODE Genetics, Sturlugata 8, 101 Reykjavik, Iceland.
[2]Department of Epidemiology & Biostatistics, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands.
[3]Department of Urology, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands.
[4]Comprehensive Cancer Center East, 6501 BG Nijmegen, The Netherlands.
[5]Department of Pathology, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands.
[6]Department of Clinical Chemistry, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands.
[7]Department of Urology, Streekziekenhuis Midden-Twente, 7550 AM Hengelo, The Netherlands.
[8]Department of Urology, Canisius Wilhelmina Ziekenhuis, 6500 GS Nijmegen, The Netherlands.
[9]Department of Experimental and Applied Medicine - Section of Occupational Medicine and Industrial Hygiene, University of Brescia, 25125 Brescia, Italy.
[10]State Health Institute, SK-975 56 Banska Bystrica, Slovakia.
[11]Environmental Health Center, 400166 Cluj Napoca j, Romania.
[12]National Institute of Environmental Health, H-1450 Budapest, Hungary.
[13]Department of General Practice, Catholic University of Leuven, 3000 Leuven, Belgium.
[14]Leuven University Centre for Cancer Prevention (LUCK), 3000 Leuven, Belgium.
[15]ISI Foundation (Institute for Scientific Interchange), Turin, Italy.
[16]Department of Genetics, Biology and Biochemistry, University of Torino, 10126 Turin, Italy.
[17]Unit of Cancer Epidemiology, University of Turin and Centre for Cancer Epidemiology and Prevention (CPO Piemonte), 10123 Turin, Italy.
[18]Division of Urology. University Hospital, 50009 Zaragoza, Spain.
[19]Health Science Institute. 50009 Zaragoza, Spain.

[20]Department of Urology. University of Zaragoza School of Medicine. 50009 Zaragoza, Spain.
[21]Dept. Molecular Medicine and Surgery, Karolinska Institutet, S171 76 Stockholm, Sweden.
[22]Institute for Occupational Physiology at the University of Dortmund, Dortmund, Germany
[23]Section of Epidemiology & Biostatistics, Leeds Institute of Molecular Medicine, St. James's University Hospital, LS9 7TF Leeds, UK.
[24]Section of Experimental Oncology, Leeds Institute of Molecular Medicine, St. James's University Hospital, LS9 7TF Leeds, UK.
[25]Department of Pathology, Landspitali-University Hospital, 101 Reykjavik, Iceland.
[26]Department of Urology, Landspitali-University Hospital, 101 Reykjavik, Iceland.
[27]Division of Medical Oncology, University Hospital, 50009 Zaragoza, Spain.
[28]Nanotechnology Institute of Aragon. Health Science Institute, 50009 Zaragoza, Spain.
[29]Department of Oncology and Pathology, Karolinska Hospital, S171 76 Stockholm, Sweden.
[30]Department of Oncology, Sahlgrenska University Hospital, S-413 45 Goteborg, Sweden
[31]Department of General Practice, Maastricht University, 6200 MD Maastricht, The Netherlands.
[32]Unit of Genetic Epidemiology, Department of Public Health and Epidemiology. University of Birmingham, B15 2TT Birmingham, UK.
[33]Department of Complex Genetics, Cluster of Genetics and Cell Biology, Nutrition and Toxicology Research Institute, Maastricht University, 6200 MD Maastricht, The Netherlands.
[34]London School of Hygiene & Tropical Medicine, WC1E 7HT London, UK.
[35]Division of Molecular Genetic Epidemiology, German Cancer Research Center, Heidelberg D-69120, Germany.
[36]Department of Epidemiology and Public Health, Imperial College, W2 1PG London, UK.
[37]Faculty of Medicine, University of Iceland, 101 Reykjavik, Iceland.
[*]These authors contributed equally to this work
#To whom correspondence should be addressed. E-mail: b.kiemeney@ebh.umcn.nl (LAK); kstefans@decode.is (KS)

Supplementary Methods:

Subjects:

Icelandic study population. Records of all urinary bladder cancer diagnoses were obtained from the Icelandic Cancer Registry (ICR) (http://www.krabbameinsskra.is). The ICR contains all cancer diagnoses in Iceland from January 1, 1955. The ICR contained records of 1,642 Icelandic UBC patients diagnosed until December 31, 2006, and all prevalent cases were eligible to participate. The mean participation rate for newly diagnosed cases was 65%. Patients were recruited by trained nurses on behalf of the patients' treating physicians, through special recruitment clinics. Participants in the study donated a blood sample and answered a lifestyle questionnaire. A total of 545 patients (76% males; diagnosed from December 1974 to June 2006) were included in a genome-wide SNP genotyping effort, using the Infinium II assay method and

either the Sentrix HumanHap 300 or HumanCNV370-duo BeadChip (Illumina). A total of 525 individuals (96%) were successfully genotyped. The median age at diagnosis for all consenting cases was 67 years (range 22-94 years) as compared to 68.5 years for all UBC patients in the ICR. The 32,504 controls (41% males; mean age 61 years; SD = 21) used in this study consisted of individuals from other ongoing genome-wide association studies at deCODE and represent over 15% of the adult population of Iceland. No individual disease group is represented by more than 10% of the total control group. Cancer patients (prostate, breast, colorectal and lung) were analyzed separately, and the frequency of the sequence variants studied did not differ from other controls (Supplementary Table 2). The controls were absent from the nationwide list of UBC patients according to the ICR. Samples from prostate, breast, colorectal and lung cancer patients as well as individuals used for the analysis of smoking variables come from other ongoing project at deCODE Genetics [1-3]. The study was approved by the Data Protection Authority of Iceland and the National Bioethics Committee. Written informed consent was obtained from all patients, relatives and controls. Personal identifiers associated with medical information and blood samples were encrypted with a third-party encryption system in which the Data Protection Authority maintains the code.

The Icelandic patients are comprised of both incident and prevalent cases. Prevalent cases were considered individuals diagnosed with UBC prior to 1996 (N=201) and incident cases were regarded as those patients diagnosed as of the year 2000 when collection of UBC cases was started (N=282). Cases diagnosed in 1996-1999 were not used in the analysis of prevalent vs. incident cases. No significant difference was detected between the two groups for the rs9642880 (T) and rs710521 (A) variants (P=0.93 and 0.41 respectively).

Nijmegen Bladder Cancer Study, the Netherlands. The Dutch patients were recruited for the Nijmegen Bladder Cancer Study (see http://dceg.cancer.gov/icbc/membership.html). The Nijmegen Bladder Cancer Study identified patients through the population-based regional cancer registry held by the Comprehensive Cancer Centre East, Nijmegen that serves a region of 1.3 million inhabitants in the eastern part of the Netherlands (www.ikcnet.nl). Patients diagnosed between 1995 and 2006 under the age of 75 years were selected and their vital status and current addresses updated through the hospital information systems of the 7 community hospitals and one university hospital (Radboud University Nijmegen Medical Centre, RUNMC) that are covered by the cancer registry. All patients still alive on August 1, 2007 were invited to the study by the Comprehensive Cancer Center on behalf of the patients' treating physicians. In case of consent, patients were sent a lifestyle questionnaire to fill out and blood samples were collected by Thrombosis Service centers which hold offices in all the communities in the region. 1,651 patients were invited to participate. Of all the invitees, 1,082 gave informed consent (66%): 992 filled out the questionnaire (60%) and 1016 (62%) provided a blood sample. The number of participating patients was increased with a non-overlapping series of 376 bladder cancer patients who were recruited previously for a study on gene-environment interactions in three hospitals (RUNMC, Canisius Wilhelmina Hospital, Nijmegen, and Streekziekenhuis Midden-Twente, Hengelo, the Netherlands). Ultimately, completed questionnaires and blood samples were available for 1,276 and 1,392 patients, respectively. All the patients that were selected for the analyses (N=1,278) were of self-reported European descent. The median age at diagnosis was 62 (range 25-93) years. 82% of the participants were males. Data on tumor stage and grade were obtained through the cancer registry. The 1,832 control individuals (46% males) were cancer free and frequency-matched for age with the cases. They were recruited within a project entitled "Nijmegen Biomedical Study". The details of this study were reported previously [4]. Briefly, this

is a population-based survey conducted by the Department of Epidemiology and Biostatistics and the Department of Clinical Chemistry of the Radboud University Nijmegen Medical Centre (RUNMC), in which 9,371 individuals participated from a total of 22,500 age and sex stratified, randomly selected inhabitants of Nijmegen. Control individuals from the Nijmegen Biomedical Study were invited to participate in a study on gene-environment interactions in multifactorial diseases, such as cancer. All the 1,832 participants in the present study are of self-reported European descent and were fully informed about the goals and the procedures of the study. The study protocols of the Nijmegen Bladder Cancer Study and the Nijmegen Biomedical Study were approved by the Institutional Review Board of the RUNMC and all study subjects gave written informed consent.

Leeds Bladder Cancer Study, United Kingdom. Details of the Leeds Bladder Cancer Study have been reported previously [5]. In brief, patients from the urology department of St James's University Hospital, Leeds were recruited from August 2002 to March 2006. All those patients attending for cystoscopy or transurethral resection of a bladder tumor (TURBT) who had previously been found, or were subsequently shown, to have urothelial cell carcinoma of the bladder were included. Exclusion criteria were significant mental impairment or a blood transfusion in the past month. All non-Caucasians were excluded from the study leaving 764 patients. Genotyping was successful in 724 patients or 95%. The median age at diagnosis of the patients was 73 years (range 30-101). 71% of the patients were male and 61% of all the patients had a low risk tumor (pTaG1/2). The controls were recruited from the otolaryngology outpatients and ophthalmology inpatient and outpatient departments at St James's Hospital, Leeds, from August 2002 to March 2006. All controls of appropriate age for frequency matching with the cases were approached and recruited if they gave their informed consent. As for the cases, exclusion criteria for the controls were significant mental impairment or a blood transfusion in

the past month. Also, controls were excluded if they had symptoms suggestive of bladder cancer, such as haematuria. 2.8% of the controls were non-Caucasian leaving 530 Caucasian controls for the study. 71% of the controls were male. Data were collected by a health questionnaire on smoking habits and smoking history (non- ex- or current smoker, smoking dose in pack-years), occupational exposure history (to plastics, rubber, laboratories, printing, dyes and paints, diesel fumes), family history of bladder cancer, ethnicity and place of birth, and places of birth of parents. The response rate of cases was approximately 99%, that among the controls approximately 80%. Ethical approval for the study was obtained from Leeds (East) Local Research Ethics Committee, project number 02/192.

Torino Bladder Cancer Case Control Study, Italy. The source of cases for the Torino bladder cancer study are two urology departments of the main hospital in Torino, the San Giovanni Battista Hospital [6]. Cases are all Caucasian men, aged 40 to 75 years (median 63 years) and living in the Torino metropolitan area. They were newly diagnosed between 1994 and 2006 with a histologically confirmed, invasive or in situ, bladder cancer. Of all the patients with information on stage and grade, 56% were low risk (pTaG1/2). The sources of controls are urology, medical and surgical departments of the same hospital in Torino. All controls are Caucasian men resident in the Torino metropolitan area. They were diagnosed and treated between 1994 and 2006 for benign diseases (such as prostatic hyperplasia, cystitis, hernias, heart failure, asthma, and benign ear diseases). Controls with cancer, liver or renal diseases and smoking related conditions were excluded. The median age of the controls was 57 years (range 40 to 74). Data were collected by a professional interviewer who used a structured questionnaire to interview both cases and controls face-to-face. Data collected included demographics (age, sex, ethnicity, region and education) and smoking. For cases, additional data were collected on tumor histology, tumor site, size, stage, grade, and treatment of the primary tumor. The response rates were 90% for cases and 75% for

controls resulting in 328 cases and 389 controls. Ethical approval for the study was obtained from Comitato Etico Interaziendale, A.O.U. San Giovanni Batista – A.). C.T.O./ Maria Adelaide.

The Brescia bladder cancer study, Italy. The Brescia bladder cancer study is a hospital-based case-control study. The study was reported in detail previously [7]. In short, the catchment area of the cases and controls was the Province of Brescia, a highly industrialized area in Northern Italy (mainly metal and mechanical industry, construction, transport, textiles) but also with relevant agricultural areas. Cases and controls were enrolled in 1997 to 2000 from the two main city hospitals. The total number of eligible subjects was 216 cases and 220 controls. The response rate (enrolled/eligible) was 93% (N=201) for cases and 97% (N=214) for controls. Only males were included. All cases and controls had Italian nationality and were of Caucasian ethnicity. All cases had to be residents of the Province of Brescia, aged between 20 and 80, and newly diagnosed with histologically confirmed bladder cancer. The median age of the patients was 63 years (range 22-80). 29% of all the patients with known stage and grade had a low risk tumor (pTaG1/2). Controls were patients admitted for various urological non-neoplastic diseases and were frequency matched to cases on age, hospital and period of admission. The study was formally approved by the ethical committee of the hospital where the majority of subjects were recruited. A written informed consent was obtained from all participants. Data were collected from clinical charts (tumor histology, site, grade, stage, treatments, etc.) and by means of face-to-face interviews during hospital admission, using a standardized semi-structured questionnaire. The questionnaire included data on demographics (age, ethnicity, region, education, residence, etc.), and smoking. ISCO and ISIC codes and expert assessments were used for occupational coding. Blood samples were collected from cases and controls for genotyping and DNA adducts analyses.

The Belgian Case Control Study of Bladder Cancer. The Belgian study has been reported in detail [8]. In brief, cases were selected from the Limburg Cancer Registry (LIKAR) and were

approached through urologists and general practitioners. All cases were diagnosed with histologically confirmed urothelial cell carcinoma of the bladder between 1999 and 2004, and were Caucasian inhabitants of the Belgian province of Limburg. The median age of the patients was 68 years. 86% of all the patients were males. For the recruitment of controls, a request was made to the "Kruispuntbank" of the social security for simple random sampling, stratified by municipality and socio-economic status, among all citizens above 50 years of age of the province. The median age of the controls was 64 years; 59% of the controls were males. Three trained interviewers visited cases and controls at home. Information was collected through a structured interview and a standardized food frequency questionnaire. In addition, biological samples were collected. Data collected included medical history, lifetime smoking history, family history of bladder cancer and a lifetime occupational history. Informed consent was obtained from all participants and the study was approved by the ethical review board of the Medical School of the Catholic University of Leuven, Belgium.

The Eastern Europe study population. The details of this study have been described previously [9]. Cases and controls were recruited as part of a study designed to evaluate the risk of various cancers due to environmental arsenic exposure in Hungary, Romania and Slovakia between 2002 and 2004. The recruitment was carried out in the counties of Bacs, Bekes, Csongrad and Jasz-Nagykun-Szolnok in Hungary; Bihor and Arad in Romania; and Banska Bytrica and Nitra in Slovakia. The cases (N=213) and controls (N=521) selected were of Hungarian, Romanian and Slovak nationalities. Bladder cancer patients were invited on the basis of histopathological examinations by pathologists. Hospital-based controls were included in the study, subject to fulfillment of a set of criteria. All general hospitals in the study areas were involved in the process of control recruitment. The controls were frequency matched with cases for age, gender, country of residence and ethnicity. Controls included general surgery, orthopedic and trauma

patients aged 30–79 years. Patients with malignant tumors, diabetes and cardiovascular diseases were excluded as controls. The median age for the bladder cancer patients was 65 years (range 36-90). 83% of the patients were males. The median age for the controls was 61 years (range 28-83). 51% of the controls were males. The response rates among cases and controls were ~70%. Of all the patients with known stage and grade information, 28% had a low risk tumor (pTaG1/2). Clinicians took venous blood and other biological samples from cases and controls after consent forms had been signed. Cases and controls recruited to the study were interviewed by trained personnel and completed a general lifestyle questionnaire. Ethnic background for cases and controls was recorded along with other characteristics of the study population. Local ethical boards approved the study plan and design.

The Swedish Bladder Cancer Study. The Swedish patients come from a population-based study of urinary bladder cancer patients diagnosed in the Stockholm region in 1995-1996 [10]. Blood samples from 349 patients were available out of a collection of 538 patients with primary urothelial carcinoma of the bladder. The average age at onset for these patients is 69 years (range 32-97 years) and 67% of the patients are males. Clinical data, including age at onset, grade and stage of tumor, were prospectively obtained from hospitals and urology units in the region. The control samples came from blood donors in the Stockholm region and were from cancer free individuals of both genders. The regional ethical committee approved of the study and all participants gave informed consent.

The Spanish Case Control study of Bladder Cancer. The Spanish study patients were recruited from the Urology and Oncology Departments of Zaragoza Hospital between September 2007 and February 2008. 173 patients with histologically-proven urothelial cell carcinoma of the bladder were enrolled (response 77%). The median time interval from bladder cancer diagnosis to collection of blood samples was 9 months (range 1 to 29 months). Clinical information including

age at onset, grade and stage was obtained from medical records. The median age at diagnosis for the patients was 65 years (range 27 to 94) and 87% were males. The 859 Spanish control individuals were part of a larger collection of control samples obtained from individuals that had attended the University Hospital in Zaragoza, Spain, for diseases other than cancer between November 2001 and May 2007. The controls were of both genders and median age was 52 years (range 11-87). Controls were questioned to rule out prior cancers before drawing the blood sample. All patients and controls were of self-reported European descent. Study protocols were approved by the Institutional Review Board of Zaragoza University Hospital. All subjects gave written informed consent.

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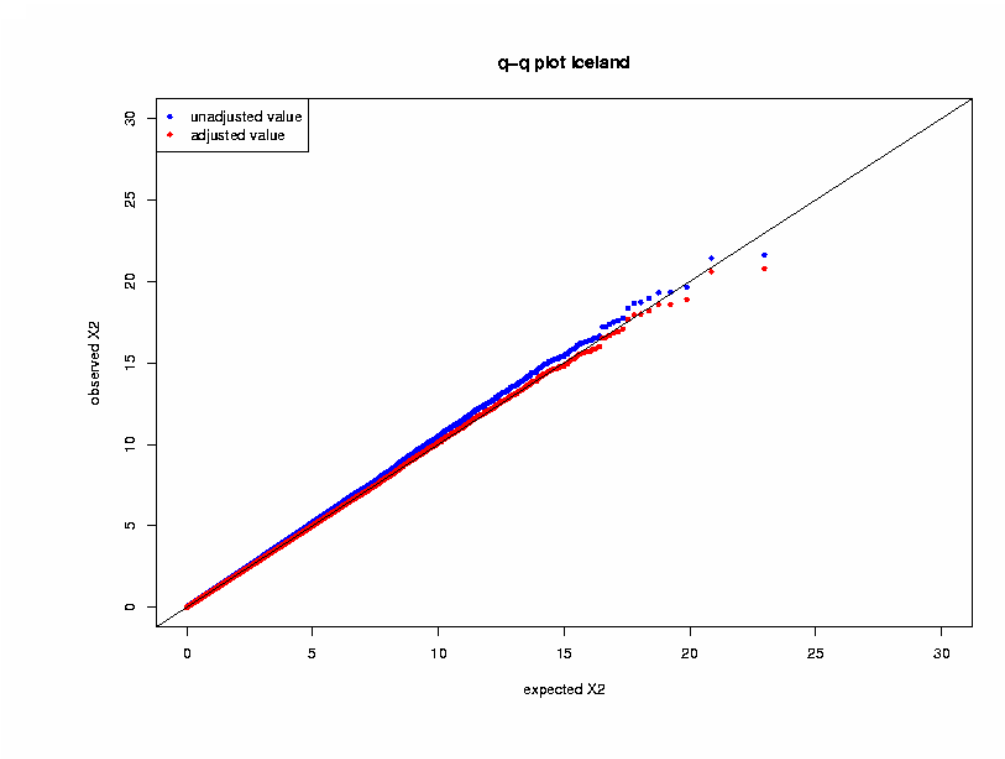
SUPPLEMENTARY FIGURE 1: Q-Q plot of genome wide association results for 302,140 SNPs genotyped in Icelandic and Dutch sample sets. The values on the y-axis are the observed Chi-squared values from the genotype data. The observed Chi-squared values were ranked and for each rank the expected Chi-squared value under the null hypothesis was determined (x-axis). The blue points correspond to unadjusted results and the red points correspond to the results adjusted using the method of genomic control.

a) Q-Q plot for Icelandic sample set

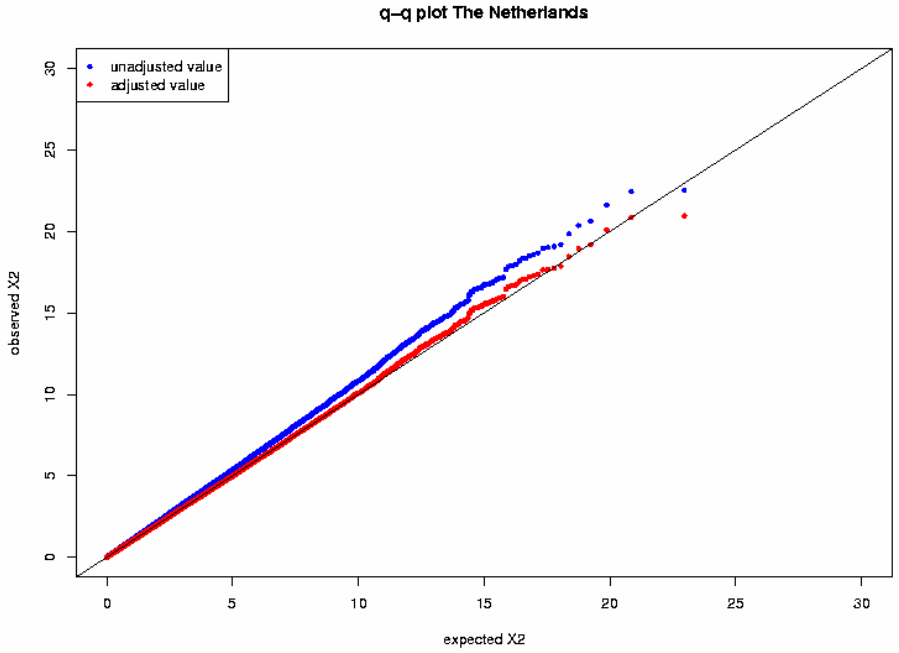
b) Q-Q plot for the Dutch sample set

c) Q-Q plot for combined data from Icelandic and Dutch sample sets.

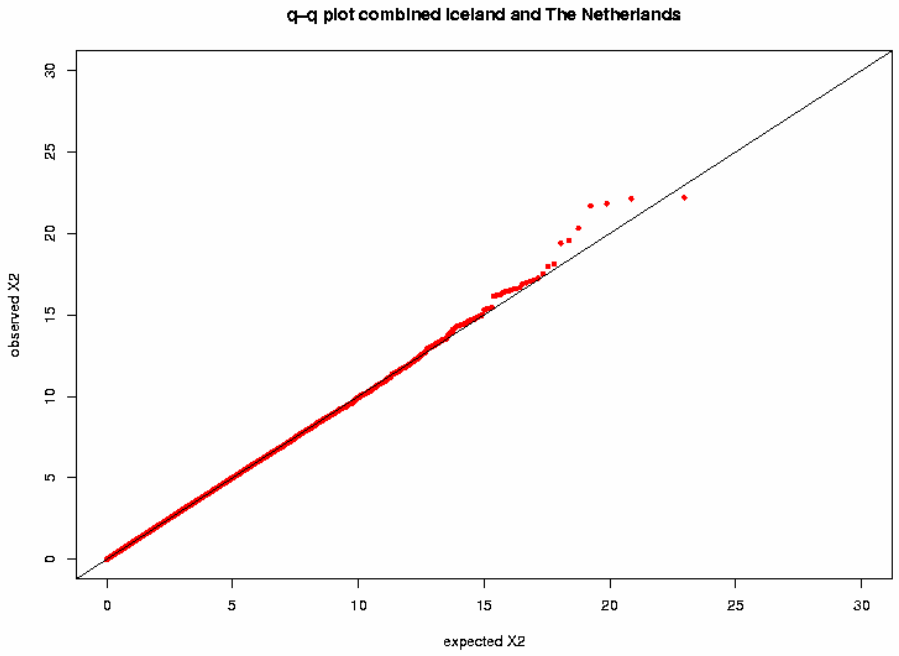
a)



b)


q–q plot The Netherlands
unadjusted value
adjusted value
observed X2
expected X2
0
5
10
15
20
25
30

c)

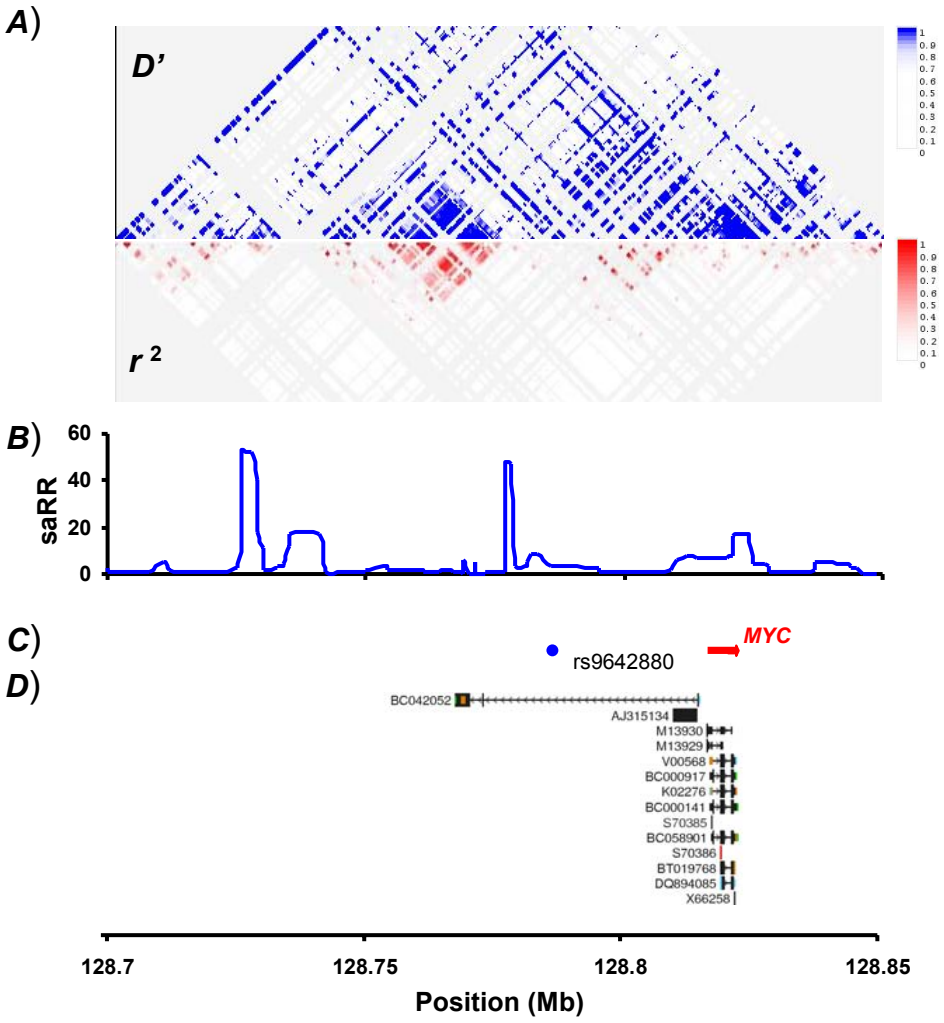

q–q plot combined Iceland and The Netherlands
observed X2
expected X2
0
5
10
15
20
25
30

SUPPLEMENTARY FIGURE 2: A schematic view of the structure of the UBC-associated region on chromosome 8q24.21. A) The pair-wise correlation structure in a 150 kb interval (128.7 – 128.85 Mb, NCBI B35) on chromosome 8q24. The upper plot shows pair-wise D' for common SNPs (with MAF > 5%) from the HapMap (v21) CEU dataset. The lower plot shows the corresponding r^2 values.

B) Estimated recombination rates (saRR) in cM / Mb from the HapMap (v21) Phase II data.

C) Location of the rs9642880 variant and the c-*Myc* gene.

D) Location of all known genetic transcripts in the region.



SUPPLEMENTARY TABLES

Supplementary Table 1. Top 10 most significant markers in the GWA for UBC

SNP	Chromosome	Position Build 36	Allele	Average control frequency	Genome wide association			Follow up groups			All combined		
					OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
rs9642880	8	128,787,250	T	45%	1.21	1.12-1.31	2.72×10^{-6}	1.22	1.13-1.33	7.98×10^{-7}	1.22	1.15-1.29	9.34×10^{-12}
rs710521	3	191,128,627	A	73%	1.23	1.13-1.35	7.10×10^{-6}	1.15	1.05-1.26	2.80×10^{-3}	1.19	1.12-1.27	1.15×10^{-7}
rs12982672	19	40,960,311	G	91%	1.33	1.17-1.52	2.35×10^{-5}	1.07	0.93-1.23	0.356	1.20	1.09-1.32	2.00×10^{-4}
rs1092116	10	80,536,170	C	88%	1.37	1.20-1.55	4.78×10^{-6}	1.00	0.88-1.13	0.944	1.16	1.06-1.27	1.25×10^{-3}
rs12584999	13	85,735,283	A	21%	1.24	1.13-1.36	2.02×10^{-5}	0.99	0.90-1.10	0.863	1.12	1.04-1.20	1.98×10^{-3}
rs17418689	2	137,706,145	G	6%	1.36	1.17-1.56	4.11×10^{-5}	0.96	0.81-1.14	0.650	1.17	1.05-1.31	4.16×10^{-3}
rs233722	12	111,515,857	T	60%	1.22	1.12-1.33	3.31×10^{-6}	0.96	0.88-1.05	0.361	1.08	1.02-1.15	8.54×10^{-3}
rs233716	12	111,524,326	A	60%	1.22	1.12-1.33	3.69×10^{-6}	0.96	0.89-1.04	0.348	1.08	1.02-1.14	0.014
rs10240737	7	131,715,919	A	88%	1.32	1.16-1.51	1.81×10^{-5}	0.94	0.83-1.06	0.335	1.11	1.01-1.21	0.027
rs6610426	X	40,305,187	A	86%	1.39	1.20-1.61	1.63×10^{-5}	0.99	0.91-1.08	0.860	1.08	1.00-1.16	0.039

Supplementary Table 2. Association of rs9642880 (T) with other cancers in Iceland

Cancer type	#cases	#controls	Cases frequency	Control frequency	OR	95% CI	*P*-value
Prostate	1,597	31,384	0.494	0.481	1.056	0.98-1.14	0.158
Breast	1,781	31,200	0.466	0.481	0.938	0.87-1.01	0.0766
Colorectal	961	32,020	0.482	0.481	1.001	0.93-1.08	0.979
Lung	731	32,268	0.483	0.481	1.007	0.91-1.12	0.897

Supplementary Table 3. Association of rs9642880 (T) on 8q24.21 and rs710521 (A) on 3q28 with disease progression in UBC patients from The Netherlands, UK, Italy, Eastern Europe, Sweden and Spain.

Study population	rs9642880 T					rs710521 A				
(N low risk/N high risk)[a]	Frequency		OR	95% CI	*P* value	Frequency		OR	95% CI	*P* value
	low risk	high risk				low risk	high risk			
The Netherlands (649/580) [b]	0.56	0.50	1.28	1.10-1.51	2.02×10^{-3}	0.77	0.74	1.15	0.96-1.39	0.129
UK (266/401)	0.48	0.50	0.91	0.73-1.14	0.42	0.74	0.76	0.93	0.72-1.19	0.545
Italy - Torino (155/117)	0.53	0.49	1.15	0.82-1.61	0.427	0.74	0.77	0.86	0.58-1.28	0.459
Italy - Brescia (50/124)	0.38	0.47	0.70	0.44-1.11	0.134	0.76	0.73	1.19	0.70-2.01	0.516
Eastern Europe (33/98)	0.65	0.48	2.03	1.15-3.58	0.015	0.84	0.79	1.41	0.67-2.96	0.363
Sweden (137/179)	0.54	0.49	1.25	0.91-1.71	0.17	0.77	0.8	0.86	0.59-1.25	0.423
Spain (28/136)	0.50	0.47	1.11	0.62-1.97	0.726	0.66	0.74	0.67	0.36-1.25	0.206
All combined (1,318/1,635) [c]			1.15	1.03-1.29	0.011			1.02	0.90-1.15	0.784

All P values shown are two-sided. Shown are the corresponding numbers of low and high risk UBC (N), allelic frequencies of variants in low and high risk individuals, the allelic odds-ratio (OR) with P values based on the multiplicative model.

[a] Classification of "low risk" and "high risk" patients. Patients were classified with regards to risk of progression based on stage and grade. Patients with low risk of progression were defined as having TNM stage pTa in combination with WHO 1973 differentiation grade 1 or 2 or WHO/ISUP 2004 low grade. All other tumors were classified as high risk of progression (stage pTis or ≥ pT1 or WHO 1973 grade 3 or WHO/ISUP 2004 high grade).

[b] Results presented for the Netherlands were individually adjusted by the method of genomic control (see Supplementary Methods).

[c] For the combined study populations, the OR and the P value were estimated using the Mantel-Haenszel model.