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RESEARCH ARTICLE

Trans-ethnic genomic informed risk assessment for Alzheimer's disease: An International Hundred K+ Cohorts Consortium study

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Abstract

BACKGROUND: As a collaboration model between the International HundredK+ Cohorts Consortium (IHCC) and the Davos Alzheimer's Collaborative (DAC), our aim

was to develop a trans-ethnic genomic informed risk assessment (GIRA) algorithm for Alzheimer's disease (AD).

METHODS: The GIRA model was created to include polygenic risk score calculated from the AD genome-wide association study loci, the apolipoprotein E haplotypes, and non-genetic covariates including age, sex, and the first three principal components of population substructure.

RESULTS: We validated the performance of the GIRA model in different populations. The proteomic study in the participant sites identified proteins related to female infertility and autoimmune thyroiditis and associated with the risk scores of AD.

CONCLUSIONS: As the initial effort by the IHCC to leverage existing large-scale datasets in a collaborative setting with DAC, we developed a trans-ethnic GIRA for AD with the potential of identifying individuals at high risk of developing AD for future clinical applications.

KEYWORDS
Alzheimer's disease, data sharing, female infertility, genomic informed risk assessment, minority population, polygenic risk score, thyroid, trans-ethnic

1 | BACKGROUND

Alzheimer's disease (AD) is characterized by irreversible neuronal degeneration with no cure to date.[1] AD affects all human populations with the prevalence of 8.4% to 13.8% in people aged ≥65 years according to the Centers for Disease Control and Prevention (CDC; https://www.cdc.gov/media/releases/2018/p0920-alzheimers-burden-double-2060.html). Early diagnosis of AD may enable early intervention to minimize the damage to the central nervous system.[2] With older age and female sex as the known risk factors,[3] AD has been recognized as a complex multifactorial genetic disease.[4] The apolipoprotein E (*APOE*) gene variants have been established as a major susceptibility locus for AD.[5] *APOE* is a major apoprotein of the lipoproteins chylomicron and very low density lipoproteins (VLDL), with the function of lipid transportation.[6] While the *APOE* action remains unclear in AD, the observed associations with the two pathological hallmarks of the disease, including extracellular amyloid beta (Aβ) plaques and intraneuronal tau pathology, as well as contributions to neural network deficits and neuroinflammation, suggest an important role for *APOE* in AD.[7–9]

Human *APOE* has three common genetic isoforms, *APOE* ε2 (112Cys-158Cys), *APOE* ε3 (112Cys-158Arg), and *APOE* ε4 (112Arg-158Arg), with different amino acid residues at positions 112 and 158 in the N-terminal domain.[9,10] The *APOE* genetic isoforms are determined by two single nucleotide polymorphisms (SNPs): (1) rs429358 (hg38, chr19:44908684:T:C) causes amino acid substitution of Cys to Arg at residue 112 and (2) rs7412 (hg38, chr19:44908822:C:T) causes amino acid substitution of Arg to Cys at residue 158.[11] Among the three *APOE* isoforms encoded by three haplotypes of rs429358 and rs7412 SNPs, the *APOE* ε3 haplotype has the most common frequency in all populations studied to date, including African populations.[12,13] Compared to the *APOE* ε3 haplotype, *APOE* ε2 is protective against AD, and *APOE* ε4 is predisposing to AD with an odds ratio (OR) value about two to four for heterozygous carriers.[12,14,15] Despite the large genetic effect, however, the *APOE* locus alone is insufficient to explain the genetic susceptibility to AD. A large number of genetic loci associated with AD, for example, WASH complex subunit 3 (*WASHC3*), bridging integrator 1 (*BIN1*), complement C3b/C4b receptor 1 (Knops blood group; *CR1*), and cathepsin B (*CTSB*), have recently been identified in the genome-wide association studies (GWAS) by Jun et al.[16] and Bellenguez et al.[17] with large sample sizes including participants with different ancestries. Additional genetic information from these AD loci may improve the risk prediction of AD and the identification of patients with high risk of AD.

In this study, we developed a genomic informed risk assessment (GIRA) algorithm for AD with both the *APOE* isoforms and the polygenic risk score (PRS) calculated by the multiple AD loci identified in previous GWAS,[16,17] as well as known non-genetic risk factors of AD including age and sex. The PRS aggregated the effects of GWAS loci other than the *APOE* locus into a single score, an approach that has been shown as an effective approach to identify patients with high risk of many complex diseases.[18–20] In particular, a PRS with selected loci has been demonstrated for precise prediction of type 1 diabetes (T1D).[21] Compared to AD with *APOE* as a major genetic locus plus a number of minor loci, T1D has also the human leukocyte antigen (*HLA*) region as a major genetic locus plus a number of minor loci.[21] Nowadays, the major challenge in GIRA models is potential health disparities due to the lack of genomic information in minority or understudied populations.[22] In many cases, effective GIRA models relying on data from large-sample GWAS are only available for the European population as the majority of GWASs have been done in people with European ancestry.[23] With the aim to

RESEARCH IN CONTEXT

1. **Systematic Review**: By literature review, the authors identified the major genetic risk factors of Alzheimer's disease (AD) to develop a genomic informed risk assessment (GIRA) algorithm for AD, including both the apolipoprotein E isoforms and the polygenic risk score calculated by the multiple AD loci.
2. **Interpretation**: We validated the performance of the GIRA model in different populations; the proteomic study in the participant sites gained insights into the molecular mechanisms of AD.
3. **Future Directions**: The International HundredK+ Cohorts Consortium (IHCC) has brought together large-scale cohorts of diverse populations from around the world, and presents a rich resource of data for collaborative research with trans-ethnic focus.

eliminate genomics-related health disparities, we leveraged an international effort supported by the International HundredK+ Cohorts Consortium (IHCC),[24] which has brought together large-scale cohorts of diverse populations from around the world, who have genome-wide genotype data.

2 | METHODS

This study was exempted by the institutional review board of the Children's Hospital of Philadelphia, USA. Human participant personal information was not shared with the research group and participants were de-identified. All human participants or their proxies provided written informed consent for their respective studies and all the studies were approved by their local and/or national ethics review boards.

2.1 | Genotyping

The genotyping data was imputed with the TOPMed (version R2 on GRC38) Reference Panel at the Trans-Omics for Precision Medicine imputation server (https://imputation.biodatacatalyst.nhlbi.nih.gov), or the Haplotype Reference Consortium (HRC) panel at the Michigan imputation server (https://imputationserver.sph.umich.edu), or the Sanger Imputation Service (African reference panel), at each participant site. No quality issue was reported for the imputation of any of the SNP markers in the GIRA model from any of participating sites. In case of quality issues for the imputation, to find alternative SNP markers based on the specific population and the genotyping arrays would be done in house upon request.

2.2 | *APOE* haplotyping

The *APOE* haplotypes were inferred from the two SNPs rs429358 and rs7412, that is, *APOE* ε2 = rs429358/T-rs7412/T; *APOE* ε3 = rs429358/T-rs7412/C; *APOE* ε4 = rs429358/C-rs7412/C.

2.3 | GWAS loci

The GWAS loci were identified by the Stage I studies from Jun et al.[16] and Bellenguez et al.[17] The study by Jun et al. included cases/controls with European ancestry (EA, n = 13,100/13,220), African Americans (AA, n = 1,472/3,511), Japanese (JPN, n = 951/894), and Israeli-Arab (IA, n = 51/64).[16] The study by Bellenguez et al. included 2447 diagnosed cases, 46,828 proxy cases of dementia and 338,440 controls, all with European ancestry.[17] Multi-allelic variants, indels, and rare SNPs with minor allele frequency <3% were excluded from further analysis. The remaining variants from the combined summary stats were linkage disequilibrium pruned using an R^2 threshold of 0.3 resulting in a final list of 74 variants (Table S1 in supporting information).

2.4 | GIRA model

The GIRA model includes three components, that is, *APOE* haplotype; PRS by genomic markers; and covariates including age, sex, and the first three principal components of population substructure for genetic ancestry correction. The PRS is calculated by the weighted sum of the effect alleles, while weights are the reported ORs.

2.5 | Validation of PRS models

The PRS markers were first validated for their allele frequencies in 4145 ancestrally diverse dementia patients from the Electronic Medical Records and Genomics (eMERGE) consortium Phase I to III dataset. Subsequently, the scoring algorithm, SNPs, and weights, as well as detailed instructions, were disseminated to participant sites (Table 1). Scores were generated on a total of 25,786 participants across a variety of endpoints and returned to the Children's Hospital of Philadelphia (CHOP) for collation. Each site was requested to follow standardized reporting metrics. As all groups did not have accurate age at onset data, we requested ORs rather than hazard ratios for the phenotype outcomes (Table 1). The cohort validations were performed at four participant sites, including Korea pheno1/Korea pheno2, East London, Japan, and UK Biobank (UKB) white. Without gold standard for AD diagnosis,[25] we acknowledge the phenotypic heterogeneity in this multinational study, and we also highlight the potential clinical importance of a transethnic PRS to assist with the AD diagnosis. Korea pheno1 and Korea pheno2 were from the Biobank Innovations for Chronic Cerebrovascular Disease with Alzheimer's Disease Study (BICWALZS) as a Korea Biobank Project.[26] Korea pheno1 defined

TABLE 1 Sites participating in the validation.

Site	Genetic ancestry	Phenotypic outcome	*N* (case/control)
Validation of PRS models			
National Center for Geriatrics and Gerontology (NCGG) Biobank	Japanese (East Asian)	AD, MCI	Case:1000 Normal Cognitive:1000
East London Genes and Health cohort	British-Pakistani/British-Bangladeshi (South Asian)	All-cause dementia (from secondary/primary care records); MCI/cognitive decline cases excluded	104 cases; 614 controls
Korean Biobank Project	Korean (East Asian)	Phenotype 1: cortical amyloid positivity (by flutemetamol PET imaging) (control: cortical amyloid negativity)	191:337 (total 528)
		Phenotype 2: CDR global score ≥1 (control: CDR global ≤0.5)	157:539 (total 696)
UKBiobank	European (White British)	ICD-9/10 diagnoses of AD/dementia derived from hospital in-patient records or patients with date of AD/dementia report	2923 cases; 226,342 controls
Proteomics study			
The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)	Brazilian (admixed)		
INTERVAL (UK Blood Donors)	European (White British)	Stroop Test (attention and reaction times), Trail Making Test (executive function), Pairs Test (episodic memory), Reasoning Tests (intelligence), > 3K proteins on the SomaLogic proteomics platform	≈9k cognitive measure; 1140 proteomics
PRS scores in African populations			
Africa Wits-INDEPTH partnership for genomic studies (AWI-Gen)	African (different ethnolinguistic and geographic groups)	Not assessed for AD	Population cross-sectional cohort: n = 10,700

Abbreviations: AD, Alzheimer's disease; CDR, Clinical Dementia Rating; ICD, International Classification of Diseases; MCI, mild cognitive impairment; NA, not applicable; PET, positron emission tomography; PRS, polygenic risk score.

cases by cortical amyloid positivity in flutemetamol positron emission tomography (PET) imaging.[26] Brain amyloid PET positivity is sensitive and specific for the diagnosis of amyloid pathology,[27] which was detected in 72% of AD cases in the BICWALZS study.[26] Korea pheno2 defined cases by Clinical Dementia Rating (CDR) global score ≥1.[28] The Japan cohort included cases with AD or mild cognitive impairment (MCI) from Japan's National Center for Geriatrics and Gerontology (NCGG).[29] The AD diagnosis was based on the clinical criteria by the National Institute of Neurological and Communicative Diseases and Stroke--Alzheimer's Disease and Related Disorders Association Work Group,[30] and the MCI diagnosis was based on expert recommendations by Petersen et al.[31] The East London cohort was based on a community-based, British Bangladeshi and British Pakistani population. The cases included all-cause dementia from secondary/primary care records with MCI/cognitive decline cases excluded.[32] The UKB White cohort defined cases by International Classification of Diseases, 9th/10th revision diagnoses of AD/dementia (https://www.ukbiobank.ac.uk/).[33]

Each validation site was required to return:

1. The OR per standard deviation of the PRS distribution with 95% confidence interval (CI).
2. Estimate of model discrimination (Area under the receiver operating characteristic [ROC] curve [AUC]) with 95% CI of (A) the non-*APOE* PRS alone; (B) the PRS and *APOE* status; (C) the non-genetic predictors alone; (D) the full model.
3. Tail discrimination: We set the cutoff for the high-risk group at 97.5% of the PRS. The ORs and 95% CI (and the *P*-value for the OR) were calculated by comparing the high-risk group versus everybody else. That is, the participants in the top 2.5% of the PRS versus the bottom 97.5%.
4. The sensitivity/specificity as well as negative predictive values (NPV) and positive predictive values (PPV) at the proposed cutoff (split by ancestry if appropriate for each cohort).

The NPV/PPV used prevalence-adjusted metrics, that is, PPV = (Sn * Pr) / ([Sn * Pr] + [(1 − Sp) * (1 − Pr)]) and NPV = (Sp * [1 − Pr]) / ([Sp

TABLE 2 Validation of PRS models (95% CIs).

Cohort	Odds ratio per SD	AUC with PRS only	AUC with genetic predictors (PRS and *APOE* haplotypes)	AUC with non-genetic covariates only	AUC with the full GIRA model[a]
Korea pheno1	1.186 (0.992—1.418)	0.548 (0.497—0.600)	0.677 (0.628—0.726)	0.627 (0.576—0.677)	0.751 (0.705—0.796)
Korea pheno2	1.040 (0.871—1.243)	0.507 (0.456—0.559)	0.612 (0.560—0.664)	0.545 (0.493—0.597)	0.637 (0.586—0.689)
East London	1.110 (0.940—1.330)	0.530 (0.470—0.590)	0.540 (0.480—0.600)	0.680 (0.610—0.750)	0.690 (0.620—0.760)
Japan	1.120	0.545 (0.520—0.570)	0.607 (0.582—0.632)	0.616 (0.591—0.641)	0.625 (0.601—0.650)
UKB White	1.003 (0.990—1.007)	0.527 (0.516—0.537)	0.542 (0.532—0.553)	0.780 (0.773—0.787)	0.746 (0.738—0.754)

[a]The full GIRA model: the model with PRS, *APOE*, and non-genetic covariates.
Abbreviations: *APOE*, apolipoprotein E; AUC, area under the curve; CI, confidence interval; GIRA, genomic informed risk assessment; PRS, polygenic risk score; SD, standard deviation; UKB, UK Biobank.

* (1 – Pr)] + [(1 – Sn) * Pr]) where Sn = sensitivity, Sp = specificity, and Pr = population-based prevalence reflective of the study population.

2.6 | Proteomics study at two participant sites

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) enrolled 15,105 civil servants aged 35 to 74 years living in six cities, addressing the incidence of non-communicable diseases. From the 15,105 participants, 9333 DNA samples were analyzed for genetic ancestry using a software tool for maximum likelihood estimation of individual ancestries from multi-locus SNP genotype datasets.[34] The INTERVAL BioResource recruited 45,263 whole blood donors (22,466 men and 22,797 women) between June 11, 2012, and June 15, 2014.[35] Donors were aged ≥18 years from 25 National Health Service Blood and Transplant (NHSBT) blood donation centers distributed across England. In addition to the GIRA validation at these two sites, the PRS scores were tested for association with 3282 plasma protein targets from the SomaLogic proteomics platform (SomaLogic Inc.).

2.7 | Exploration of the PRS model in African populations

Without an African cohort of AD patients, we explored the distribution of the PRS scores in African populations in the Africa Wits-INDEPTH Partnership for genomic studies (AWI-Gen) leveraging its access via the IHCC resources.[36] African populations from three geographic regions (south—South Africa; east—Kenya; and west—Ghana/Burkina Faso) were assessed.

3 | RESULTS

The genetic markers for the PRS model were polymorphic and informative in 4145 ancestrally diverse dementia patients from the eMERGE consortium (Table S2 in supporting information). Four cohorts from three sites, Korea Biobank, NCGG, and East London Genes & Health, reported results of the PRS in dementia cases versus controls (Table 2).

TABLE 3 Correlation of *APOE* haplotypes with apoE protein levels.

Proteomics ID	R^2	*P*	Beta	SE
APOE.2937.10.2 (isoform ε3)	6.55E-03	.0057	16.9	6.11
APOE.5312.49.3 (isoform ε2)	0.00475	.0194	15.03	6.42

Abbreviations: *APOE*, apolipoprotein E; SE, standard error.

Except the UKB White cohort, the best performance of prediction of dementia was by the full GIRA model with combination of the PRS component, the *APOE* haplotypes, and the non-genetic covariates. In the risk prediction, either genomic markers alone or non-genetic factors alone is insufficient, while the combined usage of genetic risk factors and non-genetic factors increased the performance of the prediction model. Most importantly, all four cohorts in Table 2 were non-European. A random effects restricted maximum likelihood (REML) meta-analysis of the four AUCs and their variance was 0.674 (0.643–0.706), indicating the potential of a prediction model in the non-European populations.

Further, to assess the potential application of the PRS in African populations, the PRS model was examined in the continental African AWI-Gen cohort including participants from across the continent (https://www.wits.ac.za/research/sbimb/research/awi-gen/)[37,38] to determine whether the SNP markers forming the PRS are polymorphic and informative in African populations from different geographic regions. As shown, the score is normally distributed with similar variance across African populations (Figure S1 in supporting information), indicating it is suitable for use in populations of African ancestry.

In addition to the validation of the prediction model, two sites, ELSA Brazil and INTERVAL UK reported results of the score as well as results from plasma proteomic analysis. The proteomics analysis showed correlation with *APOE* haplotypes, including also with blood *APOE* levels across two separate peptides (Table 3). Correlation of 99 proteins with the full PRS model were also observed with $P < .05$ (Table S3 in supporting information). Using the WebGestalt (WEB-based Gene Set Analysis Toolkit) web tool, over-representation analysis (ORA) of the correlated genes by the DisGeNET approach, highlighted the genes (*CEBPB*, *FSHB*, *LEP*, *LHB*, *LIF*) in the gene set C0021361:Female infertility with false discovery rate (FDR) = 0.0066779 (Table 4). ORA by the

TABLE 4 Genes in the gene-set C0021361:Female infertility associated with AD PRS.

Gene symbol	PRS_R^2	*P*	Beta	SE	Gene name
CEBPB	0.004	.032	15.645	7.274	CCAAT enhancer binding protein beta
FSHB	0.003	.018	−13.862	5.871	Follicle stimulating hormone subunit beta
LEP	0.004	.035	−15.106	7.147	Leptin
LHB	0.002	.036	−12.101	5.765	Luteinizing hormone beta polypeptide
LIF	0.003	.049	−13.995	7.109	LIF, interleukin six family cytokine

Abbreviations: AD, Alzheimer's disease; PRS, polygenic risk score; SE, standard error.

GLAD4U approach highlighted the gene sets PA445859:Thyroiditis, Autoimmune (FDR = 0.017306, including *CD3G*, *CGA*, *CXCL9*, *FAS*, *LILRB1*), PA444172:Fetal Growth Retardation (FDR = 0.044508, including *IGF1*, *IGFBP3*, *LEP*, *SELP*, *TMEM70*), and PA443588:Cachexia (FDR = 0.044508, including *IGF1*, *LEP*, *LIF*, *SELP*). Together, these results demonstrate enrichment of several genes that influence AD risk, as well as risks for multiple other conditions, including but not limited to female infertility, thyroiditis, and autoimmunity. These results warrant further evaluation for risk optimization.

4 | DISCUSSION

As one of the first IHCC multinational studies, we demonstrate the feasibility of developing a trans-ethnic AD GIRA model that is predictive of disease predisposition across diverse populations, globally. In this regard, the IHCC project served as an important resource to examine GIRA and PRS in under-represented populations in genomic studies. The GIRA model performed better than the PRS model in East Asian populations from Japan and Korea, and in South Asian populations of Pakistani/Bangladeshi origin recruited throughout the UK. While lacking a well-phenotyped AD cohort of African origin with genetic data, we demonstrate a normal distribution of the PRS scores in different regions in Africa, suggesting that the current PRS score system is potentially informative in African populations. Further assessment of the PRS model in African AD patients is warranted.

Enabled by risk prediction using GIRA, and with more attention given to the high-risk patients, this will consequently enable early diagnosis and early intervention for the disease. In addition to its clinical potential, this study uncovered associations between the AD PRS scores and other disease-related gene sets in the ELSA-Brasil and INTERVAL studies, leading to novel insights into the pathogenesis of AD. In this regard, we identified association of the AD PRS and genes related to female infertility. Clinically, it has been observed that parity is inversely associated with risk of AD.[39] The genes related to female infertility identified in this study help explain the increased risk of AD in women, as well as the molecular mechanisms of the pathogenesis of AD in women and how parity decreases the risk of AD. Among the five genes related to female infertility identified (Table 4), the lowest *P*-value was seen between PRS and lower level of follicle stimulating hormone subunit beta (encoded by *FSHB*). The physiological function of follicle-stimulating hormone is to induce egg and sperm production.[40] Genetic variants of *FSHB* have been shown to cause hypogonadotropic hypogonadism in women and men.[41,42] With the *FSHB* gene as a potential mediator of the pathogenesis of AD, it may also help to explain the clinical correlation between hypogonadism and AD.[43] More importantly, *FSHB* may represent a new opportunity to develop hormone therapy for AD.[44,45] In addition, previous studies have demonstrated correlations between abnormal levels of thyroid-stimulating hormone and the risk of AD.[46] While further studies are warranted, our study identified five genes that may mediate this correlation.

Given the increased recognition of limitations of PRS,[47] we examined GIRA and PRS in under-represented populations, and show the GIRA model performed better than the PRS model. Moreover, we were able to leverage the proteomics biomarker data to support the molecular mechanisms of the underlying pathogenesis of AD through the PRS associations with proteomic biomarkers, using statistical measures. In conclusion, given that this is the first effort by the IHCC to leverage large existing datasets that reside within the IHCC consortium for a trans-ethnic GIRA on AD, we envision an opportunity to scale this to other cohorts within the consortium and expand the number of traits that can be analyzed. As such, the IHCC presents a rich resource of data for collaborative research with trans-ethnic focus, where there is much unmet need at present as this is an area of research that has been largely neglected. We also need to emphasize that this is a proof-of-principle study for an international effort to develop a trans-ethnic GIRA model for precision medicine, whereas to improve the GIRA model as suggested by the currently limited AUC scores is still warranted through further international efforts. As our research efforts continue, we envision efficient data sharing across academia and industry, where we will focus on improving patient health-care services for AD and other diseases as well as biomedical research discoveries, leveraging our established GIRA approach.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

Supporting data from this study can be obtained by emailing the corresponding author Dr. Hakon Hakonarson.

CONSENT FOR PUBLICATION

All authors have provided consent for publication of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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