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Modeling common Alzheimer's disease with high and low polygenic risk in human iPSC: A large-scale research resource

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SUMMARY

Common forms of Alzheimer's disease (AD) are complex and polygenic. We have created a research resource that seeks to capture the extremes of polygenic risk in a collection of human induced pluripotent stem cell (iPSC) lines from over 100 donors: the IPMAR Resource (iPSC Platform to Model Alzheimer's Disease Risk). Donors were selected from a large UK cohort of 6,000+ research-diagnosed early or late-onset AD cases and elderly cognitively healthy controls, many of whom have lived through the age of risk for disease development (>85 years). We include iPSC with extremes of global AD polygenic risk (high-risk late-onset AD: 34; high-risk early-onset AD: 29; low-risk control: 27) as well as those reflecting complement pathway-specific genetic risk (high-risk AD: 9; low-risk controls: 10). All iPSC have associated clinical, longitudinal, and genetic datasets and will be available through collaboration or from cell (EBiSC) and data (DPUK) repositories.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and impaired daily functioning. At the core of Alzheimer's pathology is the accumulation of β -amyloid plaques and neurofibrillary tangles composed of hyperphosphorylated tau in the brain and the degeneration and death of neurons (Serrano-Pozo et al., 2011).

AD is broadly categorized into early onset (EOAD, \sim 5% of cases), occurring before the age of 65, and late onset (LOAD, \sim 95% of cases), typically manifesting after 65 (Reitz et al., 2020). Both categories appear to have a strong genetic component, with heritability estimates between 92% and 100% for EOAD and 60% and 80% for LOAD (Wingo et al., 2012). Within EOAD, approximately 10% of cases occur as a result of causal fully penetrant mutations in the genes encoding either amyloid precursor protein or presenilin 1 and 2 (Wingo et al., 2012); this form of disease is often referred to as familial AD (FAD). This can be contrasted with sporadic or "common" AD (EOAD and LOAD), which has no known autosomal-dominant cause and is contributed to by a combination of genetic and environmental risk factors. The apolipoprotein $\varepsilon 4$ allele (APOE $\varepsilon 4$) is the most penetrant genetic risk variant for common AD, with reported odds ratio between 3.62 and 34.3, depending on the population examined (Belloy et al., 2023; Kukull et al., 1996; Saddiki et al., 2020). In addition to *APOE* ϵ 4, common AD heritability has been associated with >70 common and rare genetic variants, identified by genome-wide association studies (GWASs) (Bellenguez et al., 2022). These genetic variants implicate roles for immune responses, complement, endocytosis, and lipid transport in AD pathogenesis, in addition to amyloid- β and tau processing (Sims et al., 2020).

Researchers can use a technique called polygenic risk score (PRS) analysis to quantify an individual's genetic susceptibility to developing common AD. PRS aggregates information from all identified genetic variants known to impact the overall risk of developing AD. By assessing an individual's genetic profile and summing up the effects of these variants, a PRS value provides a personalized estimate of an individual's likelihood of developing AD. While not a definitive predictor, the PRS offers valuable insights into the genetic component of Alzheimer's and is able to predict an individual's risk of developing the disease with 84% accuracy (Escott-Price et al., 2017).

Various models are employed to explore the mechanisms of AD, each with its own set of advantages and limitations. This includes *in vivo* and *in vitro* work using mouse models



and induced pluripotent stem cell (iPSC)-derived models containing autosomal-dominant mutations in genes associated with FAD (Drummond and Wisniewski, 2017; McKean et al., 2021; Penney et al., 2020; Raska et al., 2021). While these studies have allowed for many advances in our understanding of AD, in humans, there is significantly more severe neurofibrillary tangle formation and cerebral amyloid angiopathy in FAD than common AD, suggesting differences in the disease course (Ringman et al., 2016). Moreover, various crucial differences exist between mice and humans, which can limit translation of findings to human patients, including numerous differences in innate immune responses, known to be important in AD development (Drummond and Wisniewski, 2017; Franco Bocanegra et al., 2018; Mancuso et al., 2019). Other AD models have been engineered to contain single diseaseassociated single-nucleotide polymorphisms (SNPs) uncovered in genome-wide associated studies of common AD (Ganesan et al., 2024; Tran et al., 2023). While providing researchers with insight into specific pathways affected in AD, these models ignore the complexity and diversity of the genetic architecture of common AD (Sims et al., 2020).

Use of patient-derived iPSC is transforming many aspects of disease research. These iPSC can be generated by reprogramming patient tissues (e.g., blood or skin), prior to differentiation into any cell type of interest (Al Abbar et al., 2020). When using patient-derived iPSC to study common AD, it is crucial to consider the substantial genetic variation between individual donors (Sims et al., 2020). These variations are often unrelated to the AD phenotype, necessitating a large sample size to accurately distinguish differences between patient and control-derived cell lines and mitigate the noise introduced by these genetic variants (Sims et al., 2020). However, the fact that patient-derived iPSC retain the unique genetic makeup of the individual also presents as a huge advantage for researchers who wish to accurately represent and understand the common AD phenotype, as it allows researchers to model the genetic contribution to AD, and in particular the polygenicity of common AD (Sims et al., 2020). Existing large iPSC resources using common AD donors do not select donors based on their polygenic risk for the disease (Kondo et al., 2022; Lagomarsino et al., 2021). In order to accurately dissect the effect of common AD on cell function, it is important to utilize iPSC resources in which donors have been selected based on both their disease status and underlying genetic predisposition. It is evident that individuals with common AD each possess a unique set of genetic variants that influence disease risk. Therefore, by utilizing a large cohort of genetically informed samples, researchers can stratify individuals based on their specific genetic risk profiles. This stratification, when combined with data from functional cell assays or patient symptom analyses, could enable the identification of different underlying molecular dysfunctions within different patient cohorts. Consequently, this approach paves the way for personalized medicine in AD.

Here, we have selected and generated 109 iPSC lines: 63 from patients with common AD with high global PRS (including 34 from patients with LOAD and 29 from patients with EOAD), 27 from age-matched healthy controls with a low global PRS for common AD, 9 from patients with common AD with high complement pathway-specific PRS (henceforth termed "complement PRS"), and 10 from healthy controls with low complement PRS. We have named this iPSC resource IPMAR (iPSC Platform to Model Alzheimer's disease Risk) as a major new iPSC resource to capture both high and low polygenic risk for common AD, alongside knowledge of diagnosed AD vs. control status. Large iPSC resources such as this one provide a comprehensive and patient-reflective disease model for drug screening that cannot be achieved using small numbers of FAD or common AD lines, which do not reflect the substantial genetic diversity underlying AD (Sims et al., 2020). Furthermore, this invaluable resource can be used to explore molecular and cellular mechanisms underlying common AD. Given the aforementioned advantages of IPMAR, our resource has potential to facilitate the identification of potential AD therapeutics with widespread clinical relevance.

RESULTS

Sample selection and generation

Donors were selected from participants within the Alzheimer's Disease Cardiff Cohort (ADCC) using the aforementioned criteria. Following identification, cryopreserved peripheral blood mononuclear cells (PBMCs) were used to generate iPSC lines from the samples, with recent ("fresh") donations prioritized, as detailed in Tables 1 and 2. 109 iPSC lines were generated in total. This comprised 90 lines selected with extremes of global AD PRS: 34 from LOAD donors (mean AD PRS 2.2 ± 0.5 SD, age of onset 72 ± 6 SD, 56% female), 29 from EOAD donors (mean AD PRS 2.1 \pm 0.4 SD, age of onset 51 \pm 3 SD, 55% female), and 27 from cognitively healthy controls (mean AD PRS -1.9 ± 0.4 SD, 59% female). For more information on cell line donors used for global AD PRS iPSC, see Table 1. Also included were 19 lines selected with extremes of complement PRS: 9 from LOAD donors (mean complement PRS 2.4 \pm 0.3 SD, age of onset 71 \pm 6, 78% female) and 10 from cognitively healthy controls (mean complement PRS -1.9 ± 0.2 SD, 70% female). For more information on cell line donors used for complement PRS iPSC, see Table 1. Within this paper, the line DRICUi011-A is used



Table 1. Cell line donor information for global AD PRS iPSC APOE Cell line ID Status Sex AA0 AAI ϵ -alleles AD PRS Fresh/stored Availability DRICUi002-A LOAD F EBiSC 70 96 33 2.00 stored DRICUi003-A EOAD F EBiSC 58 68 44 2.52 stored DRICUi004-A LOAD F EBiSC 68 71 44 3.06 stored DRICUi005-B LOAD F 74 **EBiSC**^a 68 44 3.23 stored DRICUi006-A EBiSC LOAD М 77 79 33 1.84 stored DRICUi007-A LOAD EBiSC М 70 74 34 2.08 stored DRICUi008-A EBiSC^a control М N/A 88 33 -1.68stored F DRICUi009-B EBiSC^a control N/A 80 33 -1.24stored DRICUi010-A LOAD F 68 77 33 2.17 EBiSC fresh LOAD DRICUi011-A М 70 80 33 2.66 EBiSC fresh DRICUi012-A LOAD EBiSC F 67 69 34 2.20 fresh DRICUi013-A LOAD 2.81 EBiSC Μ 67 76 44 fresh DRICUi014-A F 89 EBiSC control N/A 33 -1.68fresh F EBiSC^a DRICUi015-A control N/A 95 33 -1.03fresh DRICUi016-A LOAD F 71 33 2.83 EBiSC 66 fresh F EBiSC DRICUi017-A LOAD 74 68 34 2.40 fresh DRICUi018-A LOAD М 67 78 44 2.63 fresh EBiSC LOAD F DRICUi019-A 76 3.20 EBiSC^a 66 44 fresh DRICUi020-A control М N/A 83 33 -1.77fresh **EBiSC**^a DRICUi021-A F EBiSC^a control 73 33 -2.51fresh N/A DRICUi022-A control F N/A 80 33 -1.50fresh EBiSC LOAD EBiSC DRICUi023-A М 77 2.33 68 33 fresh DRICUi024-A LOAD F 84 88 34 2.85 stored EBiSC^a EBiSC DRICUi025-A control Μ N/A 82 33 -2.61fresh DRICUi026-A control М N/A 92 33 -1.69fresh EBiSC DRICUi027-A LOAD 75 EBiSC М 80 2.07 34 stored DRICUi028-A LOAD М 68 72 34 2.44 stored EBiSC DRICUi029-A LOAD F 69 74 34 2.21 EBiSC stored DRICUi030-A control F N/A 76 33 -2.27EBiSC^a stored LOAD F 79 EBiSC^a DRICUi031-A 81 2.29 33 stored

DRICUi032-A

DRICUi033-A

DRICUi034-A

DRICUi036-A

LOAD

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(Continued on next page)

EBiSC^a

EBiSC^a

EBiSC^a

EBiSC^a

stored

fresh

stored

stored



Table 1. Continued

Cell line ID	Status	Sex	AAO	ΔΔΤ	APOE e-alleles	AD PRS	Fresh/stored	Availability
DRICUi037-A	control	F	N/A	77	33	-1.43	stored	EBiSC ^a
DRICUi038-A	control	м	N/A	76	33	-2.83	stored	EBiSC ^a
DRICUi039-A	control	м	N/A	71	33	-1.41	stored	EBiSC ^a
DRICUi040-A	control	м	N/A	79	33	-1.91	stored	EBiSC ^a
DRICUi041-A	LOAD	F	89	93	33	1.83	stored	EBiSC ^a
DRICUi042-A	LOAD	F	74	80	33	1.76	stored	EBiSC ^a
DRICUi043-A	LOAD	F	78	96	33	2.28	stored	EBiSC ^a
DRICUi044-A	control	м	N/A	73	33	-1.52	stored	EBiSC ^a
DRICUi045-A	LOAD	М	78	79	33	1.38	stored	EBiSC ^a
DRICUi046-A	control	F	N/A	73	33	-1.44	stored	EBiSC ^a
DRICUi047-A	LOAD	F	70	72	33	1.84	stored	EBiSC ^a
DRICUi048-A	LOAD	М	70	76	33	1.86	stored	on request ^a
DRICUi049-A	LOAD	М	66	71	33	1.76	stored	EBiSC ^a
DRICUi050-A	LOAD	М	68	72	33	1.78	stored	EBiSC ^a
DRICUi051-A	control	F	N/A	81	33	-1.85	stored	on request ^a
DRICUi052-A	control	М	N/A	81	33	-2.16	stored	EBiSC ^a
DRICUi053-A	LOAD	F	74	82	33	1.80	stored	EBiSC ^a
DRICUi054-A	LOAD	F	79	84	33	1.78	stored	EBiSC ^a
DRICUi055-A	LOAD	М	83	86	34	1.86	stored	EBiSC ^a
DRICUi056-A	EOAD	F	53	57	33	1.95	stored	on request ^a
DRICUi057-A	EOAD	М	48	53	33	1.94	stored	on request ^a
DRICUi058-A	EOAD	F	51	56	34	2.08	stored	on request ^a
DRICUi059-A	EOAD	F	52	55	33	1.94	stored	on request ^a
DRICUi060-A	EOAD	F	54	60	33	1.85	stored	on request ^a
DRICUi061-A	EOAD	М	51	57	33	1.80	stored	on request ^b
DRICUi062-A	EOAD	М	54	57	33	1.73	stored	on request ^a
DRICUi063-A	EOAD	F	47	53	34	2.06	stored	on request ^b
DRICUi064-A	EOAD	F	53	59	33	3.03	stored	on request ^a
DRICUi065-A	EOAD	F	50	56	33	2.55	stored	on request ^b
DRICUi066-A	EOAD	F	45	71	33	2.47	stored	on request ^b
DRICUi067-A	EOAD	М	50	69	33	1.64	stored	on request ^b
DRICUi068-A	EOAD	F	50	57	33	1.64	stored	on request ^a
DRICUi069-A	EOAD	F	53	59	34	2.68	stored	on request ^b
DRICUi070-A	EOAD	М	54	58	33	2.35	stored	on request ^a

(Continued on next page)



Table 1. Continued

					APOE			
Cell line ID	Status	Sex	AAO	AAI	ε-alleles	AD PRS	Fresh/stored	Availability
DRICUi071-A	EOAD	F	53	55	33	2.27	stored	on request ^b
DRICUi072-A	EOAD	М	47	54	33	2.22	stored	on request ^a
DRICUi073-A	EOAD	F	54	59	34	2.41	stored	on request ^b
DRICUi074-A	EOAD	М	51	56	34	2.38	stored	on request ^b
DRICUi075-A	EOAD	F	54	59	33	2.19	stored	on request ^b
DRICUi076-A	control	М	N/A	65	33	-1.88	stored	on request ^a
DRICUi077-A	EOAD	М	45	60	33	2.21	stored	on request ^b
DRICUi078-A	EOAD	F	54	56	33	1.53	stored	on request ^b
DRICUi079-A	EOAD	М	53	62	34	2.35	stored	on request ^a
DRICUi080-A	control	F	N/A	78	33	-2.34	stored	on request ^b
DRICUi081-A	control	F	N/A	78	33	-1.82	stored	on request ^b
DRICUi082-A	control	F	N/A	65	33	-1.71	stored	on request ^b
DRICUi083-A	EOAD	М	52	63	33	1.50	stored	on request ^a
DRICUi084-A	EOAD	М	49	57	33	2.07	stored	on request ^a
DRICUi085-A	EOAD	М	54	56	33	2.07	stored	on request ^a
DRICUi086-A	EOAD	F	50	58	34	2.19	stored	on request ^a
DRICUi087-A	EOAD	М	53	58	34	2.12	stored	on request ^a
DRICUi088-A	control	F	N/A	72	33	-1.81	stored	on request ^a
DRICUi089-A	control	F	N/A	78	33	-2.14	stored	on request ^a
DRICUi090-A	control	F	N/A	88	33	-1.97	stored	on request ^a
DRICUi091-A	control	F	N/A	76	33	-1.98	stored	on request ^b
DRICUi092-A	control	М	N/A	77	33	-2.23	fresh	on request ^a

F, female; M, male; AAO, age at onset; AAI, age at interview (used as a proxy for date of blood collection, first interview used for "stored" blood, and last interview used for "fresh" blood); APOE, apolipoprotein E; AD PRS, global AD polygenic risk score. Fresh indicates that iPSC were derived post 2021 following fresh blood collections from donors. Stored indicates that iPSC were obtained from PBMCs extracted from donor blood prior to 2021 and stored in liquid nitrogen. Availability: iPSC lines that can be obtained by purchase from the EBiSC biobank are labeled "EBiSC," and iPSC lines that can only be obtained from Cardiff University on request are labeled "on request."

^aiPSC lines are undergoing QC and are anticipated to be available in December 2025 or earlier.

^biPSC lines are undergoing QC and are anticipated to be available in February 2026.

as a reference line to demonstrate quality control (QC) assays used on the iPSC. iPSC were shown to express the pluripotency markers TRA-1-60 and NANOG (Figure 3A) and to successfully differentiate into all three embryonic germ layers (Figure 3B).

Establishing the basic cellular identity and pluripotency of the generated iPSC

DRICUi011-A (Figure 1A) was shown to have expected iPSC-like morphology (Figure 1B), to have cleared Cytotune virus components (Figure 1C), and were shown to be free from mycoplasma (Figure S1A). Moreover, iPSC displayed the expected karyotype when compared to the originating expanded T cells (Figures 2 and S1B). Additionally,

DISCUSSION

Most AD research uses iPSC models with individual protein-coding mutations, from familial or common AD-associated risk genes (Penney et al., 2020). While these studies allow us to develop our understanding of the pathways involved in AD pathogenesis, single-gene mutation models

Table 2. Cell line donor information for complement PRS iPSC										
DRICU ID	Status	Sex	AA0	AAI	APOE ϵ -alleles	Complement PRS	Fresh/stored	Availability		
DRICUi093-A	LOAD	М	75	85	33	2.23	stored	on request ^a		
DRICUi094-A	LOAD	F	82	86	33	2.97	stored	on request ^a		
DRICUi095-A	control	F	N/A	70	33	-1.81	stored	on request ^a		
DRICUi096-A	control	F	N/A	72	33	-1.73	stored	on request ^a		
DRICUi097-A	LOAD	М	69	72	33	2.28	stored	on request ^a		
DRICUi098-A	LOAD	F	75	76	33	2.16	stored	on request ^a		
DRICUi099-A	LOAD	F	66	69	33	2.53	stored	on request ^a		
DRICUi100-A	control	М	N/A	85	33	-2.15	stored	on request ^a		
DRICUi101-A	control	F	N/A	82	33	-2.19	stored	on request ^a		
DRICUi102-A	control	F	N/A	83	33	-1.81	stored	on request ^a		
DRICUi103-A	LOAD	F	73	78	33	2.45	stored	on request ^a		
DRICUi104-A	LOAD	F	71	74	33	2.48	stored	on request ^a		
DRICUi105-A	control	F	N/A	67	33	-1.77	stored	on request ^a		
DRICUi106-A	control	F	N/A	85	33	-1.93	stored	on request ^a		
DRICUi107-A	LOAD	F	68	73	33	2.08	stored	on request ^a		
DRICUi108-A	LOAD	F	60	67	33	2.37	stored	on request ^a		
DRICUi109-A	control	F	N/A	82	33	-2.06	stored	on request ^a		
DRICUi110-A	control	М	N/A	77	33	-1.85	stored	on request ^a		
DRICUi111-A	control	М	N/A	78	33	-1.55	stored	on request ^a		

F, female; M, male; AAO, age at onset; AAI, age at interview (used as a proxy for date of blood collection, first interview used for "stored" blood, and last interview used for "fresh" blood); APOE, apolipoprotein E; complement PRS, complement pathway-specific polygenic risk score. Fresh indicates that iPSC were derived post 2021 following fresh blood collections from donors. Stored indicates that iPSC were obtained from PBMCs extracted from donor blood prior to 2021 and stored in liquid nitrogen. Availability: iPSC lines that can only be obtained from Cardiff University on request are labeled "on request." ^aiPSC lines are undergoing QC and are expected to be available in February 2026.

do not represent the polygenic diversity seen in common AD individuals and hence do not capture the complexity of disease (Sims et al., 2020). In contrast, the iPSC resource IPMAR represents a major new resource to capture high polygenic risk for common AD within diagnosed individuals. Following differentiation of these iPSC into AD-relevant cell types, researchers will be able to determine how high PRS AD lines differ phenotypically from low PRS control lines. This could be achieved through sequencing techniques, staining, or functional assays. Any differences observed may help identify cellular phenotypes that either contribute to or protect against AD development-phenotypes that are more prevalent in high PRS AD lines may point to factors promoting disease, while those more common in low PRS control lines may suggest protective traits. To start, researchers could focus on differentiating these iPSC into known AD-relevant cell types—such as neurons,

astrocytes, and microglia—and examine key AD-related changes, such as microglial inflammatory activation. Furthermore, the iPSC platform could be used during the development of AD therapeutics to model cell dysfunction present in common AD. Where possible, analyses should stratify by APOE genotype to take into account the potential effect of APOE4 on phenotypes observed. Researchers may wish to consider the effect of sex, age, and any heterogeneity of clinical phenotype as potential confounding variables. Future research could also compare EOAD to LOAD iPSC, to explore whether the age of onset correlates with phenotypic severity or whether different phenotypes are enriched in EOAD versus LOAD.

The limitations of the resource include that only White Caucasian subjects from the UK were used; therefore, any translation of research findings will need to take into account that they may not be generalizable to other





Figure 1. iPSC generated from IPMAR clone DRICUiO11-A show expected morphology and are negative for Sendai vector transgenes

(A) Details regarding the IPMAR line featured in this paper, with human pluripotent stem cell registration (hPSC) name DRICUi011-A.

(B) Representative light microscopy image showing colonies of DRICUi011-A induced pluripotent stem cells (iPSC), scale bar: 100 µm.

(C) Cytotune Sendai viral vector components are absent from DRICUi011-A iPSC,

shown via comparison to positive control RNA. Product sizes: Sendai virus (SeV) = 181 base pairs (bp), KOS (Krüppel-like factor 4 [*KLF4*], octamer-binding transcription factor 4 [*OCT4*], and sex-determining region Y-box 2 [*SOX2*]) = 528 bp, *KLF4* = 410 bp, SeV-*c*-*MYC* = 532 bp, β -actin [*ACTB*] = 623 bp. β -actin, a housekeeping gene present in both samples, acts as a positive control. LOAD, late-onset Alzheimer's disease; *APOE*, apolipoprotein E; M, male; AAO, age at onset; AAI, age at interview.

populations and ethnicities. Furthermore, the use of expanded T cells as source material for the iPSC means that T cell receptor regions 7q34 (~0.5 Mb region) and 14q11.2 (~0.7 Mb region) have total or partial deletion in most iPSC, due to T cell receptor recombination events in T cells; therefore, we do not recommend the use of these iPSC for generating T cells, without careful characterization of the T cell receptor repertoire of the lines. iPSC-derived brain cells are also relatively immature *in vitro* and do not preserve the epigenetic profiles of primary cells caused by aging or environmental factors.

PRSs have demonstrated effective application in identifying genetic risk for AD by demonstrating associations between SNPs and AD risk. However, current SNP-based genotyping approaches, such as SNP arrays, struggle with mapping repetitive genomic regions and identifying large structural variants. Long-read sequencing technologies, such as PacBio HiFi and Oxford Nanopore, address these issues effectively but are currently not cost-effective for largescale studies. As these technologies improve and become more affordable, they will enhance PRS calculations by providing more comprehensive genetic variant detection. Furthermore, it is important to highlight that PRS must be used alongside other clinical factors, such as environmental risk, when ascertaining an overall risk for AD. However, the well-established PRS approach is an effective metric for capturing polygenic risk of AD.

Future iPSC lines developed will include those with high endocytic pathway-specific risk, which will follow the same generation methodologies and QC to allow integration with the current cohort. Given the importance of human and common AD-specific models when investigating the pathogenesis of AD, the IPMAR resource has the potential to revolutionize both AD modeling and drug screening. We enthusiastically welcome collaboration and are eager to share our innovative resource with potential partners.

METHODS

Cohort details

The donors were chosen from participants within the ADCC, which were recruited between 2001 and 2020 using Medical Research Council, Moondance Foundation, and Health and Care Research Wales (HCRW) funding. The present study was approved by the research ethics committee Wales REC 3 (REC ID 12/WA/0052). PBMCs were collected with informed consent under four studies with REC IDs 12/WA/0052, 04/9/030, 17/SS/0139, and 00/09/ 42. Donors were self-reported Caucasian of European ancestry. The cohort collection used a standardized clinical and comprehensive neuropsychological assessment to diagnose either EOAD or LOAD (see supplemental information). Informed consent was obtained from participants following assessment of capacity to consent (see supplemental information) All AD cases met criteria for either probable (National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders (McKhann et al., 1984), Diagnostic and Statistical Manual of Mental Disorders, fourth edition (Association, 2000)) or definite (Consortium to Establish a Registry for Alzheimer's Disease (Rossetti et al., 2010)) AD. All elderly controls were screened for dementia and were chosen to match case samples for sex and ethnicity. Anonymized detailed clinical, cognitive, and non-cognitive longitudinal data and genome-wide microarray data (Illumina 610 or global screening array) from the selected donors will be available upon application via the Dementia Platforms UK website (https://portal.dementiasplatform.uk).



A Karyogram: PBMC donor of DRICUi011-A



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Information on ensuring data privacy can be found in the supplemental information.

PRS analysis and donor selection

Global AD PRS lines

Quality control of genetic data was performed before conducting the AD PRS analysis on the ADCC, as detailed in the supplemental methods. Following PRS analysis, individuals were selected from within the cohort that who met one of the following criteria:

- (1) LOAD diagnosed, age of onset >65, and with a high LOAD PRS (mainly >1.8 SD).
- (2) EOAD diagnosed, age of onset <58, and with a high LOAD PRS (>1.5 SD).
- (3) Cognitively normal, *APOE* ε 3/3, over the age of 70, and with a low LOAD PRS (mainly <-1.8 SD).

During selection, a balance of male and female donors was aimed for. Additionally, donors with *APOE* ε 3/3 genotype were prioritized for the LOAD and EOAD lines. All cognitively normal donors were *APOE* ε 3/3. Information on individuals selected is provided in Table 1.

Complement PRS lines

Calculation of base and complement PRS was performed using GWAS statistics from the current largest clinically assessed AD case-control cohort (Bellenguez et al., 2022), using the PRSice-2 software package (https://doi.org/10. 1093/gigascience/giz082). The default *p* value threshold was selected, and clumping was performed at a linkage disequilibrium (LD) threshold of below 0.1 (r² correlation coefficient) within a window of 1 kb to retain weakly correlated variants and remove redundant effects of significant SNPs within high LD. Custom gene matrix transposed (.gmt) files were created containing the complement gene list defined by Carpanini et al. (2021) with loci from the Ensembl/HAVANA merged gene annotation gene transfer format (.gtf) file for human genome build GRCh37.87. SNPs were extracted within the complement gene loci with surrounding windows (-35 kb upstream, +10 kb downstream) to capture intergenic SNPs with potential cis-regulatory effects. Raw complement PRSs were adjusted based on the 8 most significant genomic principal components to control for potential population stratification in our samples and then normalized against mean and standard deviation of PRS of non-AD-affected individuals from the 1958 National Child Development cohort (N = 4,032) (University College London, UCL Social Research Institute, 2024) to obtain a PRS weighted against the background AD risk of the general population.

After AD-associated complement PRS calculation, individuals were selected based on the following criteria.

- (1) LOAD diagnosed, age of onset >65 years, *APOE* ε 3/3 with a high complement PRS (>2 SD).
- Cognitively normal, *APOE* ε3/3 with a low complement PRS (<-1.5 SD).

Information on individuals selected to generate complement PRS lines is provided in Table 2.

Generation of iPSC

PBMC preparation for recent donations

A subset of the PBMC was obtained following fresh blood collections from donors, obtained post 2021. For fresh blood donations (indicated "fresh" in Table 1), blood was collected in 3×6 mL anti-citrate dextrose (ACD) solution B tubes per patient, and PBMCs were extracted using Lymphoprep reagent in SepMate50 tubes, following the manufacturer's protocol (STEMCELL Technologies, 85460). PBMCs were frozen in cryogenic tubes with 1–2 million cells per vial in freeze media containing 90% (v/v) embryonic stem cell-qualified fetal bovine serum (FBS, Fisher, 11500526) and 10% (v/v) dimethyl sulfoxide (DMSO, Merck, D2650) and stored in liquid nitrogen.

Historical PBMC preparation

A subset of the PBMC was extracted from donor blood prior to 2021 (indicated "stored" in Table 1). For these PBMCs, samples were collected in ACD specimen collection tubes (minimum volume 5 mL). The samples were processed using either Accuspin tubes (Sigma, A2055) or Histopaque tubes (Sigma, A7054) when Accuspin tubes were unavailable.

- (1) For Accuspin tubes: initially, the blood was poured into Accuspin tubes, with the use of multiple tubes per sample as needed and subjected to centrifugation at 1,000 xg for 25 min at room temperature (RT).
- (2) For Histopaque tubes: up to 10 mL of blood was carefully layered onto 5 mL of Histopaque, taking care to

Figure 2. iPSC generated from IPMAR clone DRICUiO11-A show expected karyotype

SNP array to test for chromosomal aberrations in gene-edited iPSC clones. For each chromosome, the first dot plot displays the B-allele frequency and indicates whether the SNV (single-nucleotide variant) is heterozygous (data points fall at around 0.5) or homozygous (data point at around 0.0 of 1.0). The second plot that displays the log R value (first dot plot, indicated with R on the left side) is given, representing the probe intensity of individual SNVs. Chromosomal gains are identified by doubling of the log R value while halving the R value indicates loss.

⁽A) Karyograms from the original PBMC sample and (B) from the derived DRICUi011-A iPSC.





Figure 3. iPSC generated from IPMAR clone DRICUiO11-A express pluripotency markers and are able to differentiate into all three germ layers

(A) Flow cytometric analysis of DRICUi011-A iPSC demonstrates the expression of pluripotency markers TRA-1-60 and NANOG. Bold line indicates antigen-specific staining, and gray histograms denote isotype control staining.

(B) Following trilineage differentiation of DRICUi011-A iPSC, expression of the ectodermal markers OTX2 (green) and PAX6 (red), mesodermal markers brachyury (green) and CXCR4 (red), and endodermal markers SOX17 (green) and CXCR4 (red) was demonstrated. A secondary antibody-only staining control (including DAPI) is shown with merged channels for each germ layer. Scale bars: 200 µm.

avoid mixing of phases, followed by centrifugation at 1,000 xg for 20 min. For samples with less than 2 mL, microtubes containing 0.5 mL of Histopaque were used, with 1 mL of blood added to each tube and centrifuged at 4,500 xg for 10 min.

Subsequently, if the separation of the white cell layer from red blood cells was insufficient, the sample was centrifuged again. The supernatant above the frit was then transferred into a freshly labeled Accuspin (or Histopaque) tube and centrifuged at 1,000 xg for 20 min at $20 \pm 1^{\circ}$ C. The resultant white, cloudy layer was isolated between the filter and clear yellow serum layer and transferred to a fresh 15 mL tube. Following this, up to 10 mL of pre-warmed RPMI 1640 (without serum, Fisher, 11875093) was added to the sample, centrifuged at 250 xg for 10 min at RT. After discarding the supernatant, the pellet was resuspended in pre-warmed RPMI (without serum) and centrifuged again at 250 xg for 10 min at RT. The size of the pellet was assessed, and based on this and the quality of separation, the decision to store 1 or 2 ampoules was made. Generally, 2 ampoules were made from 7 to 10 mL blood and only 1 from 4 to 5 mL. Samples intended for freezing as PBMCs were resuspended in 1 mL of freeze media (90% (v/v) FBS +10% (v/v) DMSO) per 1.8 mL cryotube used and frozen using a Kryo 10 rate controlled freezer before transferring to permanent long-term storage in liquid nitrogen. *iPSC reprogramming*

T cells were expanded from PBMCs prior to iPSC reprogramming, by thawing PBMCs and culturing in RPMI 1640 media (Thermo Fisher Scientific, 12004997) supplemented with 10% (v/v) FBS (Fisher, 11500526) and 35 ng/mL interleukin (IL)-2 (Merck, SRP3085), in 12-well plates coated with 10 µg/mL CD3 (OKT3) monoclonal antibody (Thermo Fisher Scientific, 15276737). T cells were initially expanded for 7-10 days and were frozen in freeze media containing 90% (v/v) embryonic stem cell-qualified FBS (Fisher, 11500526) and 10% (v/v) DMSO (Merck, D2650) and stored in liquid nitrogen. Three days before reprogramming T cells were cultured in OpTmizer CTS (Gibco, A1022-01) medium with 10% embryonic stem cell grade FBS (Gibco, 16141-079), 2 mM Glutamax (Gibco, 35030-01), and 35 ng/mL IL-2 (Sigma, SRP6170) and activated with beads (ratio 1:2 or 1:1) coated with CD2, CD3, and CD28 (T cell activation expansion kit, Miltenyi Biotec, 130-091-441).

For LOAD samples (IDs up to DRICUi055-A), 300,000 cells per donor were reprogrammed using the Cytotune-iPS



2.0 Sendai Reprogramming kit (Thermo Fisher Scientific, A16517) at multiplicity of infection 5 following the manufacturer's protocol for feeder-dependent iPSC reprogramming of fibroblasts. Vector transduced cells were transferred onto mitotically inactivated CF1 Mouse Embryonic Feeder cells (Millipore, PMEF-CFL-C) on 0.1% gelatin (Sigma, G1393)-coated plates. From day 3, cells were cultured in Knock-Out serum replacement medium (Knock-out DMEM [Gibco, 10829-018], 20% KO serum replacement [Gibco, 10828-028], 2 mM Glutamax [Gibco, 35030-1], 1% non-essential amino acids [Gibco, 11140-035], 100 units/ mL penicillin and 100 µg/mL streptomycin [Gibco, 15140-122], 55 µM 2-mercaptoethanol [Gibco, 31350-010], and 5 ng/mL bFGF [Miltenyi Biotec, 130-093-842]). Daily 50% medium changes were carried out, and from day 10, MEFconditioned medium was used. Colonies with iPSC morphology were manually picked on approximately day 20 and transferred to Geltrex (Gibco, A14133-02)-coated wells with mTeSR-1 medium (STEMCELL Technologies, 85850) and 10 µM ROCK inhibitor Y-27632 (Abcam, ab120129), with daily 100% medium changes performed henceforth. iPSC lines were passaged every 5-7 days using 0.5 mM EDTA (Life Technologies, 15575-038) in PBS (Sigma, D8537) to lift and replate clumps of cells into fresh Geltrex-coated plates in mTeSR-1 or mTeSR Plus (STEMCELL Technologies, 100-0276) medium without ROCK inhibitor. Cells were frozen at passage 10 in freeze medium containing 10% (v/v) DMSO, 30% (v/v) embryonic stem cell grade FBS (Gibco, 16141-079), and 60% (v/v) Knock-out DMEM (Gibco, 10829-018) while checking clearance of Sendai vectors by PCR and were then thawed for further passage/ checking if not clear, or for expansion if clear. Expansion was carried out over a minimum number of passages, and approximately 30 vials (2 million cells per vial) master stock at P12-20 were frozen per line, in the same freeze medium used at passage 10. Bulk frozen stocks were tested for mycoplasma, and the QC assays described in the following section were performed.

For EOAD and complement PRS iPSC (IDs upward from DRCUi056-A), donor-expanded T cells were reprogrammed to iPSC by Oxford StemTech Ltd. using a proprietary Sendai vector-based method with their ReproPlex platform.

QC of iPSC

Real-time PCR to confirm clearance of Cytotune Sendai vectors

RNA was extracted from approximately 1.6 million cells by RNeasy Mini Kit (QIAGEN, 74004) at p10. 1 μ g of RNA was reverse transcribed using a RetroScript kit (Ambion, 10585595) or the RevertAid kit (Thermo Scientific, K1622), and this was then diluted 1:5 in sterile water. A 20 μ L PCR reaction of 10 μ L AmpliTaq gold DNA polymerase (Applied Biosystems, 4398881), 0.5 μ L of 10 μ M forward primer and 0.5 μ L of 10 μ M reverse primer (primer pairs shown in Table S1), 2 μ L cDNA, and 7 μ L sterile water was used to amplify genes present on the viral vectors. The PCR products were run on a 1.5% agarose TAE gel with a 100 bp ladder (NEB, N3231S) and imaged using Bio-Rad ChemiDoc XRS+ and Bio-Rad Image Lab software. Viral vector components checked included Sendai virus, Krüppel-like factor 4 (*KLF4*), Sendai virus-*c*-MYC, and KOS, which is an acronym used for the combination of genes *KLF4*, octamer-binding transcription factor 3/4, and sexdetermining region Y-box 2. A β -actin control was also run. If viral vectors were not cleared, bands would be visible for all markers; if the viral vectors had cleared, only a β -actin control band would be present. Positive controls, generated from T cells 3 days post infection, were always run in parallel to samples.

Flow cytometry for pluripotency markers

Pluripotency of iPSC was assessed in the bulk-frozen iPSC using flow cytometry for pluripotency markers TRA-1-60 and NANOG (see Table S2 for details of antibodies and isotype controls used), with appropriate isotype controls, using the same concentration and supplier. Cells were fixed for 10 min in 2% (w/v) paraformaldehyde (PFA) in PBS (Alfa Aesar) and permeabilized in 100% methanol at -20° C for at least 30 min before staining. For antibody staining, methanol was removed from the cells, and they were subsequently washed twice in staining buffer (0.1%)(w/v) bovine serum albumin in PBS). 50,000 cells were used for each condition: blank, TRA-1-60 isotype control, TRA-1-60, NANOG isotype control, and NANOG. Samples were incubated with antibodies for 45 min at RT, in the dark, and with gentle shaking. Cells were washed twice and kept on ice during flow cytometry analysis. Measurement was conducted using FACS Calibur (Becton Dickinson) or Attune NxT (Thermo Fisher Scientific) flow cytometers, with analysis using FlowJo.

Immunocytochemistry staining for trilineage markers

Trilineage differentiation was performed on all generated iPSC lines to confirm their pluripotency and ability to differentiate to all 3 germ layers (ectoderm, endoderm, and mesoderm). Differentiation was performed in 24-well plates according to manufacturer's instructions (STEMdiff Trilineage Differentiation Kit, STEMCELL Technologies, 05230). Following differentiation, cells were fixed with 4% PFA (w/v) (10 min at RT) and washed twice with PBS. Fixed cells were incubated with blocking buffer (1% [w/v])BSA, 10% [v/v] Normal Donkey Serum, and 0.3% [v/v] Triton X-100 in PBS) for 1 hour at RT prior to overnight incubation at 4°C with primary antibodies diluted in blocking buffer. Antibodies against OTX2 and PAX6 were used to confirm ectoderm identity, antibodies against brachyury and CXCR4 for mesoderm, and SOX17 and CXCR4 for endoderm (details of primary antibodies used can be found in Table S3). Following overnight incubation, cells were



washed three times with PBS prior to a 1-hour incubation at RT in the dark with fluorescent secondary antibodies diluted in PBS plus NucBlue Live ReadyProbes Reagent (Fisher, R37605). Secondary antibodies used were donkey anti-mouse Alexa Fluor Plus 555 (Fisher, 15970296), donkey anti-rabbit Alexa Fluor 568 (Fisher, 10617183), and donkey anti-goat Alexa Fluor Plus 488 (Fisher, 15930877). Cells were then washed twice with PBS prior to imaging at 10X on an Opera Phenix high-content screen system (PerkinElmer).

SNP Copy-number variant analysis

SNP copy-number variant (CNV) analysis was performed on DNA from both the bulk-frozen iPSC and the original expanded donor T cells. DNA was extracted from approximately 1.6 million cells using DNeasy blood and tissue kit (QIAGEN, 69504). 15 µL of 100 ng/µL was used for SNP CNV array, using Illumina GSA-24v3-0_A1. The SNP CNV array was performed either by Life & Brain GmbH (Germany), or in-house at the Cardiff University School of Medicine. Illumina Genome Studio 2.0 software was used to analyze the data and produce karyograms and correlation plots; PennCNV was used for detailed CNV calling. Abnormalities over 1 million base pairs were considered to fail QC, using log R ratio and B allele frequency, and furthermore any size of 20q duplication. Abnormalities over 0.4 million base pairs will be reported with the cell line record on https://hPSCreg.eu. Alignment scatterplot with parent sample was also carried out with R² to confirm the relationship between derived line and parent.

Short tandem repeat profiling

DNA from both the bulk-frozen iPSC and the original expanded donor T cells underwent short tandem repeat (STR) profiling analysis. DNA was extracted from approximately 1.6 million cells using the DNeasy blood and tissue kit (QIAGEN, 69504). Following extraction, STR profiling was carried out by Northgene (UK).

Post thaw viability, morphology, and mycoplasma assessment

iPSC stock vials were thawed to assess the morphology and viability of frozen stocks, as well as to confirm the absence of mycoplasma and microbial contaminants. One vial of approximately 2 million cells was thawed, and cells were counted using Chemometec Nucleo counter NC-3000. Cells were distributed between two Geltrex (Gibco, A14100-02)-coated wells at 80% and 20% densities, respectively. After 48 h, images were acquired using AMG Evos XL core digital inverted microscope at 10× magnification, and cells were inspected at high magnification to confirm the absence of bacteria or fungus. For the mycoplasma testing, either Mycoalert was used (Lonza, LT07-418) following manufacturer's instructions, a ratio of 0-0.999 was considered negative, or cell supernatants were tested for mycoplasma by Eurofins Genomics UK Ltd.

RESOURCE AVAILABILITY

Lead contact

• Reasonable requests for further information and resources should be directed to and will be fulfilled by the lead contact, Hazel Hall-Roberts (hall-robertsh@cardiff.ac.uk).

Materials availability

- All iPSC generated in this study will be made available on request to bona fide researchers for a specified peer-reviewed research project. iPSC will be supplied under a materials transfer agreement and for a compensation fee paid by the requestor for stock maintenance and shipping. As the iPSC were generated using CytoTune technology, they are subject to the CytoTune limited use label license (see supplemental information), which restricts commercial use to holders of the label license. Consent provisions and study ethics permit commercial use and animal use of the iPSC.
- Some iPSC generated in this study will additionally be made available via the European Bank for iPSC EBiSC (www.ebisc. org), as indicated in Table 1.
- At the time of publication, some iPSC lines are not distribution-ready, as indicated in Tables 1 and 2; however, the authors welcome requests and will communicate timescales to interested parties.

Data and code availability

- QC data for the iPSC are available on https://hPSCreg.eu for lines that are distribution-ready and will be released for the remaining lines following the timescales indicated in Tables 1 and 2.
- Anonymized detailed clinical, cognitive, and non-cognitive longitudinal data and genome-wide microarray data (Illumina 610 or global screening array) from the donors used in this study are deposited with the Dementias Platform UK Data Portal (https://portal.dementiasplatform.uk) and are publicly available, subject to approval by a data access committee and a completed data access agreement. Information on which cohorts to request access and the donor IDs for each iPSC line is provided by the Cell Line Discovery tool (https://portal.dementiasplatform.uk/ipmar/cell-linediscovery-tool/) on the Dementias Platform UK Data Portal.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon reasonable request.

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AUTHOR CONTRIBUTIONS

J. Williams, N.D.A., V.E.-P., C.W., P.R.T., R.S., S.A.C., and G.L. conceived and designed the global AD PRS iPSC project. E.S. advised on the reprogramming strategy. H.H.-R. managed the global AD PRS iPSC project. S.M.C. and J. Williams conceived and designed the complement PRS iPSC project. S.M.C. managed the complement PRS iPSC project. A.C.M. and S.K. calculated PRSs and aided with donor selection. A.E. analyzed the SNP CNV data. R.S., N.D., and J. Williams managed the human sample collections. R.M., L.L., and N.D. performed fresh blood draws and administration for the human sample collections. J. Winston and R.O. processed fresh bloods. J. Winston and S.M.C. expanded donor T cells for reprogramming. S.H.E. and L.B. reprogrammed iPSC for the global PRS LOAD lines. S.H.E., J. Winston, E.M., R.O., and B.S. cultured iPSC and performed QC assays. E.M. and H.H.-R. wrote the manuscript.

DECLARATION OF INTERESTS

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SUPPLEMENTAL INFORMATION

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