Why is There an Inverse Correlation between Alzheimer Disease and Cancer Susceptibility? Is (Immuno)Genetics to Blame?

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Outline

No paradox, no progress: inverse cancer comorbidity in people with other complex diseases

Rafael Tabarés-Seisdedos, Nancy Dumont, Anaïs Baudot, Jose M Valderas, Joan Climent, Alfonso Valencia, Benedicto Crespo-Facorro, Eduard Vieta, Manuel Gómez-Beneyto, Salvador Martínez, John L Rubenstein

Alzheimer's Disease and Cancer: When Two Monsters Cannot Be Together

Shohreh Majd[1]*, John Power[1] and Zohreh Majd[2]

Association Between Alzheimer Disease and Cancer With Evaluation of Study Biases
A Systematic Review and Meta-analysis

Monica Ospina-Romero, MD; M. Maria Glymour, ScD; Eleanor Hayes-Larson, PhD; Elizabeth Rose Mayeda, PhD; Rebecca E. Graff, ScD; Willa D. Brenowitz, PhD; Sarah F. Ackley, PhD; John S. Witte, PhD; Lindsay C. Kobayashi, PhD

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Reviews

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The Epidemiology of Alzheimer's Disease Modifiable Risk Factors and Prevention

X.-X. Zhang[1], Y. Tian[1], Z.-T. Wang[1], Y.-H. Ma[1], L. Tan[1], J.-T. Yu[2]

Investigating the genetic relationship between Alzheimer's disease and cancer using GWAS summary statistics

Yen-Chen Anne Feng[1] · Kelly Cho[4,5] · Sara Lindstrom[1,3] · Peter Kraft[1,2] · Jean Cormack[4] · IGAP Consortium, Colorectal Transdisciplinary Study (CORECT) · Discovery, Biology, and Risk of Inherited Variants in Breast Cancer (DRIVE) · Elucidating Loci Involved in Prostate Cancer Susceptibility (ELLIPSE) · Transdisciplinary Research in Cancer of the Lung (TRICL) · Liming Liang[1,2] · Jane A. Driver[4,5]

Mendelian randomization and transcriptomic analysis reveal an inverse causal relationship between Alzheimer's disease and cancer

Zehua Dong[1,2,3], Mengli Xu[1,2,3], Xu Sun[4,5]* and Xiaosheng Wang[1,2,3]*

Multiancestry analysis of the HLA locus in Alzheimer's and Parkinson's diseases uncovers a shared adaptive immune response mediated by *HLA-DRB1*04* subtypes

?????

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Epidemiology: An Inverse Correlation

No paradox, no progress: inverse cancer comorbidity in people with other complex diseases

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"A consistently lower than expected occurrence of cancer in patients with Down syndrome, Parkinson disease (PD), schizophrenia, diabetes, Alzheimer disease (AD), multiple sclerosis (MS), and anorexia nervosa"

The risk of cancer in patients with AD dementia was halved, and the risk of AD dementia in patients with cancer was 35% reduced. This relationship was observed in almost all subgroup analyses, suggesting that some anticipated potential confounding factors did not significantly influence the results (Musicco, 2013)

Parkinson disease and cancer: a systematic review and meta-analysis of over 17 million participants (Zhang, 2021): **Parkinson disease and total cancer are inversely associated.**

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Epidemiology: An Inverse Correlation

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Original Investigation | Geriatrics

Association Between Alzheimer Disease and Cancer With Evaluation of Study Biases

A Systematic Review and Meta-analysis

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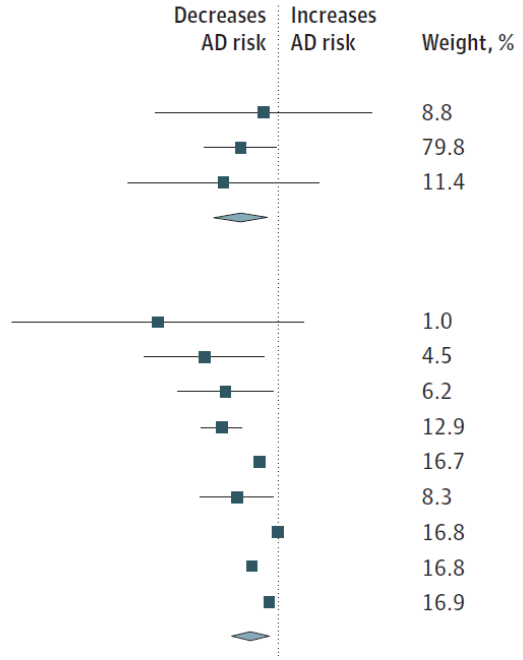
Figure 2. Forest Plot of Random-Effects Models for the Pooled Cancer–Alzheimer Disease (AD) Risk Estimates[a]

Source	AD risk, estimate (95%)	Weight, %
Case-control studies		
Realmuto et al,[44] 2012	0.89 (0.39-2.06)	8.8
Nudelman et al,[39] 2014	0.75 (0.57-0.99)	79.8
Prinelli et al,[48] 2018	0.66 (0.32-1.37)	11.4
Overall OR from case-control studies (I^2 = 0.0%)	0.75 (0.61-0.93)	
Cohort studies		
All cancer types		
Roe et al,[43] 2005[a]	0.39 (0.13-1.22)	1.0
Roe et al,[37] 2010[a]	0.57 (0.36-0.90)	4.5
Driver et al,[40] 2012[a]	0.67 (0.47-0.96)	6.2
Musicco et al,[38] 2013[a]	0.64 (0.56-0.76)	12.9
Freeman et al,[41] 2016[a]	0.87 (0.84-0.90)	16.7
Bowles et al,[10] 2017[a]	0.73 (0.55-0.96)	8.3
Frain et al,[46] 2017[a]	1.00 (0.97-1.03)	16.8
Sun et al,[42] 2020[a]	0.82 (0.80-0.85)	16.8
Ording et al,[47] 2020[a]	0.94 (0.92-0.96)	16.9
Subgroup HR (I^2 = 93.8%)	0.81 (0.70-0.94)	



CONCLUSIONS AND RELEVANCE The weak inverse association between cancer and AD may reflect shared inverse etiological mechanisms or survival bias but is not likely attributable to diagnostic bias, competing risks bias, or insufficient or inappropriate control for potential confounding factors.

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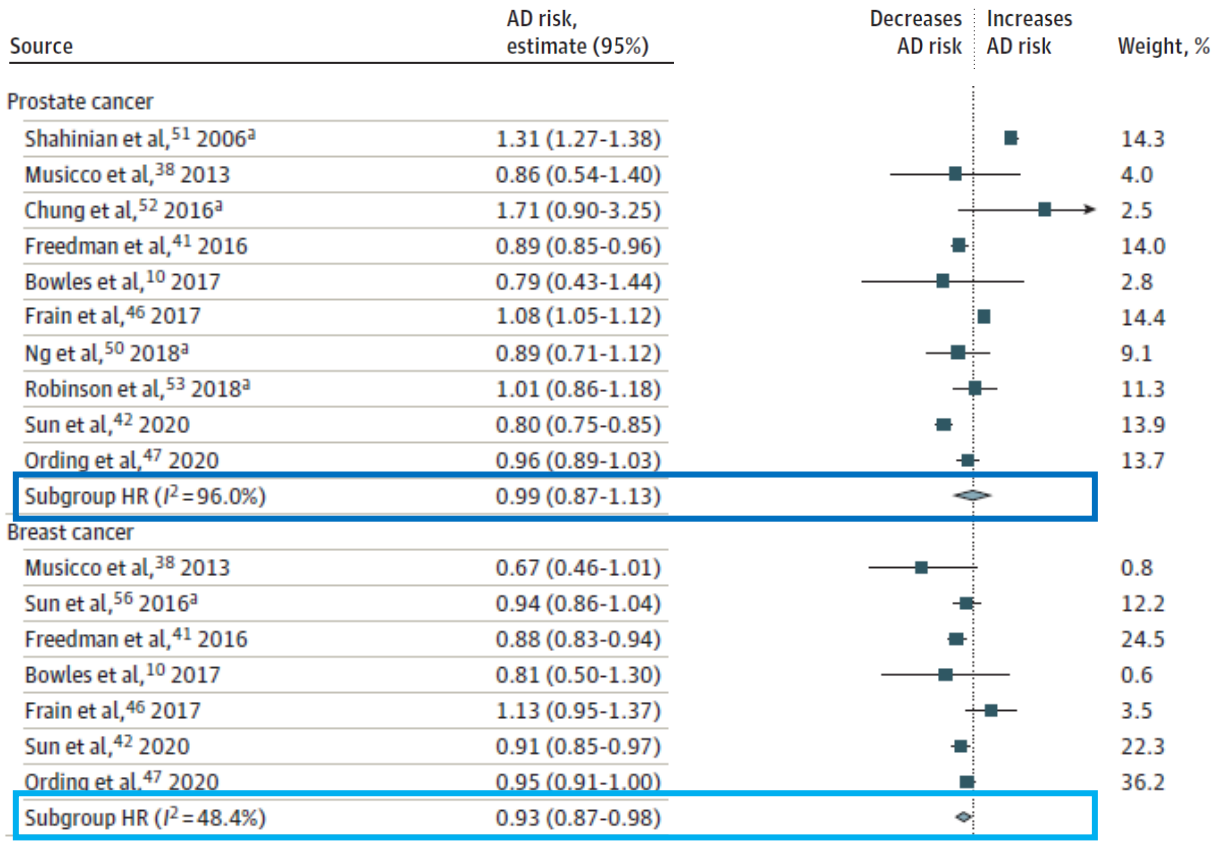
Prostate cancer risk shows no correlation with AD risk

Breast cancer risk shows a very weak inverse correlation with AD risk

Figure 2. Forest Plot of Random-Effects Models for the Pooled Cancer–Alzheimer Disease (AD) Risk Estimates[a]



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Association Between Alzheimer Disease and Cancer With Evaluation of Study Biases

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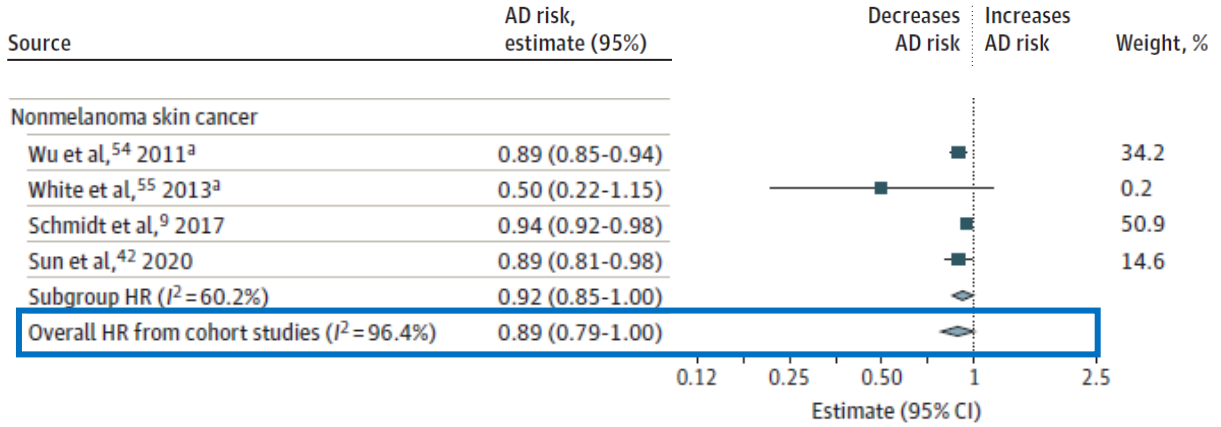
Monica Ospina-Romero, MD; M. Maria Glymour, ScD; Eleanor Hayes-Larson, PhD; Elizabeth Rose Mayeda, PhD; Rebecca E. Graff, ScD; Willa D. Brenowitz, PhD; Sarah F. Ackley, PhD; John S. Witte, PhD; Lindsay C. Kobayashi, PhD

Figure 2. Forest Plot of Random-Effects Models for the Pooled Cancer–Alzheimer Disease (AD) Risk Estimates[a]



Non-melanoma skin cancer was analyzed separately to see if a cancer without much survival bias potential would also show the inverse correlation. The observed hazard ratio was low (although not as low as the overall hazard ratio) and statistically significant. This finding suggests that survival bias is not a major contributer to the observed overall inverse correlation.

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Epidemiology: An Inverse Correlation

Some informative results from other studies:

Risk for neoplasms was significantly reduced only for women (OR = 0.5; 95% CI = 0.3 to 0.9; *P* = 0.03) and for endocrine-related tumors (OR = 0.5; 95% CI = 0.2 to 1.0; *P* = 0.04) (Realmuto et al, 2012). The Authors interpreted these results as possibly pointing out a role for estrogen.

The 2020 meta-analysis, however, did show only a very weak inverse correlation between breast cancer and Alzheimer disease risk.

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Epidemiology: Exceptions

A molecular hypothesis to explain direct and inverse co-morbidities between Alzheimer's Disease, Glioblastoma and Lung cancer

Jon Sánchez-Valle[1], Héctor Tejero[2], Kristina Ibáñez[3], José Luis Portero[4], Martin Krallinger[1], Fátima Al-Shahrour[2], Rafael Tabarés-Seisdedos[5], Anaïs Baudot[6] & Alfonso Valencia[1,7,8]

Patients suffering from Alzheimer's disease have **a lower risk of developing lung cancer** and suggest **a higher risk of developing glioblastoma** (Sanchez-Valle, 2017).

> **A functional analysis of the sets of deregulated genes points to the immune system, up-regulated** in both **Alzheimer disease** and **glioblastoma**, as a potential link between these two diseases. **Mitochondrial metabolism is regulated oppositely in Alzheimer disease and lung cancer,** indicating that it may be involved in the inverse co-morbidity between these diseases. Finally, **oxidative phosphorylation is a good candidate to play a dual role by decreasing or increasing the risk of lung cancer and glioblastoma in Alzheimer disease**.

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Epidemiology: Exceptions

Not extensively studied as a single cancer type, but Hodgkin lymphoma may be an exception to the inverse correlation between neurodegenerative diseases (AD/PD) and overall cancer risk

Cognitive impairment in hodgkin lymphoma survivors

Estherina Trachtenberg,[1] Tatiana Mashiach,[2] Rachel Ben Hayun,[3] Tamar Tadmor,[1,4] Tali Fisher,[3] Judith Aharon-Peretz[1,3] and Eldad J. Dann[1,5]

Neurocognitive Function and CNS Integrity in Adult Survivors of Childhood Hodgkin Lymphoma

Kevin R. Krull, Noah D. Sabin, Wilburn E. Reddick, Liang Zhu, Gregory T. Armstrong, Daniel M. Green, Alejandro R. Arevalo, Matthew J. Krasin, Deo Kumar Srivastava, Leslie L. Robison, and Melissa M. Hudson

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Common etiology acting in opposite directions?

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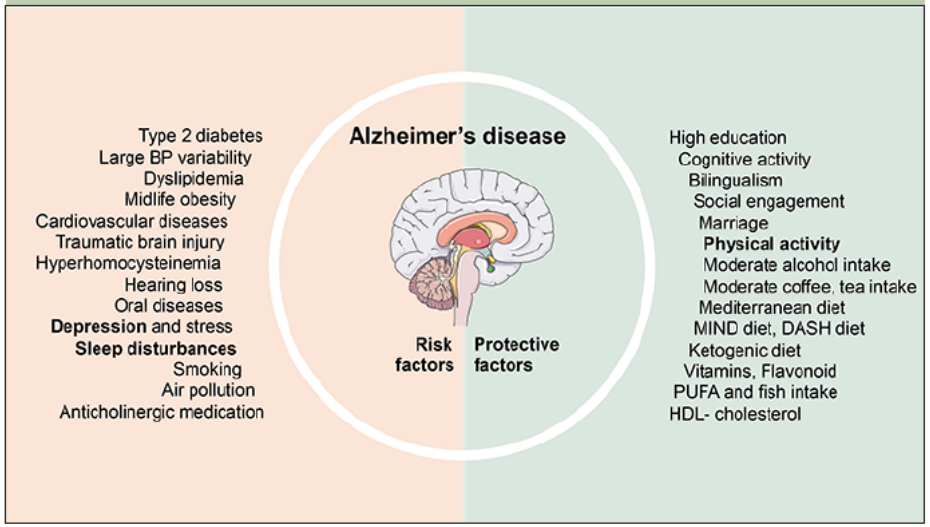
The Epidemiology of Alzheimer's Disease Modifiable Risk Factors and Prevention

X.-X. Zhang[1], Y. Tian[1], Z.-T. Wang[1], Y.-H. Ma[1], L. Tan[1], J.-T. Yu[2]

Figure 1. Potential modifiable risk factors for Alzheimer's disease



Risk factors mainly included pre-existing diseases, unhealthy lifestyles and environmental exposures, while some factors concerning psychosocial conditions as well as healthy lifestyles might protect against AD. In addition, some factors appeared to be risk factors as well as symptoms of AD, possibly due to the reverse causality, these factors were highlighted in bold. Abbreviation: BP = blood pressure, DASH = Dietary Approach to Stop Hypertension, MIND = Mediterranean-DASH diet Intervention for Neurodegeneration Delay, PUFA = polyunsaturated fatty acid, HDL- cholesterol = high-density lipoprotein cholesterol.

Known risk factors do not very considerably between cancer and Alzheimer disease (for Parkinson disease, however, smoking has an opposite association: risk for cancer, protection for Parkinson disease).

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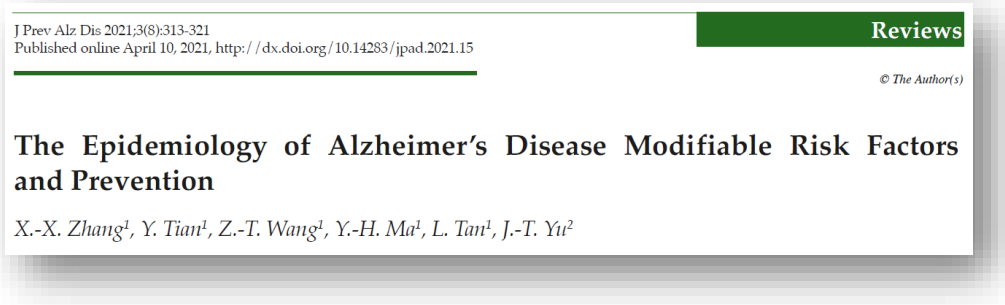
Common etiology acting in opposite directions?



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The Epidemiology of Alzheimer's Disease Modifiable Risk Factors and Prevention

X.-X. Zhang[1], Y. Tian[1], Z.-T. Wang[1], Y.-H. Ma[1], L. Tan[1], J.-T. Yu[2]

Most of the risk factors for AD and cancer are shared, including age, inflammation, smoking, lack of physical activity

Biological sex, however, has not been discussed much and it shows an opposite relationship with these two disorders:

Males have a higher risk for cancer

Females have a higher risk for Alzheimer disease

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Common etiology acting in opposite directions?

Dangerous blood condition may guard against Alzheimer's disease

Protection may result from wayward blood cells that enter brain

13 DEC 2021 • 7:50 PM ET • BY MITCH LESLIE

Clonal hematopoiesis increases the risk for cancer (mainly leukemia) but lowers the risk for Alzheimer disease

But this condition is unable to explain majority of the inverse correlation

Common etiology acting in opposite directions?

Alzheimer disease and cancer are both characterized by abnormal, but opposing, cellular behavior:

Increased cell death in Alzheimer disease

vs

Excessive cell growth in cancer

However, they share a lot of molecular pathways operating in the same direction.

Common etiology acting in opposite directions?

Inverse relationship between Alzheimer's disease and cancer, and other factors contributing to Alzheimer's disease: a systematic review

Ovais Shafi

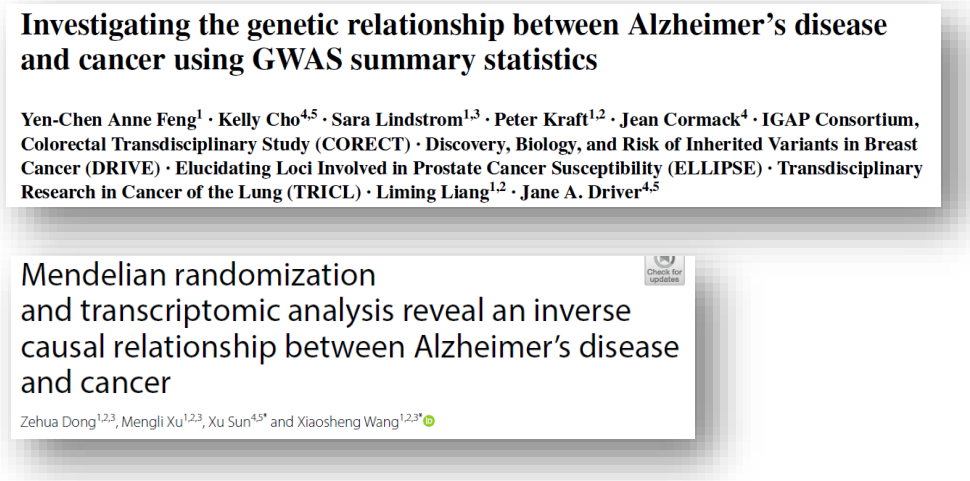
Cancer and Alzheimer disease have inverse relationship in many aspects such as P53, estrogen, neurotrophins and growth factors, growth and proliferation, cAMP, EGFR, Bcl-2, apoptosis pathways, IGF-1, HSV, TDP-43, APOE variants, notch signals and presenilins, NCAM, TNF alpha, PI3K/AKT/MTOR pathway, telomerase, ROS, ACE levels

AD occurs when brain neurons have weakened growth, cell survival responses, maintenance mechanisms, weakened anti-stress responses such as vimentin, carbonic anhydrases, HSPs, SAPK. In cancer, these responses are upregulated and maintained

Inverse Correlation Between Alzheimer's Disease and Cancer: Short Overview

Agnieszka Zabłocka[1] · Wioletta Kazana[1] · Marta Sochocka[2] · Bartłomiej Stańczykiewicz[3] · Maria Janusz[4] · Jerzy Leszek[5] · Beata Orzechowska[2]

Common etiology acting in opposite directions?



Investigating the genetic relationship between Alzheimer's disease and cancer using GWAS summary statistics

Yen-Chen Anne Feng[1] · Kelly Cho[4,5] · Sara Lindstrom[1,3] · Peter Kraft[1,2] · Jean Cormack[4] · IGAP Consortium, Colorectal Transdisciplinary Study (CORECT) · Discovery, Biology, and Risk of Inherited Variants in Breast Cancer (DRIVE) · Elucidating Loci Involved in Prostate Cancer Susceptibility (ELLIPSE) · Transdisciplinary Research in Cancer of the Lung (TRICL) · Liming Liang[1,2] · Jane A. Driver[4,5]

Mendelian randomization and transcriptomic analysis reveal an inverse causal relationship between Alzheimer's disease and cancer

Zehua Dong[1,2,3], Mengli Xu[1,2,3], Xu Sun[4,5*] and Xiaosheng Wang[1,2,3*]

Most studies did not find a shared genetic basis for these two disorders except one or two Mendelian randomisation studies. These are equivalent to randomised clinical trials, but results are also inconclusive and inconsistent

The consensus is that there is no shared genetic basis in opposite directions for cancer and Alzheimer disease

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Common etiology acting in opposite directions?

Immune activation underlies neuroinflammation which is a hallmark of neurodegeneration (seen in AD and PD)

On the other hand, immunity is a major determinant of cancer susceptibility but in the opposite direction. Diminished immune activity/response increases cancer risk. This fact underpins the success of cancer immunotherapy

Females have a greater magnitude of immune response and therefore, lower cancer risk and higher Alzheimer disease risk (as well as higher autoimmunity risk and lower infectious disease susceptibility)

Immune activation is characterised by increased HLA expression

Summary So Far…

- Alzheimer disease (as well as Parkinson disease) and cancer risk show an inverse correlation (except glioblastoma, and perhaps Hodgkin lymphoma, in AD and melanoma in PD)
- No common risk factor acting in opposite direction has been identified consistently
- Biological sex is a crucial factor as males have a higher risk of cancer and females have a higher risk for Alzheimer disease
- Immune activation is another opposing factor: it increases the risk for Alzheimer disease, but diminished immune activity/response (or evaded immune response) is a risk factor for cancer
- Immune activation is characterised by increased HLA expression
- Then, could immunogenetics shed some light on the inverse relationship?

Immunogenetics

Molecular Neurobiology (2023) 60:3086–3099
https://doi.org/10.1007/s12035-023-03260-8

Cancer and Alzheimer's Inverse Correlation: an Immunogenetic Analysis

Aditya Bhardwaj[1] · S. Imindu Liyanage[1] · Donald F. Weaver[1,2]

Nothing about immunogenetics!
HLA is not mentioned, not a single word in the whole paper beginning with immun….
(except the title!).

Cancer and Alzheimer's Inverse Correlation: an Immunogenetic Analysis
Abstract
Introduction
Cellular Proliferation Genes
Apoptotic Genes
Apoptotic and Cellular Proliferation Genes in AD and Cancer
Conclusions
Acknowledgements
References

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Immunogenetics in AD

PNAS RESEARCH ARTICLE | GENETICS

Multiancestry analysis of the HLA locus in Alzheimer's and Parkinson's diseases uncovers a shared adaptive immune response mediated by *HLA-DRB1*04* subtypes

Yann Le Guen, Guo Luo, Aditya Ambati, +146, and Emmanuel Mignot Authors Info & Affiliations

Contributed by Emmanuel Mignot; received March 2, 2023; accepted May 18, 2023; reviewed by Florence Clavaguera and Michel Goedert

August 29, 2023 120 (36) e2302720120 https://doi.org/10.1073/pnas.2302720120

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Immunogenetics in AD

PNAS RESEARCH ARTICLE | GENETICS

Table 1. *HLA-DRB1* alleles *HLA-DRB104:04 and *HLA-DRB1**04:01 are associated with a decreased risk of Parkinson's and ADs**

		PD				AD				PD + AD		
	HLA	FreqC	N	OR	*P*-val	FreqC	N	OR	*P*-val	OR	*P*-val	p-het
HLA Alleles	*HLA-DRB1**04:01	0.196	1,484,656	0.92[0.89; 0.95]	2.4E-08	0.191	486,478	0.93[0.9; 0.96]	6.4E-07	0.92[0.91; 0.94]	8.9E-14	0.56
	*HLA-DRB1**04:02	0.019	1,474,730	0.92[0.85; 0.99]	0.02	0.022	155,846	1.00[0.91; 1.10]	0.99	0.95[0.89; 1.01]	0.07	0.17
	*HLA-DRB1**04:03	0.012	980,868	0.89[0.81; 0.97]	0.01	0.072	7,587	1.09[0.91; 1.30]	0.34	0.93[0.85; 1.01]	0.07	0.04
	*HLA-DRB1**04:04	0.074	1,475,574	0.84[0.80; 0.88]	1.5E-11	0.073	476,236	0.86[0.82; 0.90]	8.9E-12	0.85[0.82; 0.88]	9.3E-22	0.60
	*HLA-DRB1**04:05	0.013	1,507,057	1.00[0.95; 1.05]	0.86	0.026	169,080	0.98[0.91; 1.06]	0.62	0.99[0.95; 1.03]	0.68	0.75
	*HLA-DRB1**04:06	0.046	32,327	0.95[0.82; 1.09]	0.46	0.058	7,587	0.95[0.78; 1.15]	0.60	0.95[0.85; 1.06]	0.37	0.99
	*HLA-DRB1**04:07	0.021	526,189	0.79[0.69; 0.91]	7.3E-04	0.019	474,840	0.88[0.81; 0.96]	4.5E-03	0.86[0.79; 0.92]	2.7E-05	0.18
	*HLA-DRB1**04:10	0.041	4,853	0.91[0.67; 1.25]	0.57	0.031	7,985	1.23[0.94; 1.59]	0.13	1.08[0.89; 1.32]	0.42	0.16
	*HLA-DRB1**01:01	0.181	1,485,033	1.05[1.01; 1.09]	7.0E-03	0.186	487,120	1.07[1.04; 1.10]	3.9E-07	1.06[1.04; 1.09]	1.3E-08	0.44
	*HLA-DQB1**03:02	0.191	1,501,065	0.91[0.88; 0.93]	2.6E-14	0.190	510,130	0.89[0.86; 0.91]	1.2E-19	0.90[0.88; 0.91]	4.7E-32	0.23
	*HLA-DQA1**03:01	0.177	1,507,147	0.89[0.87; 0.91]	2.5E-20	0.186	507,263	0.89[0.87; 0.91]	1.8E-19	0.89[0.88; 0.91]	3.E-37	0.79
	*HLA-DRB1**15:01	0.272	1,507,057	1.06[1.03; 1.10]	5.0E-04	0.263	485,383	1.02[0.99; 1.04]	0.13	1.03[1.01; 1.05]	1.1E-03	0.054

Table 2. *HLA-DRB1* H13/H33 amino acid is associated with reduced tau and neurofibrillary tangles and to a lesser extent with reduced Amyloid-β or neuritic plaques, when testing their association with AD neuropathology and CSF biomarkers

rs601945 is the SNP that shows a protective association with both AD and PD.

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Multiancestry analysis of the HLA locus in Alzheimer's and Parkinson's diseases uncovers a shared adaptive immune response mediated by *HLA-DRB1*04* subtypes

Yann Le Guen, Guo Luo, Aditya Ambati, +146, and Emmanuel Mignot Authors Info & Affiliations

Immunogenetics in AD

HLA Associations with AD/PD Susceptibility

HLA-DR4 (the main allele within the DR53 family) is associated with decreased risk (represented by **rs601945**)

vs

HLA-DR15 (the main allele within the DR51 family) is associated with increased risk

Most HLA-cancer associations, including the first HLA and childhood leukemia and lung cancer risk, concern the HLA-DR53 lineage (presumably due to low level of expression of the alleles of this lineage that diminishes immune surveillance)

and

almost none of the representatives of HLA-DR51 lineage (which shows the highest level of HLA-DR expression levels)

Immunogenetics in AD

HLA Associations with AD/PD Susceptibility

One of the hallmarks of immune activation is increased HLA-DR expression

HLA-DR53 alleles have lower levels of HLA-DR expression; this lineage has protective associations with disorders correlate with immune-activation (like AD/PD)

and

risk associations with disorders correlate with diminished immune activation (like cancer)

Immunogenetics

HLA Region and Disease Associations

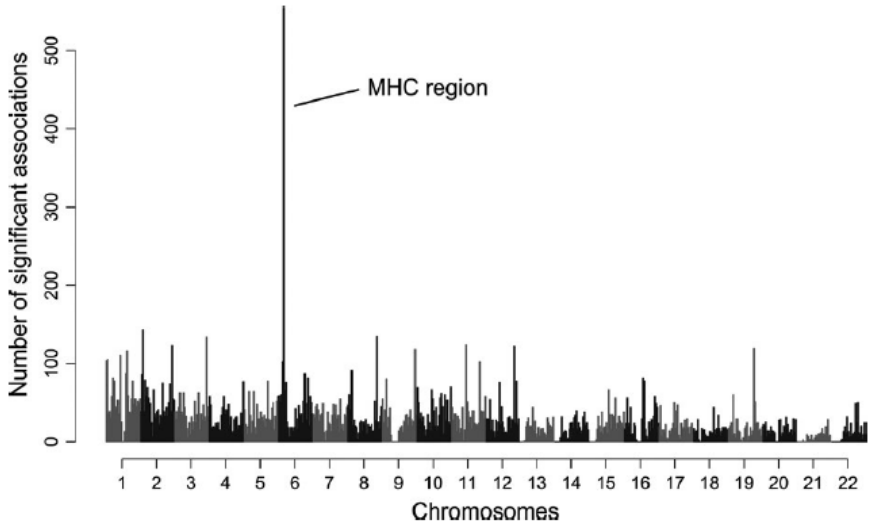

FIGURE 1 Number of significant GWAS associations along the genome. The chromosomal location of significant trait associations from GWAS (*N* = 18,682) is shown for all autosomes. Data from NHGRI GWAS catalog. Reproduced from "Lenz TL, Spirin V, Jordan DM, Sunyaev SR. Excess of Deleterious Mutations around HLA Genes Reveals Evolutionary Cost of Balancing Selection. Mol Biol Evol 2016;33(10):2555-64. https://doi.org/10.1093/molbev/msw127" by permission of Oxford University Press on behalf of the Society for Molecular Biology and Evolution

including:

- **Schizophrenia**
- **Alzheimer disease**
- **Parkinson disease**
- **Lung cancer**
- **Hodgkin lymphoma**

Received: 9 March 2017 | Revised: 16 June 2017 | Accepted: 20 July 2017

DOI: 10.1111/iji.12332

REVIEW

WILEY INTERNATIONAL JOURNAL OF IMMUNOGENETICS

What has GWAS done for HLA and disease associations?

A. E. Kennedy[1] | U. Ozbek[2,3] | M. T. Dorak[4]

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Immunogenetics

The Latest HLA Association with Somatic Mutations

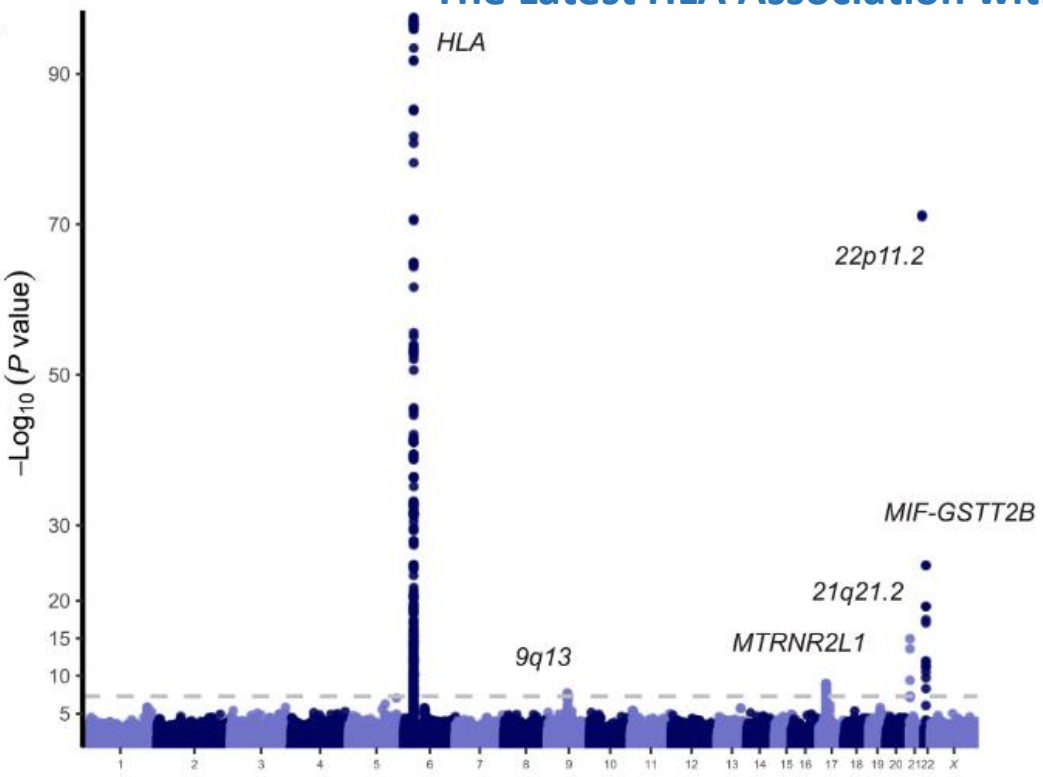

Fig. 3A. Germline determinants of recurrent non-missense somatic mutations (RNMSM) burden. Manhattan plot from GWAS of RNMSM burden, computed using SAIGE. Germline variants included had a minor allele count ≥ 600 and were distinct from the set of RNMSMs.

Germline genetic basis of RNMSMs

We performed a multi-ancestry genome-wide association study (GWAS) of the RNMSM burden using the scalable and accurate implementation of generalized mixed model (SAIGE) (*33*) and identified five genome-wide significant loci, all of which collectively highlight the influence of immune function on RNMSM burden (Fig. 3A). The strongest signal was observed in the *HLA* region at rs9271735, which is a common (MAF 28%) variant and is 2.5 kb upstream of the transcription start site (TSS) of *HLA-DQA1*, whose protein plays an essential role in antigen presentation. The A allele was associated with a 0.09 SD increase in RNMSM burden (P value = 3.8×10^{-98}). Given that there is extensive linkage disequilibrium at the *HLA* locus, this variant likely tags a specific *HLA* haplotype. To ensure that this signal was not a consequence of population stratification, we then performed both European and African ancestry–specific GWAS (Methods; fig. S3). We observed that rs9271735 was genome-wide significant in both ancestry-specific GWAS (African ancestry, P value = 4.9×10^{-18}; European ancestry, P value = 5.1×10^{-40}), indicating that the association is unlikely to be a consequence of population stratification. Consistent with the possible role of the adaptive immune system in surveillance of HSCs for excessive mutation, a recent report showed that HSCs in humans are antigen-presenting cells (*34*).

The genetic determinants of recurrent somatic mutations in 43,693 blood genomes

JOSHUA S. WEINSTOCK, CECELIA A. LAURIE, JAI G. BROOME, KENT D. TAYLOR, XIUQING GUO, ALAN R. SHULDINER, JEFFREY R. O'CONNELL, JOSHUA P. LEWIS, ERIC BOERWINKLE, [...], AND NHLBI TRANS-OMICS FOR PRECISION MEDICINE (TOPMED) CONSORTIUM +78 authors Authors Info & Affiliations

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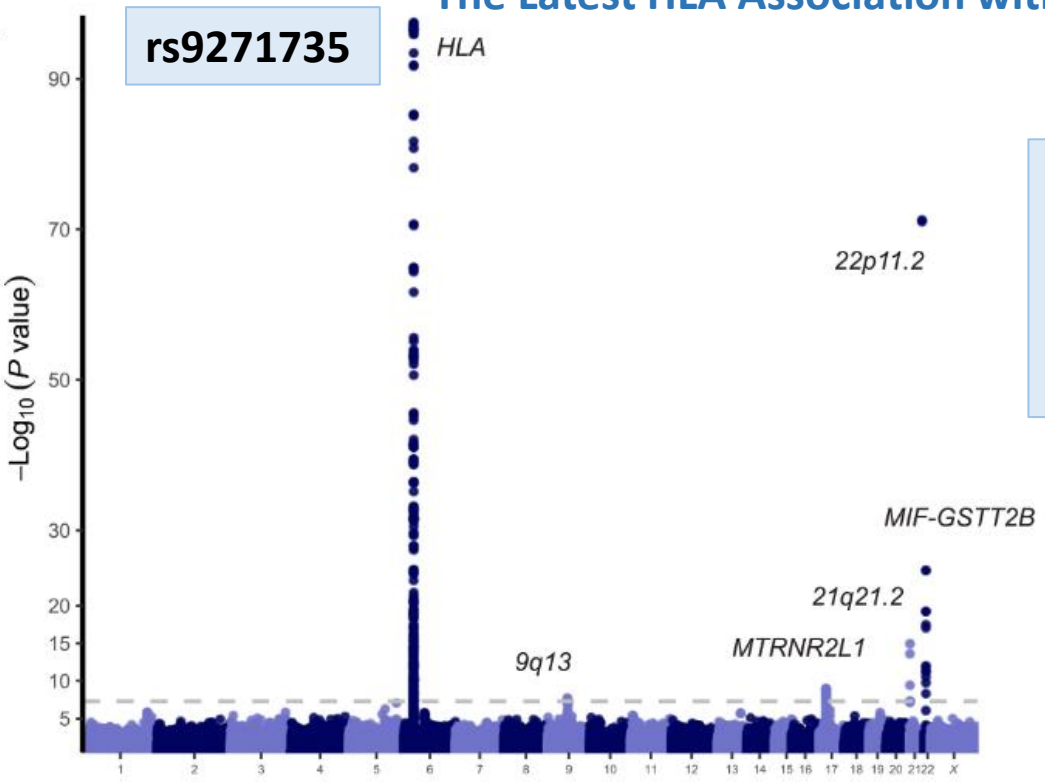
Immunogenetics

The Latest HLA Association with Somatic Mutations



rs9271735 represents the HLA-DR53 lineage, which is the protective marker for Alzheimer disease

The genetic determinants of recurrent somatic mutations in 43,693 blood genomes

JOSHUA S. WEINSTOCK, CECELIA A. LAURIE, JAI G. BROOME, KENT D. TAYLOR, XIUQING GUO, ALAN R. SHULDINER, JEFFREY R. O'CONNELL, JOSHUA P. LEWIS, ERIC BOERWINKLE, [...], AND NHLBI TRANS-OMICS FOR PRECISION MEDICINE (TOPMED) CONSORTIUM +78 authors Authors Info & Affiliations

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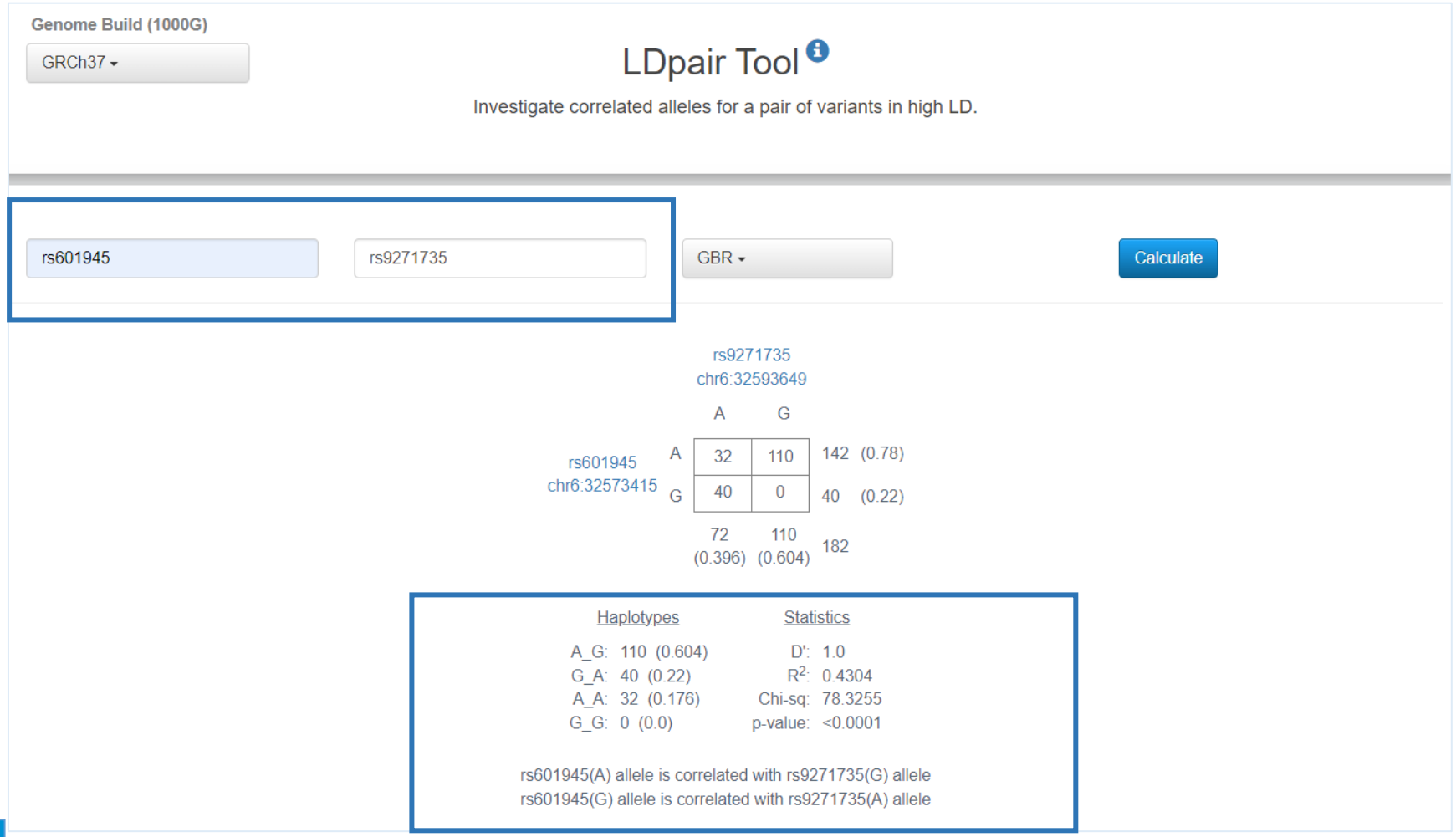
These Two HLA Region SNPs are Correlated



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How Can HLA be Involved in so many Phenotypes?
trans-eQTLs in xMHC

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]

***Trans*-acting genetic variants have a substantial, albeit poorly characterized, role in the heritable determination of gene expression. Using paired purified primary monocytes and B cells, we identify new predominantly cell type–specific *cis* and *trans* expression quantitative trait loci (eQTLs), including multi-locus *trans* associations to *LYZ* and *KLF4* in monocytes and B cells, respectively. Additionally, we observe a B cell–specific *trans* association of rs11171739 at 12q13.2, a known autoimmune disease locus, with *IP6K2* ($P = 5.8 \times 10^{-15}$), *PRIC285* ($P = 3.0 \times 10^{-10}$) and an upstream region of *CDKN1A* ($P = 2 \times 10^{-52}$), suggesting roles for cell cycle regulation and peroxisome proliferator-activated receptor γ (PPARγ) signaling in autoimmune pathogenesis. We also find that specific human leukocyte antigen (HLA) alleles form *trans* associations with the expression of *AOAH* and *ARHGAP24* in monocytes but not in B cells. In summary, we show that mapping gene expression in defined primary cell populations identifies new cell type–specific *trans*-regulated networks and provides insights into the genetic basis of disease susceptibility.**

HLA-DR53 family members have strong genome-wide trans-eQTL effects in monocytes

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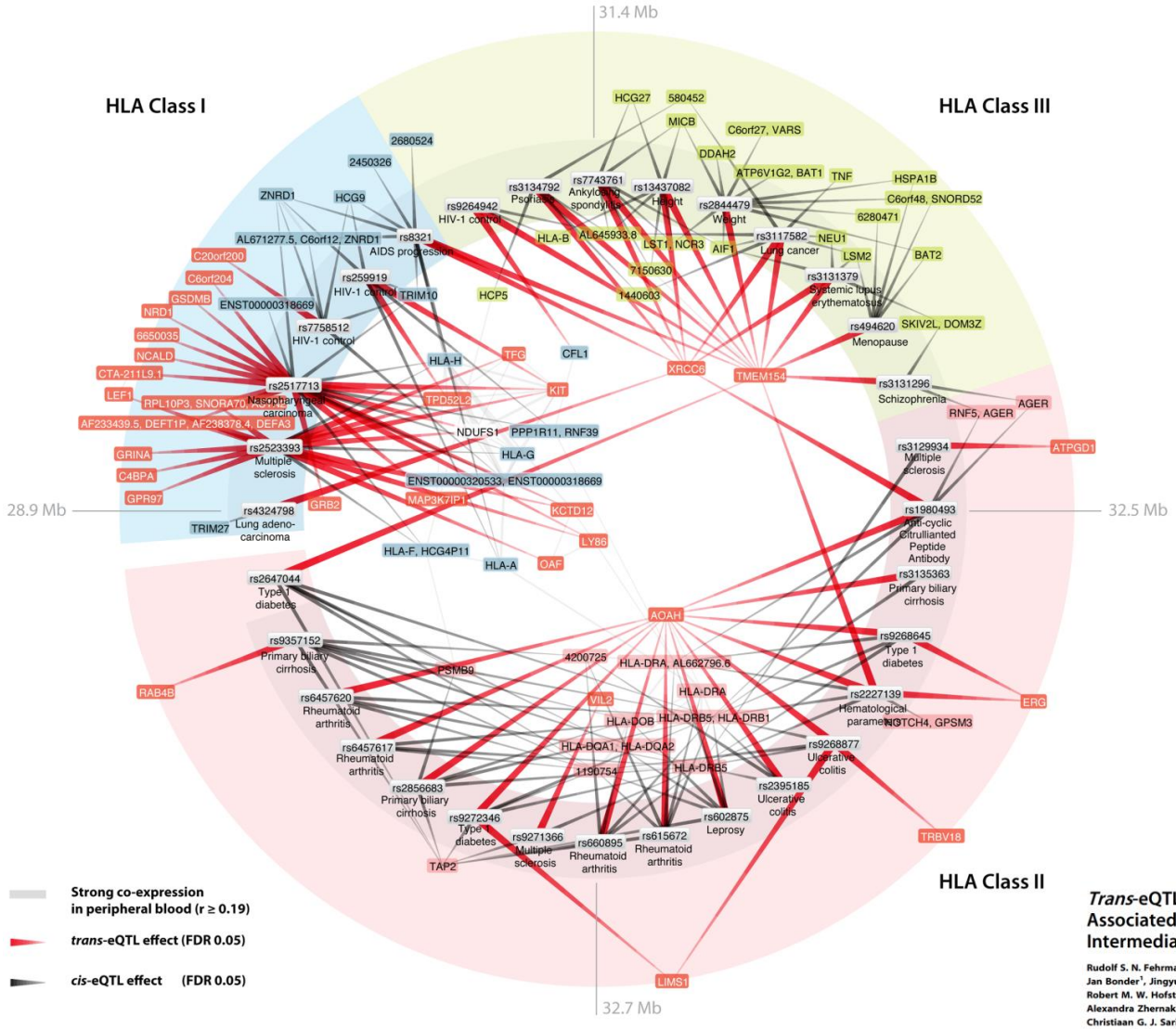

***Trans*-eQTLs Reveal That Independent Genetic Variants Associated with a Complex Phenotype Converge on Intermediate Genes, with a Major Role for the HLA**

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[3], Rinse K. Weersma[1,5], Robert M. W. Hofstra[1], Wim A. Buurman[6], Sander Rensen[6], Marcel G. M. Wolfs[7], Mathieu Platteel[7], 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*]

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Immunogenetics

How Can HLA be Involved in so many Phenotypes?
trans-meQTLs in xMHC

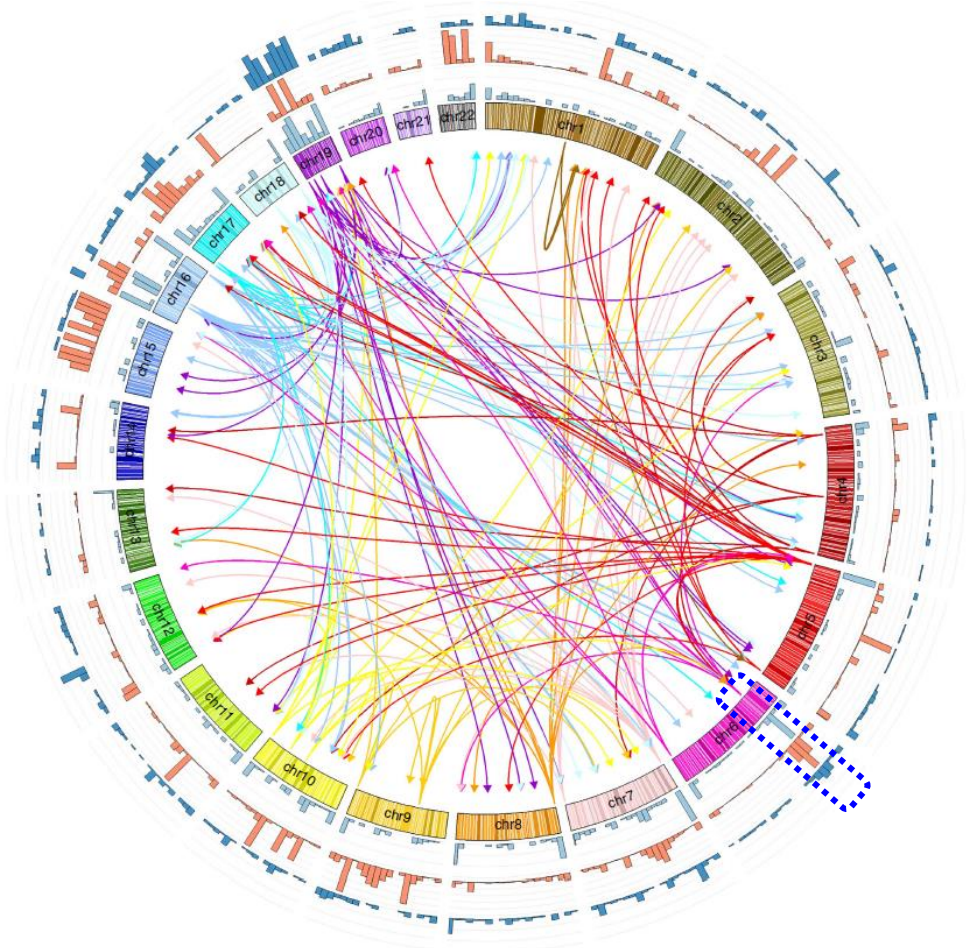

Figure 1 | Enrichment of features in regions harbouring SNPs involved in distal SNP–CpG associations. Outer histograms: number of SNPs involved in distal SNP–CpG associations (light blue), calculated in 7.5 Mb bins; number of piRNA sequences (orange); number of transcription factors (dark blue). Inner links: SNP regions associated with four or more CpG sites. Arrows are pointing from SNPs to the CpG sites they are associated with, and are coloured according to the chromosomes where the SNPs reside.

Long-range epigenetic regulation is conferred by genetic variation located at thousands of independent loci

Mathieu Lemire[1], Syed H.E. Zaidi[1], Maria Ban[2], Bing Ge[3], Dylan Aïssi[4,5,6], Marine Germain[4,5,6], Irfahan Kassam[7], Mike Wang[1], Brent W. Zanke[8], France Gagnon[7], Pierre-Emmanuel Morange[9,10,11], David-Alexandre Trégouët[4,5,6], Philip S. Wells[8], Stephen Sawcer[2], Steven Gallinger[12,13], Tomi Pastinen[3] & Thomas J. Hudson[1,14,15]

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Conclusion

HLA associations correlating with increased/decreased HLA-DR antigen levels may explain the inverse correlation with cancer

Genome-wide strong trans effects of HLA-DR53 lineage variants and their association with somatic mutation burden may be the common immunogenetic factor underlying the inverse correlation of AD and cancer risk

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Implications

Controlling immune activation may prevent Alzheimer disease initiation/progression, but mainly in HLA-DR15-positive individuals (perhaps also in females only)

On the other hand, immune activation potential should not be diminished as this would increase the risk for cancer development

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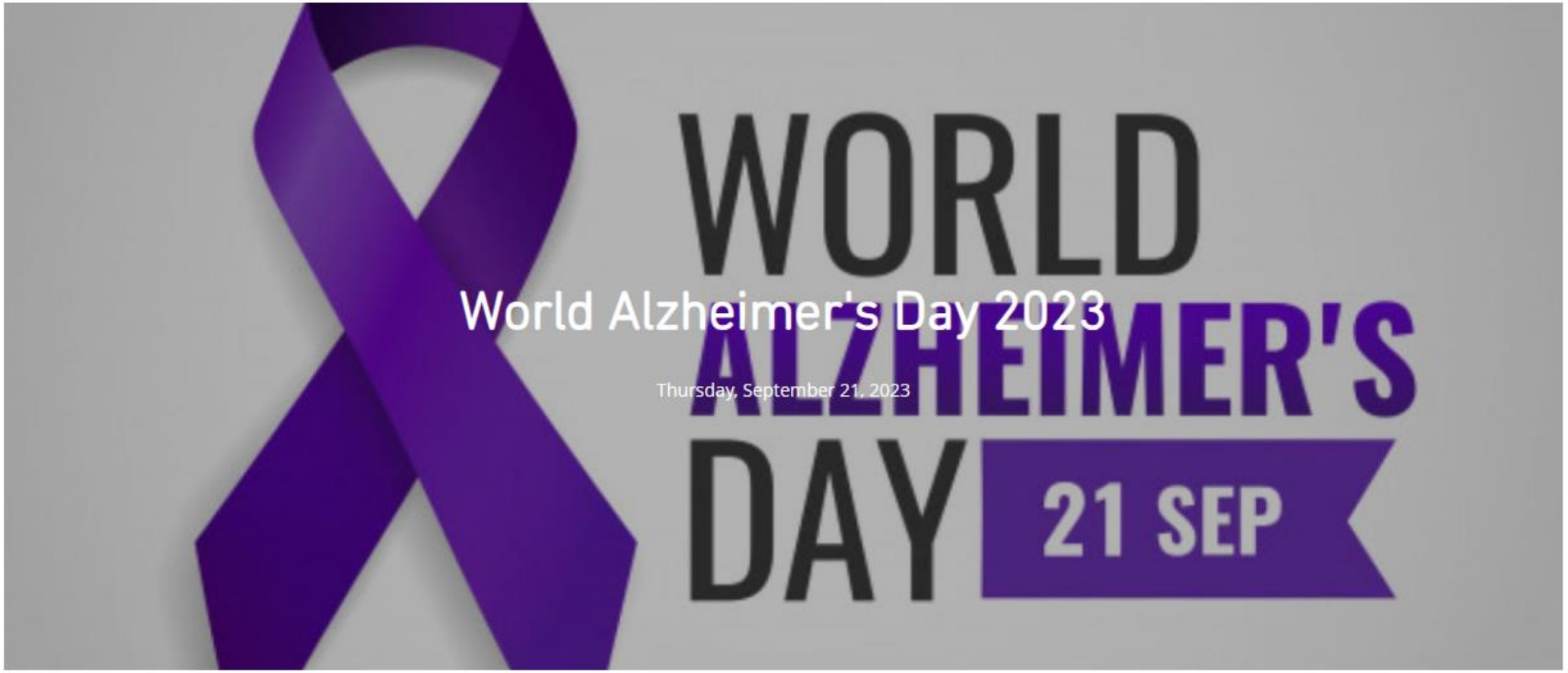
LÖSEV - LÖSANTE
2. ULUSLARARASI
KANSER VE HAYAT SEMPOZYUMU
8-10 Eylül 2023

Childhood Cancer Awareness Month 2023 'Give a Hug'

September is Childhood Cancer Awareness Month (CCAM)

Every day in the UK, 10 children and young people will receive the devastating news that they have cancer. Of those 10, two will not survive.

LÖSEV
Lösemili Çocuklar Vakfı



World Alzheimer's Day 2023

Thursday, September 21, 2023