Potential Mediation of HLA and Cancer Associations via Non-coding RNAs

Izabela Stasik [1], Ken I. Mills [2], Mehmet Tevfik Dorak [1]

[1] School of Health Sciences, Liverpool Hope University, Liverpool, U.K.;
[2] Centre for Cancer Research and Cell Biology, Queen's University Belfast, U.K.

ASHI 2015, Savannah, GA

NATIONAL CANCER INSTITUTE

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BACKGROUND

The HLA complex is the most gene dense and polymorphic part of the genome which also contains the strongest trans-eQTLs

OPEN ACCESS Freely available online

PLoS GENETICS

Trans-eQTLs Reveal That Independent Genetic Variants Associated with a Complex Phenotype Converge on Intermediate Genes, with a Major Role for the HLA

Rudolf S. N. Fehrmann[1], Ritsert C. Jansen[2☯], Jan H. Veldink[3☯], Harm-Jan Westra[1☯], Danny Arends[2], Marc Jan Bonder[1], Jingyuan Fu[1], Patrick Deelen[1], Harry J. M. Groen[4], Asia Smolonska[1], Rinse K. Weersma[1,5], Robert M. W. Hofstra[1], Wim A. Buurman[6], Sander Rensen[6], Marcel G. M. Wolfs[7], Mathieu Platteel[1], Alexandra Zhernakova[8], Clara C. Elbers[9], Eleanora M. Festen[1], Gosia Trynka[1], Marten H. Hofker[7], Christiaan G. J. Saris[3], Roel A. Ophoff[3,10,11], Leonard H. van den Berg[3], David A. van Heel[12], Cisca Wijmenga[1], Gerard J. te Meerman[1¶], Lude Franke[1,12*¶]

Genetics of gene expression in primary immune cells identifies cell type–specific master regulators and roles of HLA alleles

Benjamin P Fairfax[1], Seiko Makino[1], Jayachandran Radhakrishnan[1], Katharine Plant[1], Stephen Leslie[2], Alexander Dilthey[3], Peter Ellis[4], Cordelia Langford[4], Fredrik O Vannberg[1,5] & Julian C Knight[1]

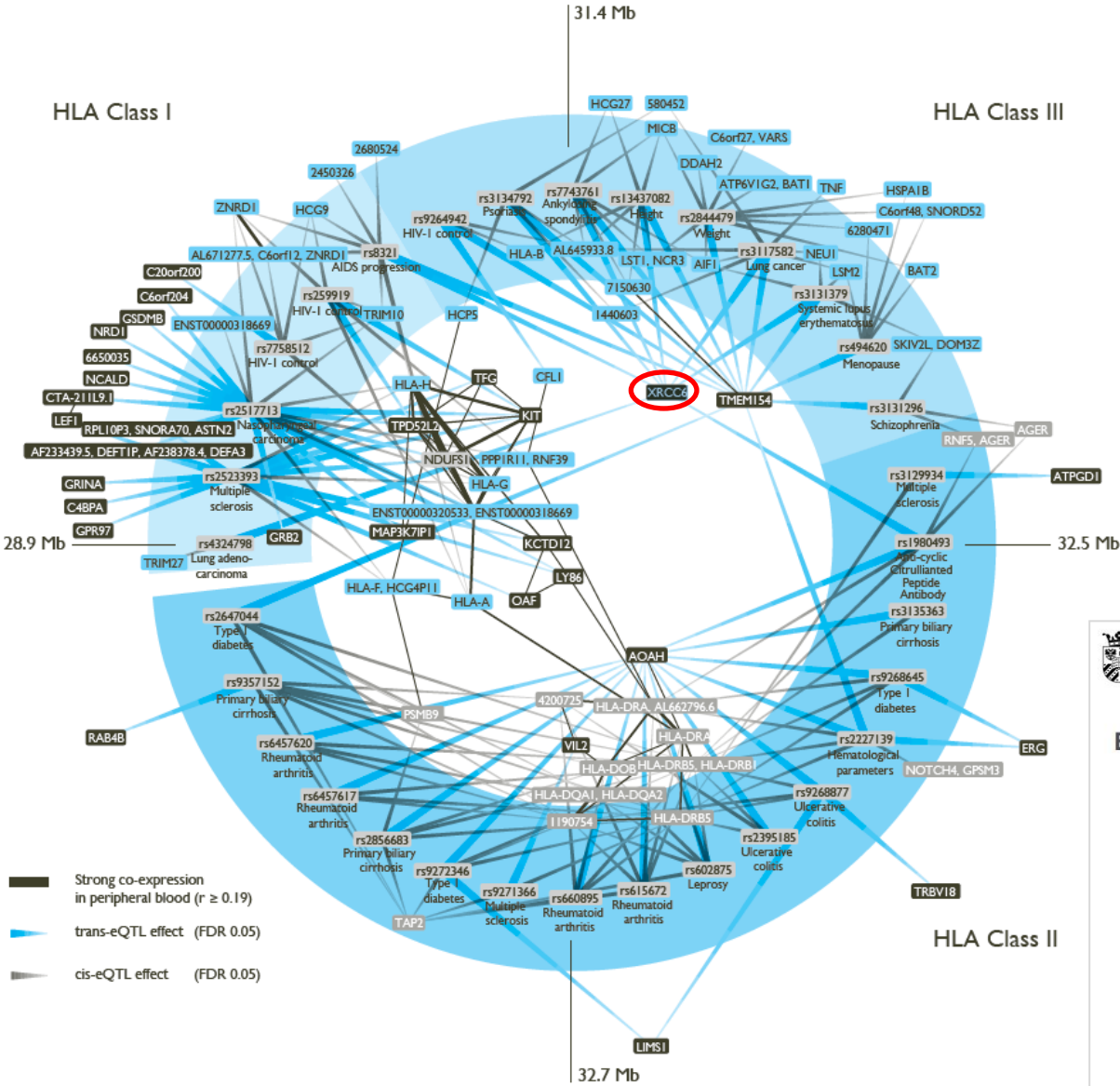
nature genetics

Systematic identification of *trans* eQTLs as putative drivers of known disease associations

Harm-Jan Westra[1,40], Marjolein J Peters[2,3,40], Tõnu Esko[4,40], Hanieh Yaghootkar[5,40], Claudia Schurmann[6,40], Johannes Kettunen[7,8,40], Mark W Christiansen[9,40], Benjamin P Fairfax[10,11], Katharina Schramm[12,13], Joseph E Powell[14,15], Alexandra Zhernakova[1], Daria V Zhernakova[1], Jan H Veldink[16], Leonard H Van den Berg[16], Juha Karjalainen[1], Sebo Withoff[1], André G Uitterlinden[2,3,17], Albert Hofman[3,17], Fernando Rivadeneira[2,3,17], Peter A C 't Hoen[18], Eva Reinmaa[4], Krista Fischer[4], Mari Nelis[4], Lili Milani[4], David Melzer[19], Luigi Ferrucci[20], Andrew B Singleton[21], Dena G Hernandez[21,22], Michael A Nalls[21], Georg Homuth[6], Matthias Nauck[23], Dörte Radke[24], Uwe Völker[6], Markus Perola[4,8], Veikko Salomaa[8], Jennifer Brody[9], Astrid Suchy-Dicey[25], Sina A Gharib[26], Daniel A Enquobahrie[25], Thomas Lumley[27], Grant W Montgomery[28], Seiko Makino[10], Holger Prokisch[12,13], Christian Herder[29], Michael Roden[29–31], Harald Grallert[32], Thomas Meitinger[12,13,33,34], Konstantin Strauch[35,36], Yang Li[37], Ritsert C Jansen[37], Peter M Visscher[14,15], Julian C Knight[10], Bruce M Psaty[9,38,41], Samuli Ripatti[7,8,39,41], Alexander Teumer[6,41], Timothy M Frayling[5,41], Andres Metspalu[4,41], Joyce B J van Meurs[2,3,41] & Lude Franke[1,41]

nature genetics

BACKGROUND



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rijksuniversiteit groningen

Endothelial-specific delivery of siRNA by novel SAINT-based lipoplexes

An in vitro and in vivo study

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

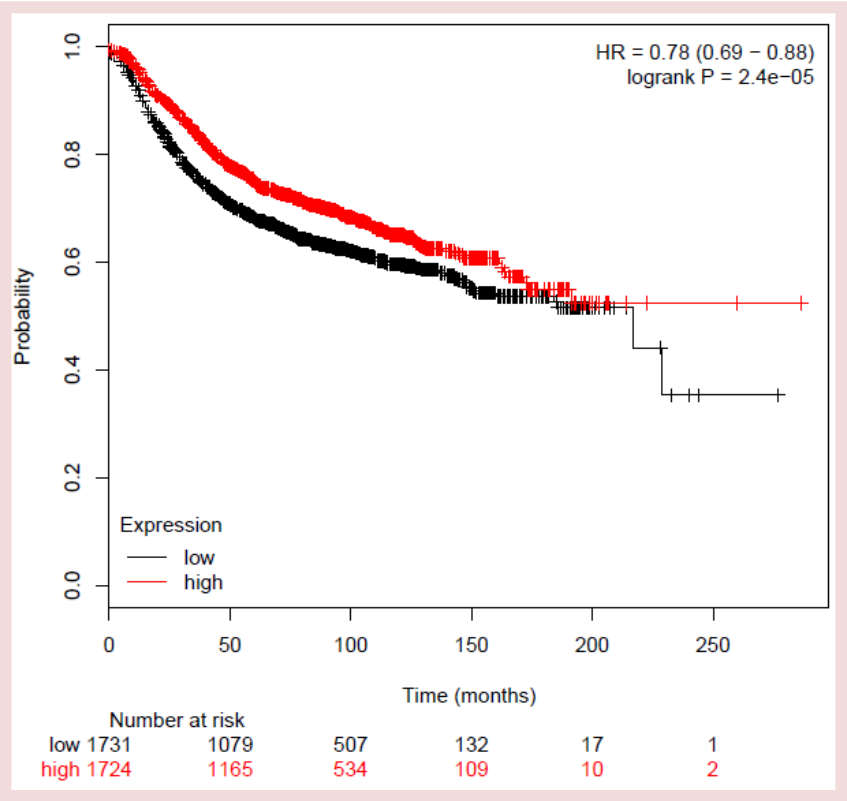
De openbare verdediging zal plaatsvinden op
woensdag 8 oktober 2014 om 14.30 uur

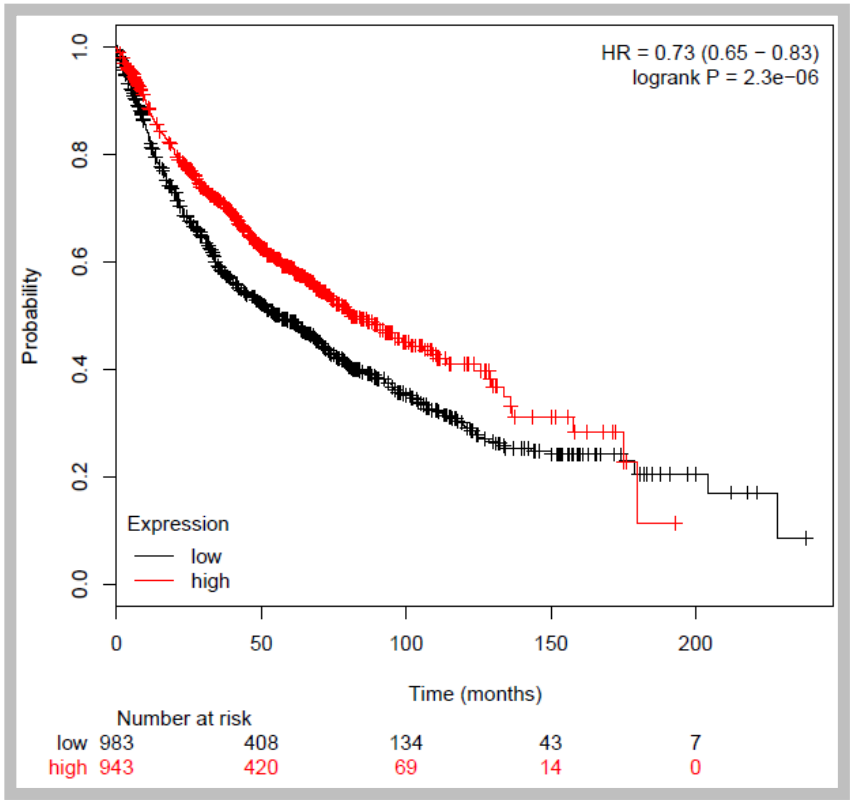
door

Niek Gerrit Jan Leus

BACKGROUND

XRCC6 expression levels show correlations with survival of cancer patients





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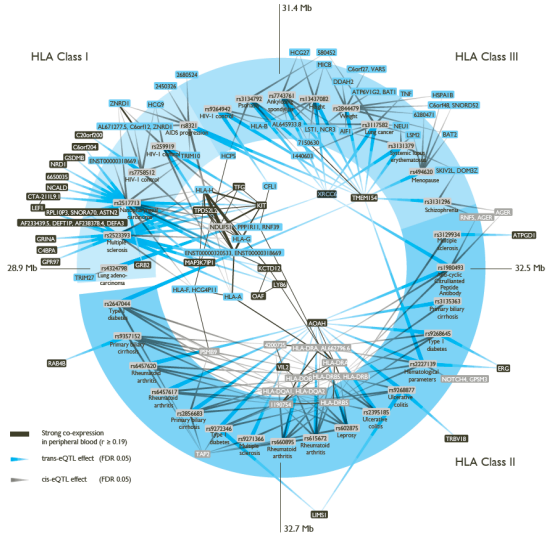
AIM

To annotate the trans-eQTLs for *XRCC6* and check whether they may play a role in HLA-linked cancer susceptibility



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METHODS

eQTL Browsers

Chicago Blood NCBI GTEx

SNP Functional Annotations

CADD RegulomeDB SNPnexus PheGenI SNiPA

Disease Associations

GWAS catalog dbGAP GRASP Kaplan-Meier plotter

Gene Expression Co-variance

Microarray Innovations in Leukemia (MILE) Study
CORD (Co-regulation databases)

RESULTS

XRCC6 has no cis-eQTLs

All trans-eQTLs map to the HLA region

Query eQTL Results

Or, you can query the *cis*- and *trans*-eQTLs below (examples: rs7807018 or *VWCE*):

Gene or SNP name: XRCC6 Search

Your query: XRCC6

Trans-eQTLs

P-value	SNP	SNP Chr.	SNP Chr. position	Probe	Probe Chr.	Probe Chr. position	SNP Alleles	Minor Allele	Z-score	Gene name	FDR
4.993959233035421E-19	rs2524054	6	31360375	6380347	22	40389758	C/A	A	-8.91	XRCC6	0.00
3.203718409825412E-16	rs1063635	6	31487910	6380347	22	40389758	G/A	A	8.17	XRCC6	0.00
7.58793280063431E-13	rs2844665	6	31114834	6380347	22	40389758	T/C	T	-7.17	XRCC6	0.00
1.0667196745260456E-11	rs2227139	6	32521437	6380347	22	40389758	G/A	G	-6.80	XRCC6	0.00
5.3663632204727914E-11	rs2523608	6	31430538	6380347	22	40389758	G/A	G	-6.56	XRCC6	0.00
3.45612186194326E-10	rs6457327	6	31182009	6380347	22	40389758	A/C	A	-6.28	XRCC6	0.00
2.378359526821619E-9	rs13437082	6	31462539	6380347	22	40389758	T/C	T	5.97	XRCC6	0.00
3.1727674114665877E-9	rs1521	6	31458683	6380347	22	40389758	T/C	C	-5.92	XRCC6	0.00
3.2508856428536355E-9	rs7743761	6	31444079	6380347	22	40389758	C/A	A	5.92	XRCC6	0.00
9.478842759131973E-9	rs9264942	6	31382359	6380347	22	40389758	T/C	C	5.74	XRCC6	0.00
1.0654024278121931E-7	rs2269426	6	32184477	6380347	22	40389758	G/A	A	5.32	XRCC6	0.01
1.2019434463360447E-7	rs3135388	6	32521029	6380347	22	40389758	A/G	A	-5.29	XRCC6	0.01
1.8924818645448748E-7	rs3117181	6	32178995	6380347	22	40389758	C/G	C	-5.21	XRCC6	0.02
2.0057919721729475E-7	rs9268853	6	32537621	6380347	22	40389758	T/C	C	5.20	XRCC6	0.02
2.4354319375644347E-7	rs2395185	6	32541145	6380347	22	40389758	G/T	T	5.16	XRCC6	0.03
3.035974364549539E-7	rs9271366	6	32694832	6380347	22	40389758	G/A	G	-5.12	XRCC6	0.03
3.48373280795737E-7	rs185819	6	32158045	6380347	22	40389758	T/C	T	-5.10	XRCC6	0.04
8.05624393582649E-7	rs7756521	6	30956232	6380347	22	40389758	T/C	C	4.93	XRCC6	0.07
1.9340121245290004E-6	rs9275572	6	32786977	6380347	22	40389758	A/G	A	-4.76	XRCC6	0.15
3.2682296890855E-6	rs2076529	6	32471933	6380347	22	40389758	T/C	C	4.65	XRCC6	0.21
3.6320141057043426E-6	rs9275596	6	32789609	6380347	22	40389758	C/T	C	-4.63	XRCC6	0.23
7.969560945092498E-6	rs2647012	6	32772436	6380347	22	40389758	T/C	T	-4.47	XRCC6	0.36
1.056863231492124E-5	rs9469003	6	31515807	6380347	22	40389758	T/C	C	4.41	XRCC6	0.41
1.0785250021248313E-5	rs9268645	6	32516505	6380347	22	40389758	C/G	G	4.40	XRCC6	0.42

Cis-eQTLs

P-value SNP SNP Chr. SNP Chr. Position Probe Probe Chr. Probe Chr. position SNP Alleles Minor Allele Z-score Gene name FDR

No records found

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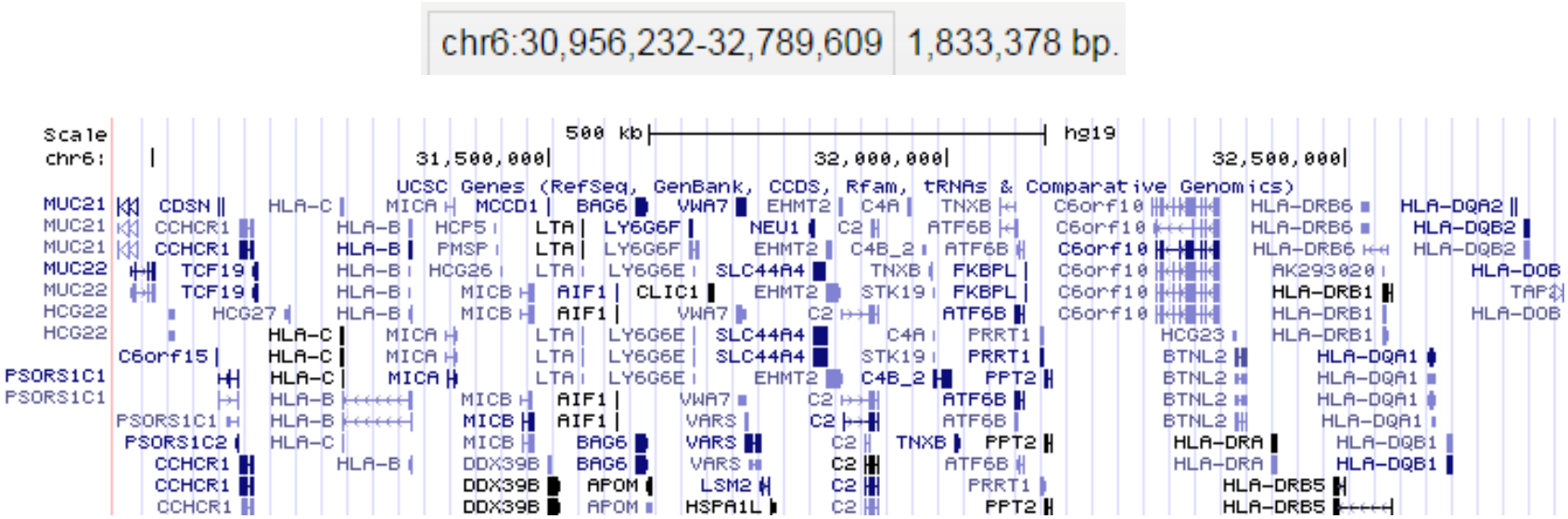
Systematic identification of *trans* eQTLs as putative drivers of known disease associations

Harm-Jan Westra[1,40], Marjolein J Peters[2,3,40], Tõnu Esko[4,40], Hanieh Yaghootkar[5,40], Claudia Schurmann[6,40], Johannes Kettunen[7,8,40], Mark W Christiansen[9,40], Benjamin P Fairfax[10,11], Katharina Schramm[12,13], Joseph E Powell[14,15], Alexandra Zhernakova[1], Daria V Zhernakova[1], Jan H Veldink[16], Leonard H Van den Berg[16], Juha Karjalainen[1], Sebo Withoff[1], André G Uitterlinden[2,3,17], Albert Hofman[2,17], Fernando Rivadeneira[2,3,17], Peter A C 't Hoen[18], Eva Reinmaa[4], Krista Fischer[4], Mari Nelis[4], Lili Milani[4], David Melzer[19], Luigi Ferrucci[20], Andrew B Singleton[21], Dena G Hernandez[21,22], Michael A Nalls[21], Georg Homuth[6], Matthias Nauck[23], Dörte Radke[24], Uwe Völker[6], Markus Perola[4,8], Veikko Salomaa[8], Jennifer Brody[9], Astrid Suchy-Dicey[25], Sina A Gharib[26], Daniel A Enquobahrie[27], Thomas Lumley[27], Grant W Montgomery[28], Seiko Makino[29], Holger Prokisch[13,13], Christian Herder[30], Michael Roden[30–31], Harald Grallert[32], Thomas Meitinger[12,13,33,34], Konstantin Strauch[35,36], Yang Li[37], Ritsert C Jansen[37], Peter M Visscher[14,15], Julian C Knight[10], Bruce M Psaty[9,38,41], Samuli Ripatti[7,8,39,41], Alexander Teumer[6,41], Timothy M Frayling[5,41], Andres Metspalu[4,41], Joyce B J van Meurs[2,3,41] & Lude Franke[1,41]

RESULTS

All trans-eQTLs for *XRCC6* were within the classical HLA complex



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RESULTS

Trans-eQTLs for *XRCC6* are not related to one another (not on the same haplotype or lineage), however, some show correlations with HLA types or lineages.

A Catalog of HLA Region SNPs with Functional Annotations, Disease Associations and Correlations with HLA Types

Amy E. Kennedy [1], Sushmita Mustafi [2], Sandeep K. Singh [2], Ioanna Konidari [3], Jacob L. McCauley [3], Alejandro M. Barbieri [2], Mehmet T. Dorak [4]

[1] National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; [2] Florida International University, Miami, FL, USA; [3] John P. Hussman Institute for Human Genomics, University of Miami, Miami, FL, USA; [4] Liverpool Hope University, Liverpool, UK

P-121

RESULTS

Some of the trans-eQTLs map to non-coding RNA genes

LINC01149 long intergenic non-protein coding RNA 1149 [*Homo sapiens* (human)]

Gene ID: 101929111, updated on 17-Mar-2015

Summary

Official Symbol	LINC01149 provided by HGNC
Official Full Name	long intergenic non-protein coding RNA 1149 provided by HGNC
Primary source	HGNC:HGNC:39757
Gene type	ncRNA
Organism	Homo sapiens
Lineage	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

LINC00243 long intergenic non-protein coding RNA 243 [*Homo sapiens* (human)]

Gene ID: 401247, updated on 12-May-2015

Summary

Official Symbol	LINC00243 provided by HGNC
Official Full Name	long intergenic non-protein coding RNA 243 provided by HGNC
Primary source	HGNC:HGNC:30956
See related	Ensembl:ENSG00000214894
Gene type	ncRNA
RefSeq status	VALIDATED
Organism	Homo sapiens
Lineage	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
Also known as	C6orf214; NCRNA00243

HCG9 HLA complex group 9 (non-protein coding) [*Homo sapiens* (human)]

Gene ID: 10255, updated on 12-May-2015

Summary

Official Symbol	HCG9 provided by HGNC
Official Full Name	HLA complex group 9 (non-protein coding) provided by HGNC
Primary source	HGNC:HGNC:21243
See related	Ensembl:ENSG00000204625; HPRD:17092; MIM:615797
Gene type	ncRNA
RefSeq status	VALIDATED
Organism	Homo sapiens
Lineage	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
Also known as	HCGIX; HCGIX4
Summary	This gene lies within the MHC class I region on chromosome 6p21.3. This gene is believed to be non-coding, but its function has not been determined. [provided by RefSeq, Jul 2009]

XXbac BPG248L24.11
XXbac-BPG181B23.7
RNU6-1133P
RNU6-1133P
HCP5
XXbac BPG248L24.11

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RESULTS

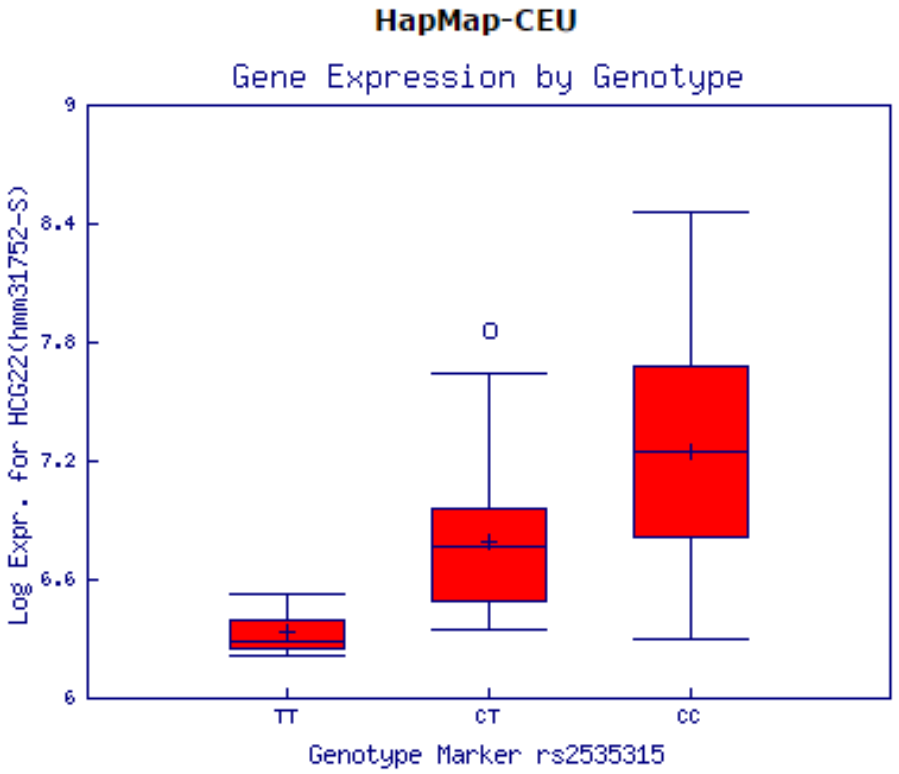
Four of the trans-eQTLs are also cis-eQTLs for the non-coding RNA gene *HCG22*

HCG22 HLA complex group 22 [*Homo sapiens* (human)]

Gene ID: 285834, updated on 19-Jul-2015

Summary

Official Symbol	HCG22 provided by HGNC
Official Full Name	HLA complex group 22 provided by HGNC
Primary source	HGNC:HGNC:27780
See related	Ensembl:ENSG00000228789; MIM:613918
Gene type	ncRNA
RefSeq status	VALIDATED



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RESULTS

Among HLA region SNPs that show an associations with cancer:
> None alter transcription factor binding sites for TP53, c-Myb, c-Myc, c-Jun, or c-Fos
> None is in a CpG island
> None is in a miRNA sequence or miRNA binding site
BUT:
Most HLA region cancer associations were with SNPs that have trans-eQTL effects on a cancer-related gene (*XRCC6*, *ERG*, and others)

Analysis of HLA Region Polymorphisms Associated with Cancer

Amy E. KENNEDY, Sandeep K. SINGH, Karina VILLALBA, M. Tevfik DORAK

ASHI 2013

Liverpool Hope University EST. 1844

RESULTS

Most trans-eQTLs have already shown cancer associations with cancer susceptibility in GWAS.

SNP	SNP ID	Trait	Pubmed
rs10484561	rs10484561	Follicular lymphoma	20639881
rs130067	rs130067	Prostate cancer	21743467
rs2395185	rs2395185	Lung cancer	23143601
rs2395185	rs2395185	Hodgkin's lymphoma	22286212
rs2517713	rs2517713	Nasopharyngeal carcinoma	19664746
rs2647012	rs2647012	Follicular lymphoma	21533074
rs2860580	rs2860580	Nasopharyngeal carcinoma	20512145
rs2894207	rs2894207	Nasopharyngeal carcinoma	20512145
rs29232	rs29232	Nasopharyngeal carcinoma	19664746
rs3117582	rs3117582	Lung adenocarcinoma	19836008
rs3129055	rs3129055	Nasopharyngeal carcinoma	19664746
rs6457327	rs6457327	Follicular lymphoma	20639881
rs674313	rs674313	Chronic lymphocytic leukemia	21131588
rs6903608	rs6903608	Nodular sclerosis Hodgkin lympho	22086417
rs6903608	rs6903608	Hodgkin's lymphoma	21037568
rs9267673	rs9267673	Hepatocellular carcinoma	21105107
rs9268853	rs9268853	Lymphoma	23349640
rs9272535	rs9272535	Chronic lymphocytic leukemia	21131588
rs9275572	rs9275572	Hepatocellular carcinoma	21499248

NCBI Resources

PheGenI

Phenotype-Genotype Integrator

U.S. Department of Health & Human Services

NIH National Heart, Lung, and Blood Institute

GRASP Search - v2.0.0.0

Screening of GRASP database for associations of the 42 trans-eQTLs with cancer risk revealed an additional association with breast cancer (rs3130544), and another SNP (rs2596503) has a reported association with glioblastoma.

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RESULTS

The examination of the Microarray Innovations in Leukemia (MILE) data revealed highly significant inverse correlations between HCG22 and XRCC6 expression levels:

$P = 0.0001$, r = -0.43, n = 74 in normal bone marrow

$P < 10^{-36}$, r = -0.27, n = 2022 in leukemia

VOLUME 28 · NUMBER 15 · MAY 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

From the European LeukemiaNet, Gene Expression Profiling Working Group; MLL Munich Leukemia Laboratory, Munich; Department of Hematology and Oncology, University Hospital Benjamin Franklin, Charité, Berlin, Germany; Laboratorio di Ematologia e Oncologia Pediatrica, Università di Padova, Padova; Division of Hematology, "Sapienza" University, Rome, Italy; Centre Hospitalier Universitaire Montpellier, Hôpital St Eloi, Institut de Recherche en Biothérapie, Montpellier, France; Centro de Investigación del Cáncer–Instituto de Biología Molecular y Celular del Cáncer, Universidad de Salamanca–Consejo Supe-

Clinical Utility of Microarray-Based Gene Expression Profiling in the Diagnosis and Subclassification of Leukemia: Report From the International Microarray Innovations in Leukemia Study Group

Torsten Haferlach, Alexander Kohlmann, Lothar Wieczorek, Giuseppe Basso, Geertruy Te Kronnie, Marie-Christine Béné, John De Vos, Jesus M. Hernández, Wolf-Karsten Hofmann, Ken I. Mills, Amanda Gilkes, Sabina Chiaretti, Sheila A. Shurtleff, Thomas J. Kipps, Laura Z. Rassenti, Allen E. Yeoh, Peter R. Papenhausen, Wei-min Liu, P. Mickey Williams, and Robin Foà

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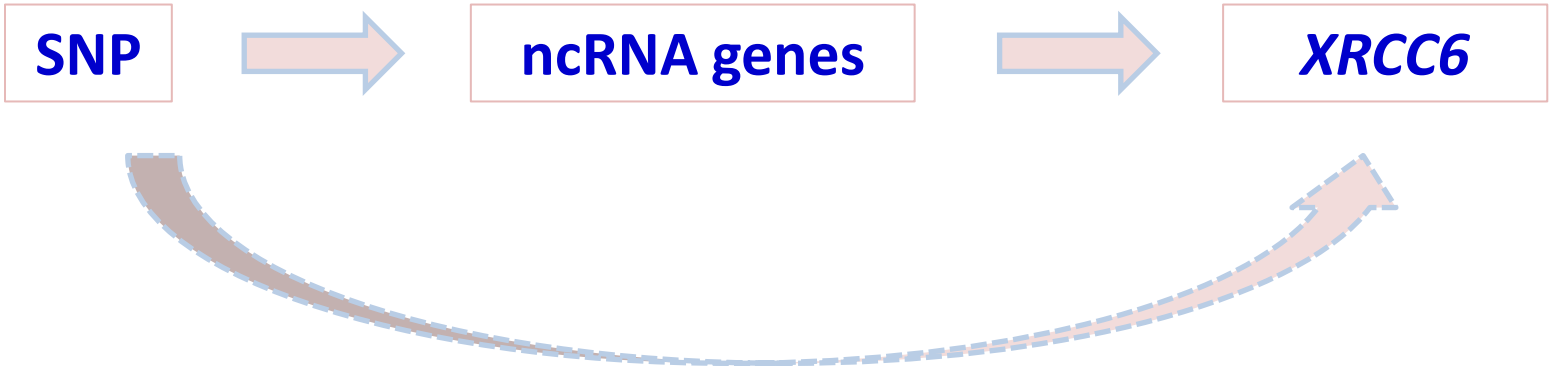
DISCUSSION

The data presented suggest that HLA region SNPs act as cis-eQTLs for ncRNA genes and as trans-eQTLs for *XRCC6*, *ERG* and other cancer-related genes



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DISCUSSION

XRCC6 (*aka* Ku70) is one of 430 extremely multifunctional proteins in humans

nature COMMUNICATIONS

ARTICLE

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DOI: 10.1038/ncomms8412 OPEN

Extreme multifunctional proteins identified from a human protein interaction network

Charles E. Chapple[1,2], Benoit Robisson[1,2], Lionel Spinelli[1,2,3,4,5], Céline Guien[1,2,†], Emmanuelle Becker[1,2,†] & Christine Brun[1,2,6]

Moonlighting proteins are a subclass of multifunctional proteins whose functions are unrelated. Although they may play important roles in cells, there has been no large-scale method to identify them, nor any effort to characterize them as a group. Here, we propose the first method for the identification of 'extreme multifunctional' proteins from an interactome as a first step to characterize moonlighting proteins. By combining network topological information with protein annotations, we identify 430 extreme multifunctional proteins (3% of the human interactome). We show that the candidates form a distinct sub-group of proteins, characterized by specific features, which form a signature of extreme multi-functionality. Overall, extreme multifunctional proteins are enriched in linear motifs and less intrinsically disordered than network hubs. We also provide MoonDB, a database containing information on all the candidates identified in the analysis and a set of manually curated human moonlighting proteins.

DISCUSSION

[Cell Cycle 4:3, 438-441; March 2005]; ©2005 Landes Bioscience

Perspective

The Double Life of the Ku Protein

Facing the DNA Breaks and the Extracellular Environment

Catherine Muller*
Jenny Paupert
Sylvie Monferran†
Bernard Salles

Institut de Pharmacologie et de Biologie Structurale, CNRS UMR 5089; Toulouse Cedex, France

†Present address: Institut Claudius Regaud; 20-24 rue du pont Saint-Pierre; 31052 Toulouse Cedex, France

*Correspondence to: Dr. C. Muller; Institut de Pharmacologie et de Biologie Structurale; 205 route de Narbonne; Toulouse 31077 France; Tel.: +33.561.17.59.08; Fax: +33.561.17.59.33 ; Email: catherine.muller@ipbs.fr

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ABSTRACT

The Ku heterodimer (Ku70/Ku80) plays a central role in DNA double strand break recognition and repair. It has been shown, more than ten years ago, that Ku is also expressed at the cell surface of different cells types along with its intracellular pool within the nucleus and the cytoplasm but involvement of Ku in cell-cell and cell-extracellular matrix adhesion has been only recently demonstrated. In addition, we have shown that Ku may have a second and unexpected activity in cell/microenvironment interaction. Indeed, Ku appears to be involved in extracellular proteolytic processes through its specific interaction, on the cell surface, with the matrix metalloprotease 9. Taken together, these results suggest that Ku function at the cell surface is likely to be important in tumour invasion. Various fundamental questions arise from these observations. How Ku is expressed on the cell surface, why a protein with completely unrelated functions also serve as an integrin-like molecule once expressed at the cell surface and is this functional moonlighting of Ku related to cell transformation remain open issues that will be discussed here.

Table 1 **Human cell lines or primary normal and tumor cells that express Ku on their cell surface**

Cell Type	Origin
Normal human primary cells	Monocytes-derived macrophages[15], Endothelial cells (HUVEC)[13]
Primary human tumor cells	Freshly isolated multiple myeloma**[3,18]
Hematopoietic tumor cell lines	Acute monocytic leukemia(THP-1,[15] HL-60,[13,15] U-937*[1,13]), Acute lymphoblastic leukemia (Jurkat*,[1,13] MOLT-4[13]), Multiple myeloma (ARH-77,[3] HS-sultan,[3] RPMI8226[18])**
Solid tumor cell lines	Rhabdomyosarcoma (RD)[13], Neuroblastoma (Kelly)*[14], Mammary carcinoma (MCF-7)*[14], Cervix epitheloid carcinoma (Hela)[1,10,11]

*Ku expression on the cell surface is upregulated under hypoxia; **Ku is expressed on the cell surface only upon CD40L stimulation.

DISCUSSION

Overexpression of Ku leads to excessive DNA repair that can have detrimental effects on the organism by increasing its resistance to genotoxic agents, hence increasing the likelihood for the development of aggressive neoplasia. Thus, although most proteins contribute to the development of carcinogenesis when they are overexpressed (i.e., oncoproteins, e.g., c-myc), or underexpressed (i.e., tumor suppressor proteins, e.g., TP53), Ku may contribute to cancer in either condition (Fig. 2).

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BBA
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Review

The biology of Ku and its potential oncogenic role in cancer

Charles Gullo [a,b], Melvin Au [a,c], Ge Feng [a], Gerrard Teoh [a,d,*]

[a] Multiple Myeloma Research Laboratory (MMRL), Singapore Health Services (SingHealth), 7 Hospital Drive, Block A #02-05, Singapore 169611, Republic of Singapore
[b] Department of Clinical Research (DCR), Singapore General Hospital (SGH), Outram Road, Singapore 169608, Republic of Singapore
[c] Division of Research, SGH, Outram Road, Singapore 169608, Republic of Singapore
[d] Department of Hematology, SGH, Outram Road, Singapore 169608, Republic of Singapore

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Abstract

Ku is a heterodimeric protein made up of two subunits, Ku70 and Ku80. It was originally identified as an autoantigen recognized by the sera of patients with autoimmune diseases. It is a highly versatile regulatory protein that has been implicated in multiple nuclear processes, e.g., DNA repair, telomere maintenance and apoptosis. Accordingly, Ku is thought to play a crucial role in maintenance of chromosomal integrity and cell survival. Recent reports suggest that there is a positive relationship between Ku and the development of cancer, making Ku an important candidate target for anticancer drug development. Specifically, prior studies suggest that a delicate balance exists in Ku expression, as overexpression of Ku proteins promotes oncogenic phenotypes, including hyperproliferation and resistance to apoptosis; whereas deficient or low expression of Ku leads to genomic instability and tumorigenesis. Such observations through various experimental models indicate that Ku may act as either a tumor suppressor or an oncoprotein. Hence, understanding the link between the various functions of Ku and the development of cancer in different cell systems may help in the development of novel anticancer therapeutic agents that target Ku. These studies may also increase our understanding of how Ku autoantibodies are generated in autoimmune diseases.

Keywords: Carcinogenesis; Apoptosis; Genomic instability; DNA repair

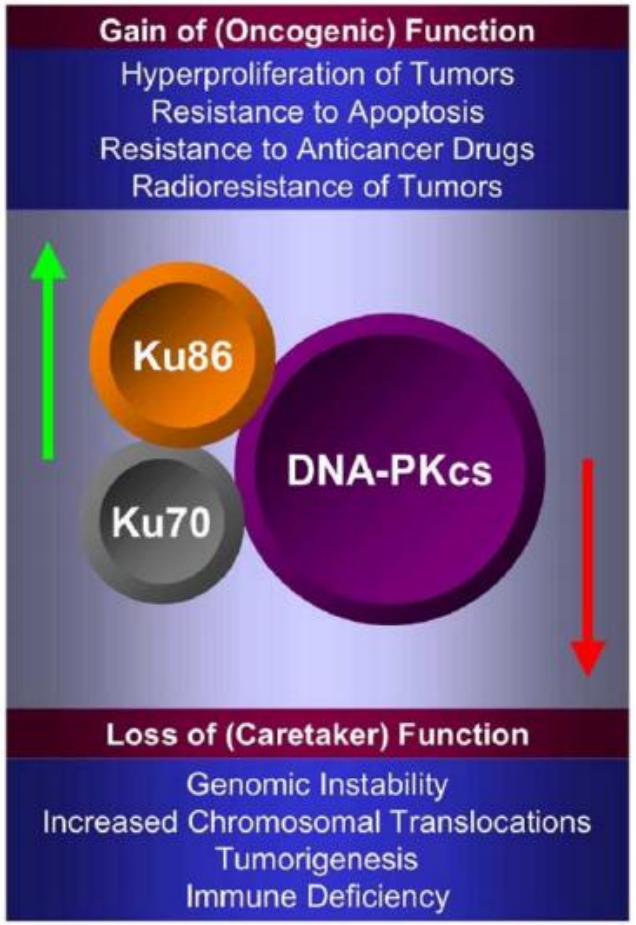

Fig. 2. Ku as an oncoprotein or a tumor suppressor protein. A schematic diagram of the DNA-PK holoenzyme is shown. DNA-PK is composed of the Ku70/Ku86 heterodimer and DNA-PKcs. In cancer, gain of DNA-PK function [22] is associated with gain of oncogenic function; whereas loss of DNA-PK function (red arrow) is associated with loss of caretaker or tumor suppressor function. The consequences of such changes are shown (blue boxes).

CONCLUSIONS

The HLA region sequence variation shows associations with cancer risk, and the present study provides an insight into the potential mechanism of these associations.

The overall observations suggest a non-immunological mechanism for the involvement of HLA region genetic variation in inherited cancer susceptibility, and implicate an ncRNA-mediated mechanism for trans-eQTL effect on *XRCC6*.

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