Received: 16 December 2025 | Revised: 15 March 2026 | Accepted: 19 March 2026

DOI: 10.1002/alz.71390

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

SHORT REPORT

Alzheimer's disease risk single nucleotide polymorphism rs11218343 is linked to functional expression of *SORL1* in microglia

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Funding information
Novo Nordisk Foundation, Grant/Award Number: NNF18OC0033928

Abstract

INTRODUCTION: The rs11218343 is a non-coding variant of genome-wide significance for sporadic Alzheimer's disease (AD) with one of the most protective effects known to date. It localizes to *SORL1*, encoding the AD risk factor Sortilin-related receptor with A type repeats (SORLA). Still, the functional significance of rs11218343 for AD-related processes remains unclear.

METHODS: We used induced pluripotent stem cell (iPSC) lines from donors, or genome-engineered to carry major and minor rs11218343 alleles, to study the impact of rs11218343 on cellular activities.

RESULTS: We show that rs11218343 is uniquely linked to functional expression of SORLA in microglia, with increased expression in the protective allele correlating with reduced pro-inflammatory responses. These anti-inflammatory effects are seen in donor lines but not in single nucleotide polymorphism (SNP) -engineered isogenic lines, arguing that this polymorphism alone is insufficient but acting context-dependent.

DISCUSSION: Our data infer genetically defined expression of *SORL1* in microglia as a determinant of protection from pro-inflammatory stimulation, a function likely encoded by a haplotype linked to rs11218343.

KEYWORDS
functional validation of risk genotype, genome-wide association, human induced pluripotent stem cells, microglia, pro-inflammatory response, SORLA, sporadic Alzheimer disease

Highlights

- The rs11218343 linked to expression of Alzheimer's disease (AD) risk gene *SORL1*.
- Expression control by linked haplotype is specific to microglia.
- Increased *SORL1* levels with minor allele reduce inflammatory responses.

1 | INTRODUCTION

Sortilin-related receptor with A type repeats (SORLA), encoded by *SORL1*, is a type-1 transmembrane receptor expressed in multiple mammalian cell types (reviewed in[1]). It is a member of the VPS10P domain receptor gene family, composed of a large extracellular domain for ligand binding,[2,3] a single transmembrane anchor, and short cytoplasmic tail that interacts with cytosolic adaptors to direct receptor trafficking.[4–6] SORLA is perceived as an intracellular sorting receptor moving multiple target proteins between Golgi, cell surface, and endo-lysosomal compartments, sorting paths central to endocytic and secretory capabilities of cells. With relevance to Alzheimer's disease (AD), SORLA has been identified as a neuronal sorting receptor for the amyloid precursor protein, preventing its intracellular processing into noxious amyloid-β peptides in neurons.[7,8] More recently, novel roles for SORLA in microglia also came into focus, a cell type exceedingly considered central to AD pathology. Microglial functions relevant to AD include their ability to catabolize amyloid-β peptides, to provide inflammatory responses to amyloid plaques, or to impact structural integrity of neurons (reviewed in References).[9–11] SORLA actions presumed important in this context include the control of functional integrity of the endo-lysosomal system[12,13] as well as functions in secretion of cytokines and extracellular vesicles[14,15] by microglia.

A causal role for SORLA in AD gained major support from genetic studies showing association of *SORL1* with both familial[16–18] but also late-onset sporadic forms of AD.[19–22] In particular, recent studies document aberrant receptor sorting as well as lysosomal dysfunction with coding variants found in familial AD cases.[23–26] While these findings provide important evidence for genotype–phenotype correlation in neurodegenerative disease, coding variants of *SORL1* as a cause of familial AD are rare. By contrast, non-coding *SORL1* variants of genome-wide significance for risk of sporadic AD are more common, yet their functionality still remains incompletely explained. To gain further mechanistic insights into the involvement of *SORL1* variants in sporadic AD, we studied rs11218343, a non-coding variant (T > C) of genome-wide significance that localizes to intron 21 of *SORL1*. Frequencies of the minor C allele vary between 4% and 30% in European and Asian populations.[20,27] The rs11218343 is unique among known single nucleotide polymorphisms (SNPs) of genome-wide significance as it shows one of the most protective effects across multiple ethnicities, representing a 19% reduced AD risk for carriers of the C allele.[28] The rs11218343 localizes to a distal enhancer region, linked to several microglia gene promoters by proximity ligation-assisted ChIP-seq. Thus, it was predicted to regulate microglial gene signatures that may include *SORL1*, but also other microglia-specific genes.[29] However, this hypothesis has not been corroborated experimentally so far.

Using human induced pluripotent stem cell (iPSC) -derived cell models from donors or SNP genome-edited, we now document that a haplotype linked to rs11218343 is associated with the expression and anti-inflammatory action of SORLA in microglia, suggesting that expression in this brain cell type contributes to genetically determined protective effects of the receptor in AD.

RESEARCH IN CONTEXT

1. **Systematic review**: Reviewing the literature on single nucleotide polymorphisms (SNPs) showing genome-wide association with the risk of sporadic Alzheimer's disease (AD), we learned that prior studies identified rs11218343 as a major predictor of protection from the disease. We also learned that this SNP localizes to *SORL1*, encoding the AD risk factor Sortilin-related receptor with A type repeats (SORLA). However, no data were available whether this SNP controls functional expression of SORLA or other AD-related proteins in brain cell types.
2. **Interpretation**: Our study indicates that rs11218343 is linked to expression control of *SORL1* in iPSC-derived human microglia. Increased expression of SORLA in the minor allele correlates with decreased inflammatory responses in this cell type. These findings argue that the ability of SORLA to contain pro-inflammatory actions of microglia contributes to its protective effect in AD.
3. **Future directions**: Our data document that the penetrance of rs11218343-linked effects on *SORL1* expression control is modulated by donor-specific genetic or epigenetic factors that warrant further elucidation in larger cohorts. Such information will be essential to mechanistically resolve the mode of action of the most protective genotype in sporadic AD known to date.

2 | METHODS

2.1 | iPSC culture and differentiation

All human iPSC donor lines used in this study are listed in the Human Pluripotent Stem Cell Registry. Cell lines BIHi005-A (https://hpscreg.eu/cell-line/BIHi005-A), MDCi053-A-49 (https://hpscreg.eu/cell-line/MDCi053-A-49), BIHi242-C (https://hpscreg.eu/cell-line/BIHi242-C), BIHi004-B (https://hpscreg.eu/cell-line/BIHi004-B), BIHi013-A (https://hpscreg.eu/cell-line/BIHi013-A), MDCi240-A (https://hpscreg.eu/cell-line/MDCi240-A), MDCi240-B (https://hpscreg.eu/cell-line/MDCi240-B), and MDCi241-A (https://hpscreg.eu/cell-line/MDCi241-A) were provided by the Stem Cell Facility of the MDC, Berlin. Line BIHi043-A was generously provided by the Institute of Diabetes and Regeneration Research, Munich (https://hpscreg.eu/cell-line/HMGUi001-A). Line TMOi001-A is commercially available (Thermo Fisher Scientific, https://hpscreg.eu/cell-line/TMOi001-A). All cell lines were subjected to initial quality control, including SNP karyotyping,[30] and routinely tested to be free of mycoplasma contamination. Generation of isogenic *SORL1* rs11218343 T > C iPSC line by CRISPR/Cas9-based editing as well as *SORL1* and apolipoprotein E (*APOE*) genotyping protocols are detailed in the supplementary method section.

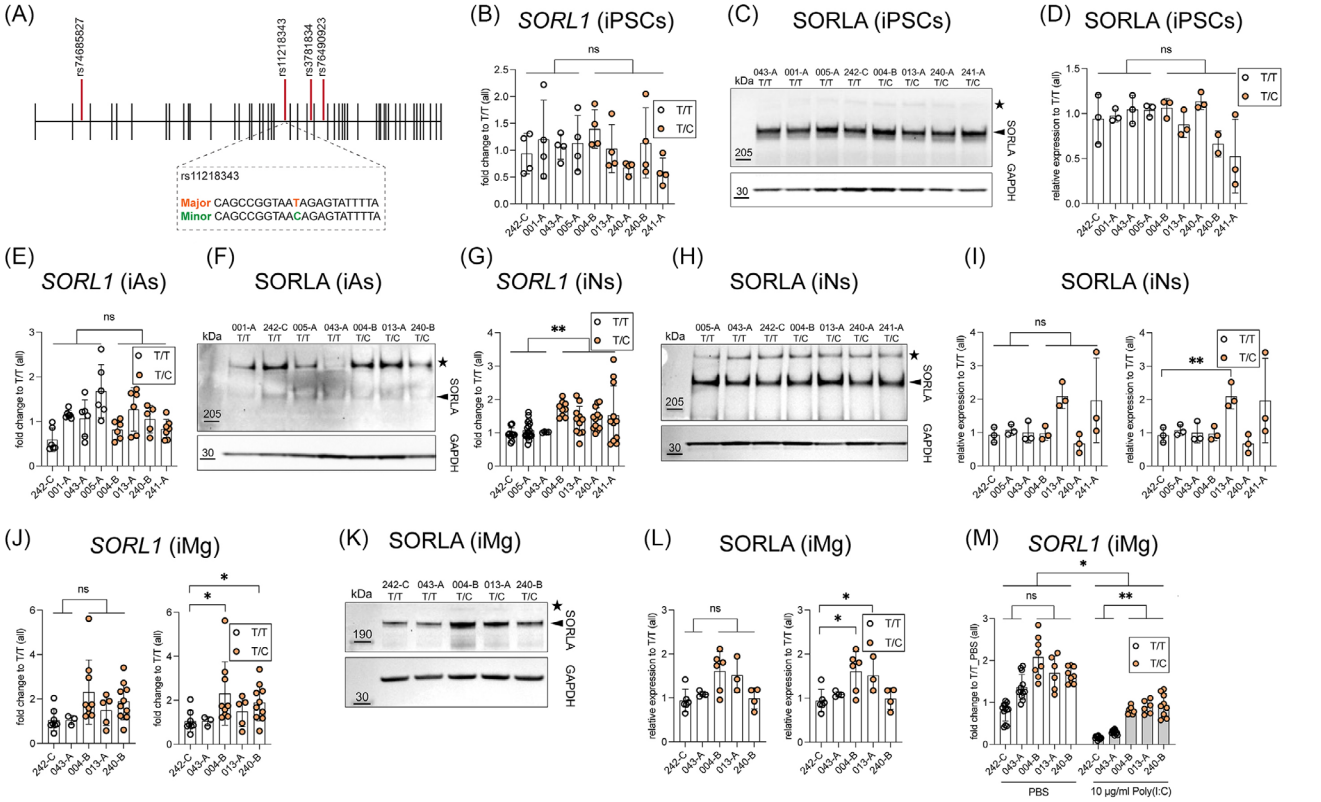

FIGURE 1 The rs11218343 is linked to *SORL1* transcription in neurons and microglia from donor iPSC lines. (A) SNPs in human *SORL1* associated with sporadic AD at genome-wide significance (from alzforum.org/mutations/sorl1-haplotype). Sequence variants for rs11218343 are given below. (B) Quantitative RT-PCR analysis of *SORL1* transcript levels in donor iPSC lines. Data are as mean ± SD of four biological replicates (from four independent differentiations) for each donor line. Statistical significance of data was determined using nested *t* test comparing genotypes. ns, not significant. (C, D) Levels of SORLA in lysates of iPSC lines of the indicated genotypes were quantified by Western blot analyses (C) and densitometric scanning of replicate blots (D). Relative levels of SORLA in each sample was normalized to the GAPDH loading control in each sample. Data are as mean ± SD of two to three biological replicates (from two to three independent differentiations) for each donor line. Statistical significance of data was determined using nested *t* test comparing genotypes. In panel C, immunoreactive bands respresenting SORLA are marked by an arrowhead, while unspecific bands are indicated by an asterisk. (E) *SORL1* transcripts in induced astrocytes (iAs) carrying T/T or T/C genotypes of rs11218343. Data are mean ± SD (five to seven biological replicates), expressed as fold change compared to the mean of T/T lines (set to 1, nested *t* test). (F) SORLA levels in iAs lysates. The arrowhead marks SORLA, while unspecific bands are indicated by an asterisk. GAPDH served as loading control. (G) *SORL1* transcripts in induced neurons (iNs) carrying T/T or T/C genotypes. Analysis performed as in (B) from four to 18 biological replicates. $^{**}p < 0.01$. (H, I) SORLA levels in iNs determined by Western blot (H) and densitometric scanning of replicate blots (I). Data are mean ± SD (three biological replicates). Significance determined by nested *t* test (comparing genotypes, left) or Student's *t* test (comparing all lines to line 242-C, right). In panel H, immunoreactive bands respresenting SORLA are marked by an arrowhead, while unspecific bands are indicated by an asterisk. (J) *SORL1* transcript levels in induced microglia (iMg) carrying T/T and T/C genotypes. Data analysis as in (B) from three to 10 biological replicates. Significance determined as in (I). $^{*}p < 0.05$. (K, L) SORLA levels in iMg determined as by Western blot (K) and densitometric scanning of replicate blots (L). Data are mean ± SD (four to seven replicates). Significance determined by nested *t* test (left) or Student's *t* test comparing individual lines to line 242-C (right). In panel K, immunoreactive bands respresenting SORLA are marked by an arrowhead, while unspecific bands are indicated by an asterisk. (M) *SORL1* transcript levels in iMg treated with PBS or 10 µg/ml poly(I:C). Analysis as in (B) from six to 12 biological replicates per cell line. Statistical significance of data was determined using nested *t* test comparing transcript levels between PBS and poly(I:C) treated iMg or between genotypes within each cell type. AD, Alzheimer's disease; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; iPSC, induced pluripotent stem cell; PBS, phosphate buffered saline; RT-PCR, reverse transcriptase-polymerase chain reaction; SD, standard deviation; SNP, single nucleotide polymorphism; SORLA, Sortilin-related receptor with A type repeats.

Culture and differentiation of iPSC lines into neurons,[31] astrocytes,[32] or microglia[33] were performed according to published protocols, with adaptations described in the supplementary methods. Protocols for gene and protein expression analysis using quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) and Western blotting are also given in the supplementary methods.

2.2 | Statistical analysis

Data are presented as mean ± standard deviation (SD). Statistical significance of data was determined by nested *t* test when comparing genotype groups, or Student's *t* test when comparing individual T/C or C/C cell lines to a reference T/T line as stated in the respective figure legends.

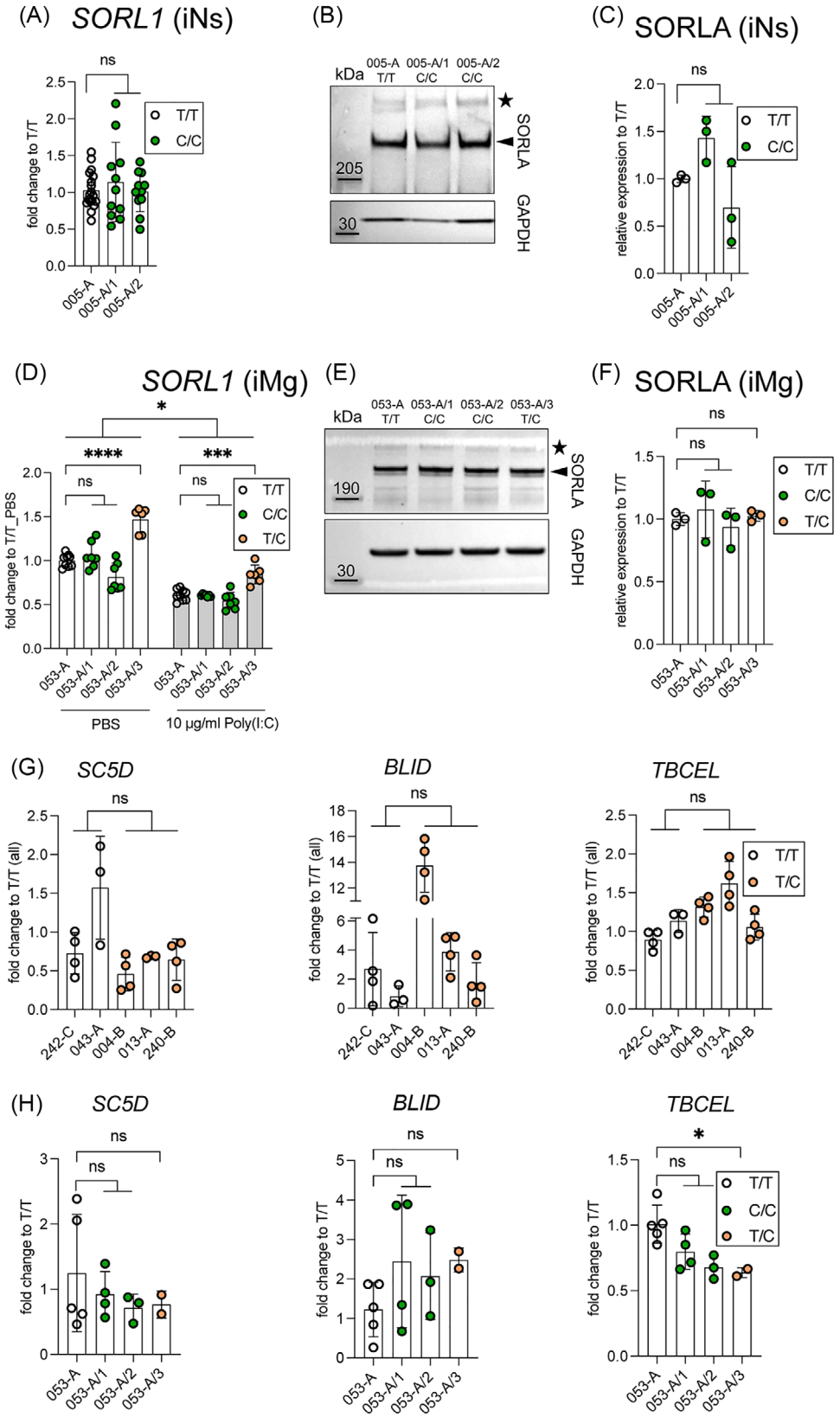

FIGURE 2 Single nucleotide polymorphism in rs11218343 is not linked to *SORL1* expression in neurons and microglia from genome-edited isogenic cell lines. (A) Quantitative RT-PCR analysis of *SORL1* transcript levels in induced neurons (iNs) derived from parental iPSC line 005-A (T/T) and two independent isogenic cell clones, genome-edited to carry the C/C genotype (005-A/1, 005-A/2) on day 14 of culture. For each cell line, data are given as mean ± SD of 11–18 biological replicates (from eight to 11 independent differentiations), expressed as fold change compared to the T/T cell line (mean set to 1). Statistical significance of data was determined using nested *t* test comparing the two genotype groups. ns, not significant. (B) Western blot analysis of SORLA levels (arrowhead) in lysates of iNs of the indicated genotypes. The star marks a non-specific band

3 | RESULTS

To interrogate the impact of rs11218343 on *SORL1* expression (Figure 1A), we studied human iPSC lines from donors with T/T (4 lines) or T/C (5 lines) genotype (Figure S1A,B). All donor cell lines were homozygous for *APOEε3* (Figure S1C). SNP genotype did not impact expression of pluripotency markers (Figure S1D), nor did it affect levels of *SORL1* transcript (Figure 1B) or SORLA protein (Figure 1C,D) in stem cells.

Next, we differentiated donor iPSC lines into induced astrocytes (iAs, Figure S2A,B), neurons (iNs, Figure S3A,B), or microglia (iMg, Figure S4A,B), resulting in the expected decrease in pluripotency markers and a concomitant induction of astrocyte (Figure S2C), neuron (Figure S3C), or microglia (Figure S4C,D) -specific genes. Comparable levels of *SORL1* transcript were detected in iAs of both genotypes (Figure 1E) but did not translate into appreciable amounts of receptor protein (Figure 1F). In iNs, levels of *SORL1* transcripts increased with T/C as compared to T/T genotypes (Figure 1G), but only resulted in significantly higher protein levels in one of the four T/C lines tested (Figure 1H,I). By contrast, levels of *SORL1* transcript (Figure 1J) and protein (Figure 1K,L) increased in two of three T/C lines tested when differentiated to iMg. A link between rs11218343 genotype and microglial expression levels of *SORL1* was also seen in iMg treated with poly(I:C), a pro-inflammatory stimulus known to modulate *SORL1* transcript levels.[14] *SORL1* transcript levels were always higher in T/C compared to T/T genotypes, both under basal and poly(I:C)-treatment conditions (Figure 1 M).

To test causality for rs11218343, we used genome editing to convert the T/T donor line 005-A to isogenic lines homozygous for C/C (Figure S5A-B). No impact of genotype conversion on expression of pluripotency markers (Figure S5C), or levels of *SORL1* transcript (Figure S5C) or protein (Figure S5D,E) were seen. Subsequently, the isogenic lines were differentiated into iNs, showing comparable appearance (Figure S5F) and induction of neuronal marker expression (Figure S5G) in T/T and C/C clones. Neither *SORL1* transcript (Figure 2A) nor SORLA protein (Figure 2B,C) were impacted by the presence of the C allele when comparing isogenic T/T and C/C genotypes.

As donor line 005-A failed to generate iMg, we also genome-edited the donor cell line 053-A into isogenic clones, either heterozygous (T/C) or homozygous (C/C) clones (Figure S6A,B). Again, no impact of SNP conversion on expression of pluripotency markers (Figure S6C) or levels of *SORL1* transcript (Figure S6C) or protein (Figure S6D,E) were seen comparing (T/T) and (C/C) genotypes. There was a significant increase in *SORL1* transcript (Figure S6C) but not protein (Figure S6D,E) levels seen when comparing the heterozygous (T/C) clone to the parental (T/T) line. The isogenic clones were then differentiated into iMg, showing comparable microglial morphology (Figure S6F) and marker expression (Figure S6G,H) in T/T, C/C, and T/C variants. In iMg, levels of *SORL1* transcript at basal or poly(I:C) stimulated conditions (Figure 2D) or SORLA protein (Figure 2E-F) were not affected by the presence of the C allele comparing isogenic C/C and T/T genotypes. As seen for iPSC, we observed a modest but significant increase in *SORL1* transcript (Figure 2D) but not protein (Figure 2E,F) levels in iMg when comparing the heterozygous (T/C) clone to the parental (T/T) line. Taken together, these findings argued that rs11218343 may be linked to, but not functional in *SORL1* expression control. The activity of exemplary microglial gene promoters, spatially associated with the enhancer region harboring rs11218343,[29] did not show consistent differences when comparing transcript levels in iMg from donor (Figure 2G) or isogenic cell lines (Figure 2H) of the various genotypes. Although not proven directly by enhancer studies, these data infer that this SNP may exhibit specificity for *SORL1*.

reacting with the SORLA antiserum. Detection of GAPDH served as loading control. (C) Levels of SORLA in iNs lysates were determined by densitometric scanning of replicate Western blots (as exemplified in B). Relative expression of SORLA was normalized to GAPDH in the respective sample. Data are given as mean ± SD of three biological replicates (from three independent differentiations) for each cell line. Significance of data was determined using nested *t* test comparing the two genotype groups. (D) Quantitative RT-PCR analysis of *SORL1* transcript levels in iMg derived from parental iPSC line 053-A (T/T) and three independent isogenic cell clones, genome-edited to carry the C/C (053-A/1, 053-A/2) and T/C genotypes (053-A/3) treated with PBS or 10 µg/ml poly(I:C). Analysis was performed using data of six to nine biological replicates. The significance of data was determined using nested *t* test comparing transcript levels between PBS and poly(I:C) treated iMg. Statistical significance of data between genotypes within each cell line was determined using nested *t* test (comparing T/T and C/C genotypes) or Student's *t* test (comparing T/T and T/C lines). (E, F) Levels of SORLA in lysates of isogenic iMg lines of the indicated genotypes were determined by Western blot analysis (E) and densitometric scanning of replicate blots (F). Relative expression levels of SORLA were normalized to the GAPDH loading control in each sample. Data are shown as mean ± SD of 3 biological replicates (from three independent differentiations) for each cell line. Statistical significance of data was determined using nested *t* test (comparing T/T and C/C genotypes) or Student's *t* test (comparing T/T and T/C genotypes). In panel E, immunoreactive bands respresenting SORLA are marked by an arrowhead, while unspecific bands are indicated by an asterisk. (**G**) Quantitative RT-PCR analysis of transcript levels for *SC5D*, *BLID*, and *TBCEL* in induced human microglia (iMg) derived from donor iPSC lines of the indicated T/T and the T/C genotypes (day 38 of culture). For each donor cell line, data are given as mean ± SD of three to four biological replicates (from three to four independent differentiations), expressed as fold change compared to all T/T cell lines (mean set to 1). Statistical significance of data was determined using nested *t* test comparing the two genotypes. ns, not significant. (H) Analysis as in panel (G) comparing transcript levels of *SC5D*, *BLID*, and *TBCEL* in iMg derived from isogenic iPSC lines of the indicated T/T, C/C, and T/C genotypes (day 38 of culture). Significance of data was tested by nested *t* test (comparing the T/T and C/C genotypes) or Student's *t* test (comparing T/T and T/C lines). Data are shown as mean ± SD of two to five biological replicates from two to five differentiation experiments) for each isogenic line. GAPDH, glyceraldehyde-3-phosphate dehydrogenase; iPSC, induced pluripotent stem cell; PBS, phosphate buffered saline; RT-PCR, reverse transcriptase-polymerase chain reaction; SORLA, Sortilin-related receptor with A type repeats.

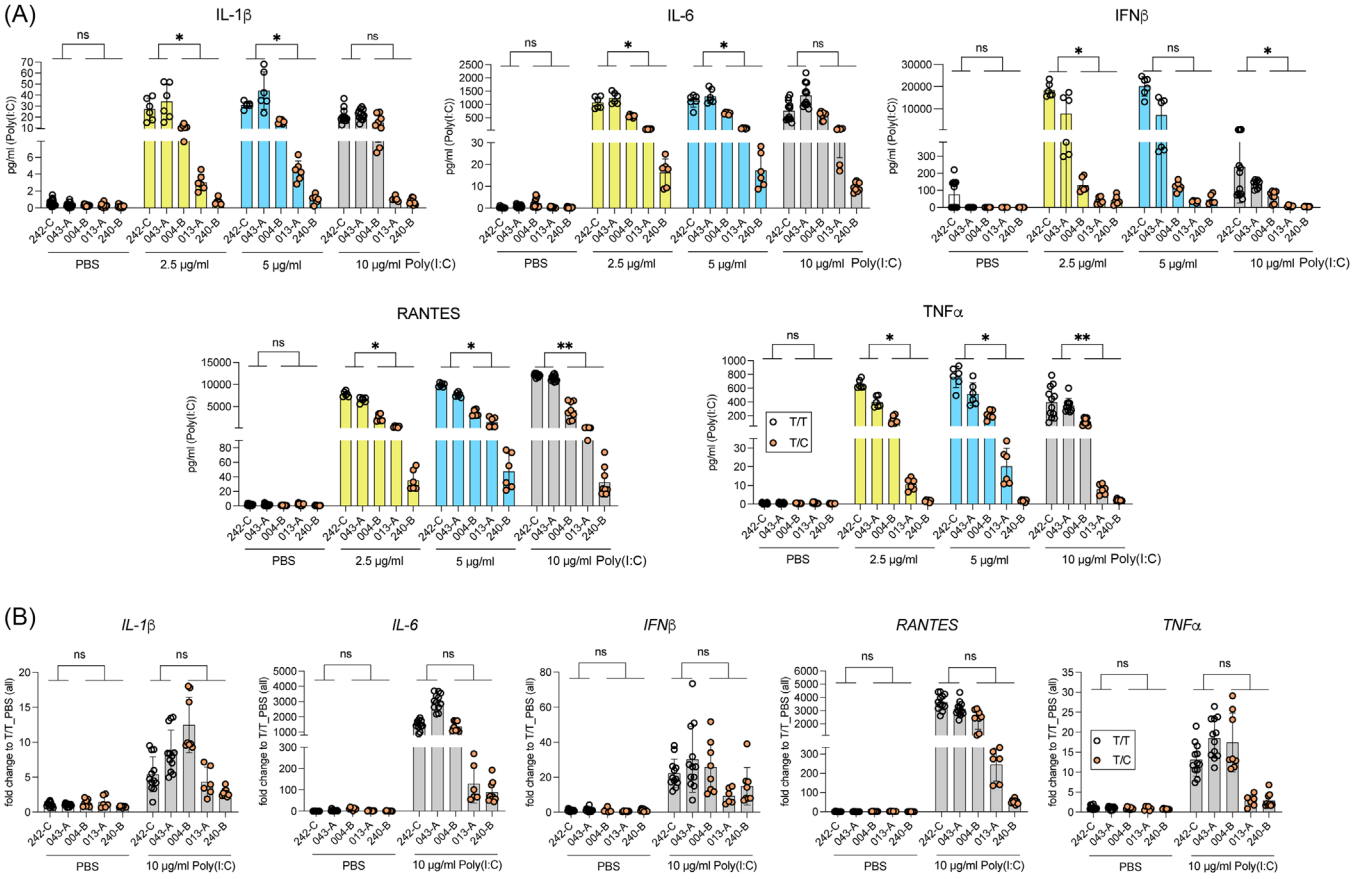

FIGURE 3 The rs11218343 predicts pro-inflammatory cytokine release by induced microglia from donor cell lines. (A) Cytokine levels in supernatants of iMg lines carrying T/T or T/C genotypes treated with PBS or poly(I:C). Data are mean ± SD (six to 18 biological replicates, nested *t* test). (B) Cytokine transcript levels in iMg carrying T/T or T/C genotypes treated with PBS or 10 μg/ml poly(I:C). Data are mean ± SD of six to 12 biological replicates (nested *t* test). ns, not significant; $^{*}p < 0.05$; $^{**}p < 0.01$. iMg, induced microglia; PBS, phosphate buffered saline.

Because of the more robust correlation between rs11218343 genotype and *SORL1* expression in microglia, we focused in this cell type to interrogate the predictive value of this SNP for SORLA activity. To do so, we exposed iMg derived from donor cell lines to pro-inflammatory stimuli by poly(I:C), an activity related to the ability of SORLA to control functional expression of the pattern recognition receptor CD14.[14] Microglia from donors with T/C genotype showed a decreased pro-inflammatory response as documented by reduced levels of cytokines released following poly(I:C) stimulation. This impacted response was pronounced in two of the three T/C donor lines (Figure 3A). A reduced pro-inflammatory response was due to reduced levels of cytokine gene transcription (Figure 3B), in line with the mode of poly(I:C) action on pro-inflammatory gene expression.[34] Consistent with comparable *SORL1* expression levels, pro-inflammatory responses to poly(I:C) were similar in isogenic T/T and C/C lines (Figure 4A,B).

4 | DISCUSSION

According to current hypotheses, intracellular sorting of cargo by SORLA supports several cellular pathways protective against neurodegenerative processes. With relevance to our study, SORLA has been shown to modulate endo- and exocytic activities in human microglia,[13,15] providing arguments for increased receptor expression as determinant of protection against inflammatory insults in AD. Early studies provided support for this hypothesis by documenting some AD risk genotypes in *SORL1*, identified in smaller cohorts, to affect efficiency of translation[35] or inducibility of the gene by brain-derived neurotrophic factor.[36,37]

Now, our study extends these findings to a *SORL1* genotype of genome-wide significance, associated with risk of sporadic AD. In line with a presumed protective role for SORLA, the minor allele variant of rs11218343 is associated with increased levels of expression and activity of the receptor. Of note, this effect is not seen uniformly in all cell types tested here. Rather, the link of rs11218343 with functional expression of SORLA seems most prominent in microglia, a cell type implicated in the neuroprotective actions of this receptor by prior work.[13–15] As a proof of concept, we document pro-inflammatory response to poly(I:C) as a function of SORLA linked to rs11218343. Obviously, future studies need to resolve the relevance of this SNP for other receptor functions in this cell type, such as endo-lysosomal activity or extracellular vesicle release. Because functionality of rs11218343 is inferred from phenotypes in donor cell lines, not seen in genome-edited iPSC lines, this SNP alone is insufficient

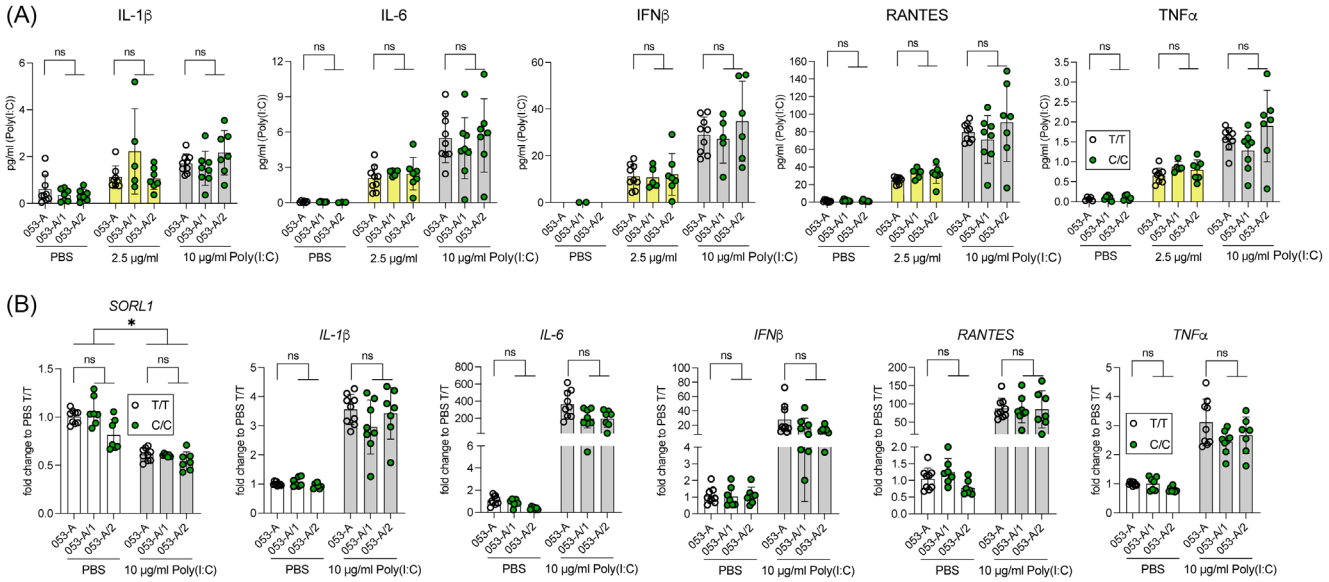

FIGURE 4 The rs11218343 does not predict pro-inflammatory responses of induced microglia from genome-edited isogenic iPSC lines. (A) Cytokine levels in supernatants of iMg derived from isogenic iPSC lines of the indicated T/T and C/C genotypes treated with PBS or poly(I:C). Data are mean ± SD (five to nine biological replicates, nested *t* test). (B) Cytokine and *SORL1* transcript levels in iMg derived from isogenic iPSC lines of the indicated T/T and C/C genotypes treated with PBS or 10 µg/ml poly(I:C). Data are mean ± SD of seven to nine biological replicates (nested *t* test). ns, not significant; $^*p < 0.05$. iMg, induced microglia; iPSC, induced pluripotent stem cell; PBS, phosphate buffered saline.

to explain *SORL1* expression control. Rather, receptor expression control is likely exerted through a yet unidentified sequence variation in linkage disequilibrium with this SNP, or through the entire haplotype.

Here, we have analyzed a total of 10 donor and seven isogenic cell lines. Noticeably, the penetrance of rs11218343-linked effects on *SORL1* expression control is modulated by donor-specific genetic or epigenetic factors that warrant further elucidation in larger cohorts. The relevance of modifying factors is further inferred by our findings that enhanced levels of *SORL1* transcription not necessarily translate into a corresponding increase in receptor mass, as seen in neurons herein. This finding argues for additional post-transcriptional mechanisms to play an important role in SORLA expression control and cautions the mere use of *SORL1* transcript levels as a proxy of functional expression of the receptor in cell types and tissues.

AUTHOR CONTRIBUTIONS

Malgorzata Gorniak-Walas: designed and conducted the experiments and analyzed data, conceptualized the study and evaluated data, wrote the manuscript. **Narasimha S. Telugu**: designed and conducted the experiments and analyzed data. **Ina-Maria Rudolph**: designed and conducted the experiments and analyzed data. **Sebastian Diecke**: conceptualized the study and evaluated data. **Thomas E. Willnow**: conceptualized the study and evaluated data, wrote the manuscript.

ACKNOWLEDGMENTS

We are indebted to N. Hübner (MDC) and Fadumo Abdullahi Mohamed (AU) for helpful discussions, and K. Kampf, T. Pasternack, C. Kruse, K.-M. Pedersen, and A. Højland for expert technical assistance. We acknowledge Heiko Lickert (HMGU Munich) for providing parental cell line (BIHi043-A).

Open access funding enabled and organized by Projekt DEAL.

Studies were funded in part by a grant from the Novo Nordisk Foundation (NNF18OC0033928) to T.E.W.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

No informed consent from human subjects was necessary for this study.

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SUPPORTING INFORMATION

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

How to cite this article: Gorniak-Walas M, Telugu NS, Rudolph I-M, Diecke S, Willnow TE. Alzheimer's disease risk single nucleotide polymorphism rs11218343 is linked to functional expression of *SORL1* in microglia. *Alzheimer's Dement*. 2026;22:e71390. https://doi.org/10.1002/alz.71390