The Role of X Chromosome in Alzheimer's Disease Genetics.

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Key points

Question: Does the X chromosome play a role in the genetics of Alzheimer's Disease (AD)?

Findings: In a genetic meta-analysis across 1,152,284 individuals, several X chromosome loci were associated with AD. Four loci showed evidence of shared genetic associations between AD risk and regulation of nearby gene expression in brain tissue. The top association signal was intronic on *SLC9A7* and linked to its expression.

Meaning: We performed the first large-scale X chromosome-wide association study of AD and prioritized *SLC9A7* as a novel risk locus. This study significantly advances our knowledge of AD genetics and provides novel biological drug targets.

Abstract

Importance: The X chromosome has remained enigmatic in Alzheimer's disease (AD), yet it makes up 5% of the genome and carries a high proportion of genes expressed in the brain, making it particularly appealing as a potential source of unexplored genetic variation in AD.

Objectives: Perform the first large-scale X chromosome-wide association study (XWAS) of AD. Primary analyses are non-stratified, while secondary analyses evaluate sex-stratified effects.

Design: Meta-analysis of genetic association studies in case-control, family-based, population-based, and longitudinal AD-related cohorts from the US Alzheimer's Disease Genetics Consortium (ADGC) and Alzheimer's Disease Sequencing Project (ADSP), the UK Biobank (UKB), the Finnish health registry (FinnGen), and the US Million Veterans Program (MVP). Risk for AD evaluated through case-control logistic regression analyses. Data were analyzed between January 2023 and March 2024.

Setting: Genetic data available from high-density single-nucleotide polymorphism (SNP) microarrays and whole-genome sequencing (WGS). Summary statistics for multi-tissue expression and protein quantitative trait loci (QTL) available from published studies, enabling follow-up genetic colocalization analyses.

Participants: 1,629,863 eligible participants were selected from referred and volunteer samples, of which 477,596 were excluded for analysis exclusion criteria. Number of participants who declined to participate in original studies was not available.

Main Outcome and Measures: Risk for AD (odds ratio; OR) with 95% confidence intervals (CI). Associations were considered at X-chromosome-wide (P-value<1e-5) and genome-wide (P-value<5e-8) significance.

Results: Analyses included 1,152,284 non-Hispanic White European ancestry subjects (57.3% females), including 138,558 cases. 6 independent genetic loci passed X-chromosome-wide significance, with 4 showing support for causal links between the genetic signal for AD and expression of nearby genes in brain and non-brain tissues. One of these 4 loci passed conservative genome-wide significance, with its lead variant centered on an intron of *SLC9A7* (OR=1.054, 95%-CI=[1.035, 1.075]) and colocalization analyses prioritizing both the *SLC9A7* and nearby *CHST7* genes.

Conclusion and Relevance: We performed the first large-scale XWAS of AD and identified the novel *SLC9A7* locus. *SLC9A7* regulates pH homeostasis in Golgi secretory compartments and is anticipated to

have downstream effects on amyloid beta accumulation. Overall, this study significantly advances our knowledge of AD genetics and may provide novel biological drug targets.

Introduction

The X chromosome has remained enigmatic, not just in AD, but in the broader field of genome-wide association studies. It is typically excluded due to technical challenges and power limitations because of its complex inheritance pattern[1]. The X chromosome however makes up 5% of the genome and carries a high proportion of genes expressed in the brain. Additionally, it may contribute to the well-established higher prevalence of AD in women relative to men[2]. We thus set out to fill in this gap by performing the first meta-analysis of XWAS conducted on various publicly available AD-related cohorts, as well as multiple biobanks where AD phenotypes were available. To ensure maximal power, this study was designed as a large-scale discovery combining all available samples.

Methods

An in-depth overview of all methodologies is provided in the **eMethods**. The current study followed STREGA reporting guidelines. Participants or their caregivers provided written informed consent in the original studies. The current study protocol was granted an exemption by the Stanford Institutional Review Board because the analyses were carried out on "de-identified, off-the-shelf" data; therefore, additional informed consent was not required.

Data Ascertainment

Case-control, family-based, and longitudinal AD genetic cohorts from the ADGC and ADSP (release-3) were available through public repositories, with genetic data from SNP microarrays and WGS (**eTable1-2**)[3,4]. These cohorts contributed clinically diagnosed AD cases (40.0% pathology verified; **eTable3**). Analyses in UKB, FinnGen, and MVP used genetic data from SNP microarrays[5–8]. UKB data and FinnGen summary results (v10) were publicly available. UKB contributed health-registry-confirmed AD cases and proxy Alzheimer's disease-and-dementia (ADD) cases; FinnGen contributed health-registry-confirmed AD cases; MVP contributed health-registry-confirmed and proxy ADD cases.

Quality Control and Processing

ADGC and ADSP data underwent extensive quality control (QC) and imputation to the TOPMed reference panel (**eTable4-5**). Specific consideration was given to X-chromosome QC as in prior work (cf. **eMethods**)[9]. Genetic data processing for UKB, FinnGen, and MVP followed cohort-specific protocols[5–8]. Non-Hispanic White, European ancestry cases and controls, carrying XX or XY with concordant self-reported sex and ages >60 years (>18 and median=63 in FinnGen), were retained for analyses (**eFigure1; eTable3**). Variants were filtered using cohort-specific minor allele frequency (MAF) criteria, which on average correspond to MAF>0.05% (**eTable5**).

X chromosome Considerations

X chromosome analyses considered non-pseudoautosomal regions. Genotype encoding was 0/2 in men (XY) and 0/1/2 in women (XX), following a random X chromosome inactivation (XCI) model in women. In UKB, most cases were proxy cases, i.e. family history of ADD in first-degree relatives. This proxy approach has been established to replicate AD autosomal genetic risk factors and be adaptable to XWAS[10]. To maximize power, the health-registry and proxy status were unified into a single phenotype for which

association coefficients were adjusted onto a regular case-control scale (**eTable6-7**). After rescaling, UKB showed consistent coefficient distributions with ADGC+ADSP (**eFigure2**). A similar approach was used in MVP, but in line with MVP protocols, analyses were separated for health-registry and proxy phenotypes[7].

Statistical Analyses

XWAS evaluated case-control logistic regressions on AD risk, adjusting for sex, age, technical covariates, and genetic principal components (capturing population stratification) as applicable per dataset. Mixed models to include related subjects were used in ADGC, ADSP, UKB (LMM-BOLT v2.4)[11], and FinnGen (Regenie)[6]. Association results across datasets were combined through fixed effects inverse-variance weighted meta-analyses. Primary analyses were non-stratified. Secondary analyses were sex-stratified, and conducted across ADGC, ADSP, and UKB. Association results were considered at the X-chromosome-wide (P-value<1e-5) and conservative genome-wide thresholds (P-value<5e-8). Sex effects were evaluated through heterogeneity tests and considered significant at P<0.05. Evidence for escape from XCI was evaluated by comparing variant beta coefficients derived from men and women-stratified XWAS (ratio=1 indicates escape; ratio=2 indicates no escape)[12].

Genetic Colocalization

To identify potentially causal genes in associated risk loci, statistical colocalization was evaluated between the local genetic association signal for AD and the genetic association signal for molecular traits such as expression levels of genes within that locus (R-v.4.2.1, *coloc*)[13]. We leveraged public datasets where quantitative trait loci (QTL) for expression and protein levels were available for the X chromosome in brain and non-brain tissues (cf. **eMethods**).

Results

The study design is provided in **Figure1A**. 1,152,284 individuals (138,558 cases: 15,081 clinically diagnosed cases, 41,091 health-registry-confirmed cases, and 82,386 proxy cases) were included in the XWAS (**eTable3**). There was no sign of genomic inflation (**eFigure3**). We associated 2 rare (MAF<1%) lead variants in the *NLGN4X* and *MID1* loci, and 4 common lead variants in the *SLC9A7*, *ZNF280C*, *ARGRG4*, and *MTM1* loci (**Table1**; locus zoom and forest plots in **eFigures4-5**). All common variant loci showed colocalization for at least one nearby gene in brain tissue (**Table2; eTable8**). The overall top association signal (cross-cohort allele frequencies in **eTable9**), intronic on *SLC9A7*, passed conservative significance criteria and showed colocalization for several genes, most notably *SLC9A7* and *CHST7*. Colocalization plots for top prioritized genes are in **eFigures6-10**.

The *ZNF280C* and *ARGRG4* lead variants showed evidence for escape from XCI, while the *MID1* variant appeared female-specific (**eTable10**). Sex-stratified XWAS only revealed 1 X-chromosome-wide significant, female-specific rare variant association without colocalization support (**eFigure11**, **eTable11**) and indicated that evidence for escape from XCI was apparent only for a few common, small effect size variants (**eFigure12**).

Discussion

We performed an XWAS of AD in 1,152,284 individuals, making this the largest genetic association study of AD to date[14]. The top signal showed support for a causal link between the genetic regulation of *SLC9A7* or *CHST7* expression and AD risk. *CHST7* encodes a chondroitin 6-sulfotransferase that confers negatively charged sulfate groups to glycosaminoglycans, which may relate to promoting tau fibrillization and spreading[15]. Notably, *SLC9A7* (a.k.a *NHE7*) is a paralog of *SLC9A6* (a.k.a *NHE6*), previously implicated in experimental work as an X-linked AD modifying gene[16]. These are highly conserved genes that regulate pH homeostasis in Golgi secretory compartments and endosomes and might thus be expected to contribute to increased amyloid accumulation across aging when their expression levels are increased (a detailed background and rationale are provided in **Appendix-A**). In line with this expectation, QTL data support that the top risk allele is associated with increased expression of *SLC9A7* in brain tissue, increasing expression by 17-44% for an active allele (**eTable12**). Although the *SLC9A7* top variant has a small effect size (OR=1.054, 95%-CI=[1.035, 1.075]), given this relatively small effect on *SLC9A7* expression in the brain, it may be that more substantial reduction or pharmacological inhibition of *SLC9A7* would prove to be an effective therapeutic strategy for AD.

Despite this study's formidable sample size, only the *SLC9A7* locus reached conservative significance criteria with a small effect size, suggesting the X chromosome contributes relatively little to AD prevalence. In addition, only 2 lead variants of small effect size indicated escape from XCI and only 1 rare lead variant appeared female-specific, such that these XWAS results have little bearing on sex-stratified AD prevalence. Similarly, sex-stratified XWAS did not reveal striking results, which would have been expected if the X chromosome played a significant role in the observations that 2/3 of AD patients across the lifespan are women[2]. Overall, our results suggest that while the X chromosome plays only a small role in the population prevalence of AD, the specific pathways highlighted here open the door to novel pathogenic pathways and associated drug targets.

Limitations

This study focused on European ancestry individuals. When larger cross-ancestry samples become available, future studies should extend AD XWAS into these populations. Similarly, future, larger sex-stratified AD XWAS may help identify sex-specific risk genes and genes escaping from XCI. Lastly, this study did not provide conclusive insight into the causal gene at the *SLC9A7* locus, which future experimental studies should interrogate.

Conclusion

We performed the first large-scale XWAS of AD and identified the novel *SLC9A7* risk locus. Overall, this study significantly advances our knowledge of the genetics of AD and may provide novel biological drug targets.

Consent for publication

Not applicable.

Availability of data and materials

Data used in the XWAS are available upon application to:

- dbGaP (https://www.ncbi.nlm.nih.gov/gap/)
- NIAGADS (https://www.niagads.org/)
- LONI (https://ida.loni.usc.edu/)
- AMP-AD knowledge portal / Synapse (https://www.synapse.org/)
- Rush (https://www.radc.rush.edu/)
- NACC (https://naccdata.org/)
- UKB (https://www.ukbiobank.ac.uk/)
- FinnGen (https://www.finngen.fi/en)
- MVP (https://www.mvp.va.gov/)

The specific data repository and identifier for ADGC and ADSP data are indicated in **eTable1** of the supplement.

The data, code, and phenotypes used to generate MVP results are accessible to researchers with MVP data access. Due to VA policy, MVP is currently only accessible to VA researchers with a funded MVP project, either through a VA Merit Award, career development award, or NIH R01. Additional information is available at https://genhub.va.gov/file/view/897656. GWAS summary results for the MVP cohort will be posted to dbGAP after publication.

Colocalization datasets are available from:

- AMP-AD knowledge portal / Synapse (https://www.synapse.org/; identifier: syn51150434)
- eQTL catalogue (https://www.ebi.ac.uk/eqtl/)
- GTEx (https://www.gtexportal.org/home/)

Summary statistics generated by this study will be deposited in both NIAGADS and the EMBL-EBI GWAS Catalog.

Competing/Conflicting interests

The authors declare no competing or conflicting interests.

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Role of Funder/Sponsor

The funding organizations and sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Authors' contributions

M.E.B., Y.L. and M.D.G. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. M.E.B. performed data acquisition and analyses, designed analyses, designed study, wrote paper, and obtained funding. Y.L. performed data acquisition and analyses, designed analyses, designed study, and wrote paper. I.S. performed data acquisition and analyses. J.H. co-wrote the paper. M.W.L. and J.M.G were involved in data, funding, and resource acquisition. M.W.L, R.S., V.M., M.S.P., and R.L.H. were involved in conceptualization and study design. R.Z and R.S. analyzed and curated data. V.N. performed data acquisition and analyses, designed study, designed analyses, supervised analyses, and supervised work. M.D.G designed study, designed analyses, supervised analyses, supervised work, wrote paper, and obtained funding. All authors contributed to critical revision of the manuscript.

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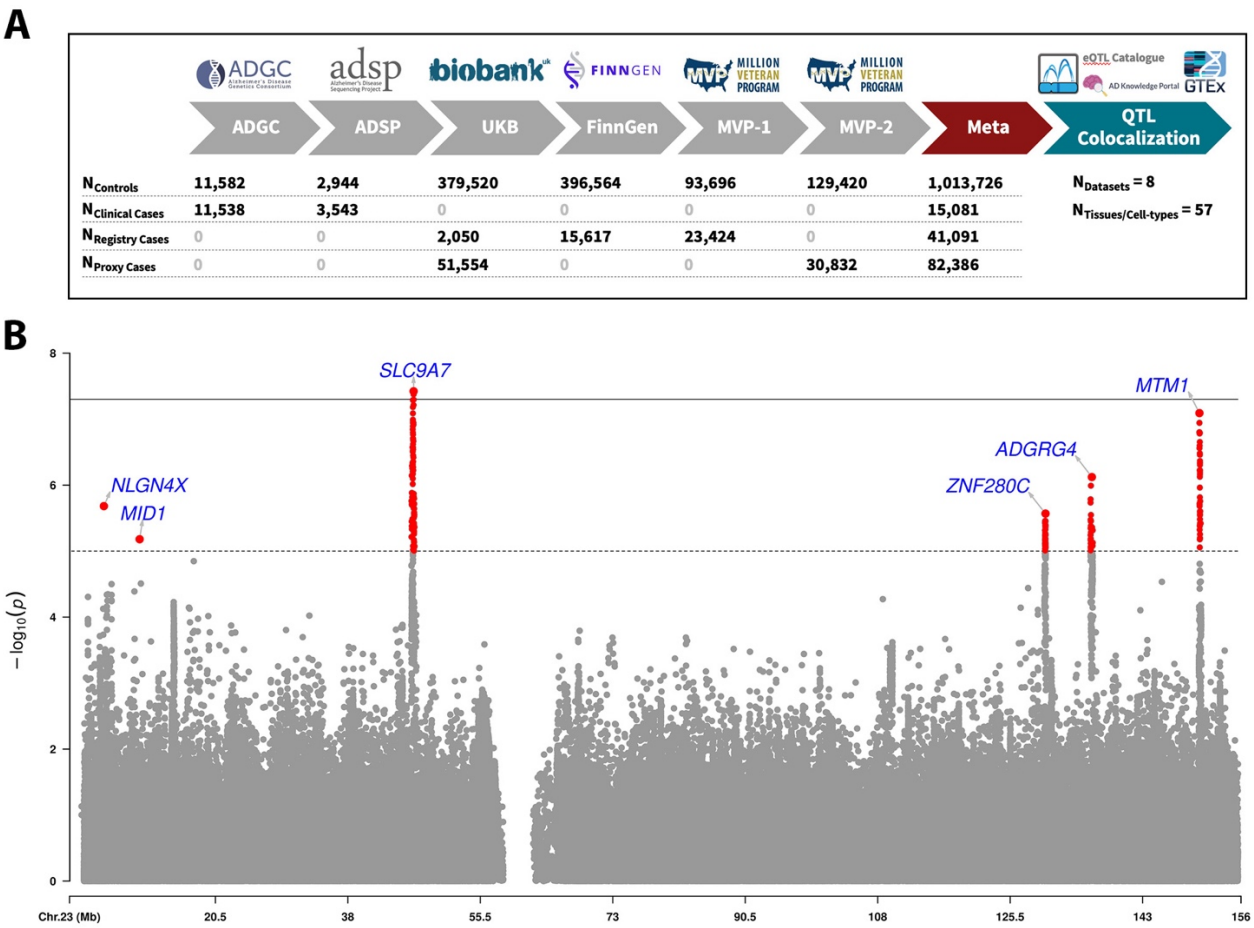

Figure 1. X chromosome-wide association study of Alzheimer's disease. A) Overview of study design and sample sizes. To increase specificity to AD (rather than ADD), the XWAS meta-analysis was intersected to variants with association results in ADGC (which used only clinically confirmed cases and controls). **B)** Manhattan plot for the XWAS meta-analysis. The dotted line indicates X-chromosome-wide significance (P-value<1e-5) and full line indicates genome-wide significance (P-value<5e-8). Lead variants for independent loci are annotated with their nearest protein-coding gene (Gencode v42).

Table 1. X chromosome-wide association study of Alzheimer's disease: Associated lead variants. The Direction column indicates the association effect direction across meta-analyzed cohorts following the order of ADGC, ADSP, UKB, FinnGen, MVP-1 (using health registry status), and MVP-2 (using proxy status). A question mark indicates the variant was not available in the respective cohort. Variants are annotated using dbSNP153. Association signals passing genome-wide significance are bolded.

Lead variant	Nearest protein coding gene	Consequence	BP	EA	OA	No. Subjects	EAF	OR [95%-CI] ‡	P	Direction
rs150798997	*NLGN4X*	intergenic	5,733,126	A	T	1,145,553	0.32%	0.644 [0.537, 0.772]	2.08E-06	- ? - - - -
rs12852495	*MID1*	intronic	10,458,864	T	C	1,151,353	0.26%	1.538 [1.276, 1.855]	6.60E-06	+ + + + + +
rs2142791	***SLC9A7***	**intronic**	**46,691,127**	**C**	**A**	**1,152,185**	**46.12%**	**1.054 [1.035, 1.075]**	**3.78E-08**	**+ + + + + +**
rs209215	*ZNF280C*	intronic	130,251,839	T	C	1,145,797	39.90%	1.048 [1.028, 1.069]	2.70E-06	+ ? + + + +
rs5975709 †	*MAP7D3*	intronic	136,256,153	C	T	1,145,797	43.25%	0.953 [0.935, 0.972]	1.02E-06	- ? - - - -
rs5930938 †	*ADGRG4*	intronic	136,380,525	T	C	733,616	32.62%	0.943 [0.921, 0.965]	7.55E-07	- ? - ? - -
rs146964414	*MTM1*	intronic	150,608,170	T	C	1,152,184	8.23%	1.096 [1.060, 1.133]	8.10E-08	+ - + + + +

‡ The odds ratios are reported with regard to a single active allele. In women, due to random XCI, the relative risk conferred would be half that reported here.

† Rs5975709 was the lead variant in its respective locus, but it had no association results in ADSP and FinnGen. The second most significant variant in this locus, rs5930938, did have association results in FinnGen and was therefore additionally listed to provide additional insight.

Abbreviations: OR, odds ratio; CI, confidence interval; EA, effect allele; OA, other allele; EAF, effect allele frequency; BP, base pair; No., number.

Table 2. Genetic colocalization with quantitative trait locus data. Colocalization was evaluated for genes in each AD associated locus using a 2Mb window centered on the lead variant. Evidence for colocalization was considered at colocalization posterior probability (PP4)>0.7 (bolded). The table presents PP4 results and is restricted to genes and datasets/tissues where at least one colocalization reached PP4>0.7. As such, the table is partitioned into 4 common variant loci that showed colocalization support. Bolded entries with an asterisk (*) indicate the lead variant was also a significant QTL in the respective data/tissue. Missing entries indicate that no QTL data were available. The total number of times a gene was prioritized (PP4>0.7) is summarized to help identify the most likely causal gene per locus (blue bolded genes and numbers). Overlapping datasets were considered as those where subjects partially or fully overlapped (non-overlapping datasets are separated by dashed lines).

			SLC9A7								*ZNF280C*				*ADGRG4*					*MTM1*
Dataset	Tissue	QTL	*ENSG00000286306*	*KRBOX4*	***CHST7***	***SLC9A7***	*RP2*	*JADE3*	*UBA1*	*ELK1*	*ELF4*	*AIFM1*	***ZNF280C***	*RBMX2*	*FHL1*	***MAP7D3***	*BRS3*	*HTATSF1*	*AL683813.2*	***MTMR1***
Wingo et al. 2023 (AD Knowledge Portal)	Brain - Dorsolateral prefrontal cortex	pQTL				0.56	**0.89***		0.05			0.02			0.12	0.05		0.03		0.01
Wingo et al. 2023 (AD Knowledge Portal)	Brain - Dorsolateral prefrontal cortex	eQTL		**0.77***	**0.95***	0.56	0.04	**0.70***	0.04	0.00		0.16	0.45	0.00	**0.78***	**0.93***		0.05		0.05
CommonMind (eQTL Catalogue)	Brain - Dorsolateral prefrontal cortex	eQTL	**0.88**	0.04	**0.92***	**0.86***	0.07	0.07	**0.93***	0.04	0.05	0.12	0.09	0.29	0.13	**0.92***	0.04	0.03		0.16
GTEx	Brain - (9 brain areas)	eQTL		**0.74**	**0.86***	0.64	0.13	0.51	0.12	0.33	0.11	0.56	**0.77***	0.07	0.10	**0.77***	0.04	0.04	0.07	**0.88**
GTEx	Whole blood	eQTL		0.23	0.20	0.39	0.03	0.06	0.07	0.03	0.02	0.19	0.05	0.02	0.02	**0.92***		0.01	0.02	0.01
GTEx	Other (20 tissues not brain or blood)	eQTL		**0.92**	**0.71**	**0.98***	0.14	**0.76**	0.10	0.16	**0.78***	**0.78***	**0.92***	**0.77**	0.13	**0.89***	**0.73**	**0.87***	**0.77**	**0.79**
Fairfax et al. 2014 (eQTL Catalogue)	Monocytes (4 conditions)	eQTL		0.10	0.27	**0.93***	0.50	0.10	0.13	**0.86**	0.01	**0.73**	0.19	0.04	**0.85**	0.13	0.04	0.07		0.18
CEDAR (eQTL Catalogue)	Monocytes	eQTL		0.05	0.15	**0.93***	0.05	0.43	0.12	0.08	0.06	**0.78***	0.04	0.05	0.29	0.08	0.04	0.06		0.11
No. times prioritized across datasets & tissues			1	4	**10**	**12**	1	2	1	1	1	6	**17**	1	2	**10**	1	2	1	**2**
No. times prioritized in non-overlapping datasets			1	2	**3**	**4**	1	2	1	1	1	3	**1**	1	2	**3**	1	1	1	**1**

Abbreviations: QTL, quantitative trait locus; eQTL, expression quantitative trait locus; pQTL, protein quantitative trait locus; No., number.