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Expression dynamics of IL-1 family genes in the healthy human brain suggest non-immune functional roles

Isaac Adeyemi Babarinde[1,2,*] **and Diana Boraschi**[1,2,3,4,5,*]

*Correspondence: diana.boraschi@itb.cnr.it (D.B.); adeyemi@siat.ac.cn (I.A.B.)

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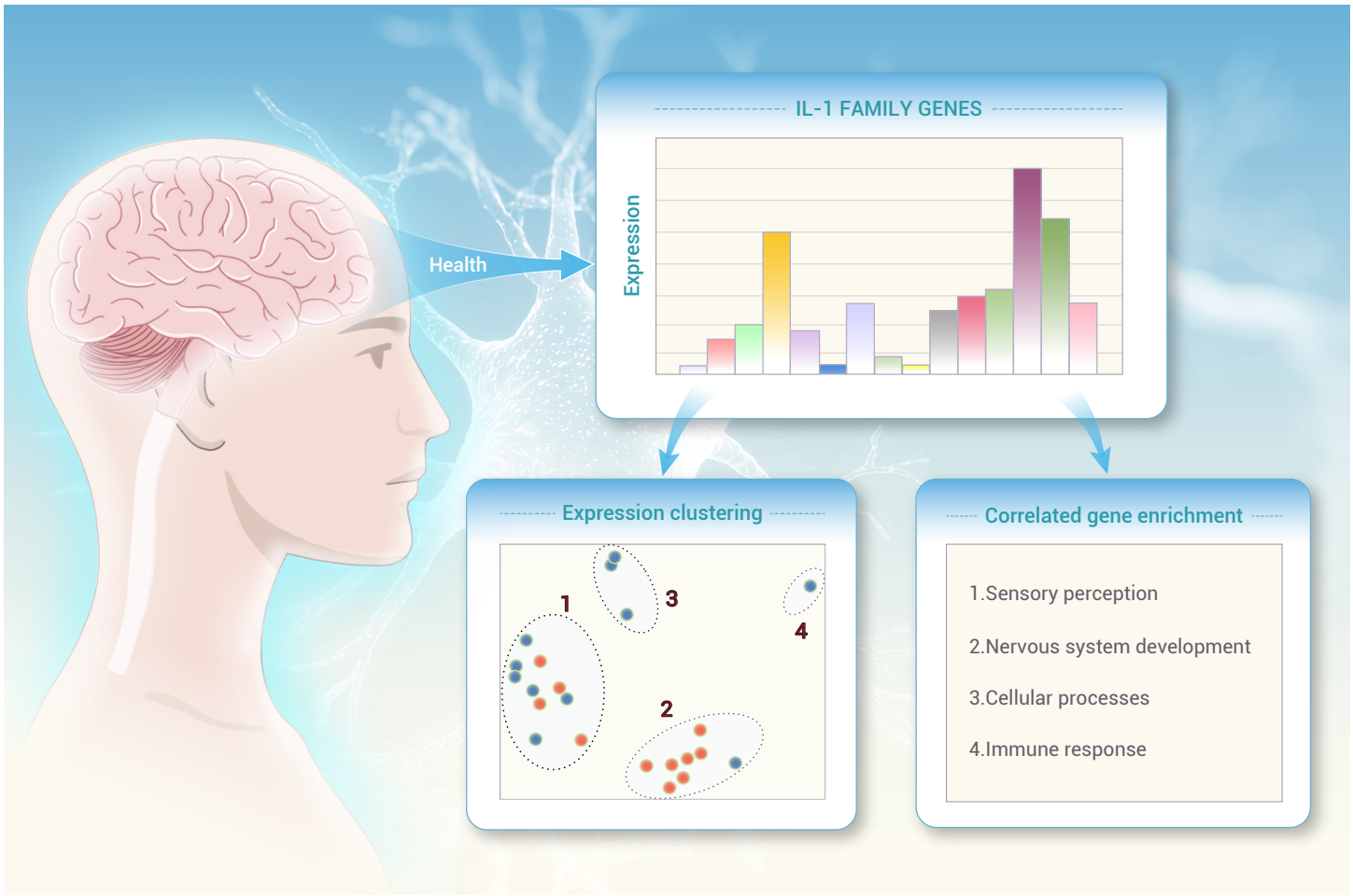
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Cytokines and receptors of the IL-1 family are mediators of inflammation and defense immune functions in the human body.
- However, their substantial expression in the healthy brain suggests that they may have other functions.
- Analysis of gene expression and co-expression suggests brain-specific roles.
- These molecules may have physiological functions in neurogenesis, neurometabolism and neurotransmission.

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Expression dynamics of IL-1 family genes in the healthy human brain suggest non-immune functional roles

Isaac Adeyemi Babarinde[1,2,*] and Diana Boraschi[1,2,3,4,5,*]

[1]Laboratory of Inflammation and Vaccines, Shenzhen Institutes of Advanced Technology (SIAT), Chinese Academy of Sciences (CAS), Shenzhen 518055, China

[2]China-Italy Joint Laboratory of Pharmacobiotechnology for Medical Immunomodulation, Shenzhen 518055, China

[3]School of Pharmacy, Shenzhen University of Advanced Technology (SUAT), Shenzhen 518055, China

[4]National Research Council, 80131 Napoli, Italy

[5]Stazione Zoologica Anton Dohrn, 80121 Napoli, Italy

*Correspondence: diana.boraschi@itb.cnr.it (D.B.); adeyemi@siat.ac.cn (I.A.B.)

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Interleukin-1 (IL-1) family genes include 22 cytokines and receptors with different evolutionary histories. While generally associated with inflammation-related immune defensive reactions, several IL-1 family genes are expressed at measurable levels in the healthy brain, as assessed in animal models, although their functions are still obscure. In this study, we investigated the expression and possible functions of these genes in the healthy human brain, using RNA-seq samples retrieved from three different databases. Some of them, such as *SIGIRR*, *IL33* and *IL1RAPL1*, are highly expressed across multiple regions, while others, *e.g.*, *IL1F10* and *IL36B*, are undetectable. Co-expression analysis identified genes with positive and negative expression correlation with IL-1 family genes. Upon enrichment analysis of the correlated genes, it was found that, at variance with their systemic expression and immune-related function, expression of several IL-1 family genes shows a brain-specific pattern that correlates with neurological functions. For instance, *IL1RAPL2* expression positively correlates with genes involved in brain development and synaptic functions and negatively correlates with genes involved in fatty acid oxidation, suggesting promotion of neurogenesis. *IL1RL1*, *IL1RAP* and *IL1RAPL1* positively correlate with genes involved in sensory smell perception and transmission. *SIGIRR* positively correlates with genes involved in translation and protein synthesis in the brain. *IL33* positively correlates with genes involved in fatty acid oxidation, suggesting regulation of neurogenesis. Thus, this study suggests that several IL-1 family genes, which are constitutively expressed in the healthy human brain, may have a non-immune non-inflammatory role in sustaining and regulating brain-specific functions.

INTRODUCTION

Interleukin-1 (IL-1) gene family members include a wide range of structurally related cytokines and receptors involved in innate immunity and inflammation.[1–3] At variance with other innate immune and inflammatory genes that are present in invertebrates, members of IL-1 family are estimated to have evolved more recently. Their evolution time roughly coincides with the evolution of the adaptive immune system in vertebrates, suggesting an integral role in the regulation of adaptive immunity.

The IL-1 family encompasses 11 cytokines and 11 receptor-like molecules that have independent evolutionary histories.[1-4] Specifically, while most IL-1 receptor genes, except *IL1RAPL1,* are present across all vertebrates, several genes encoding IL-1 family cytokines, including *IL1A* and *IL33,* are specific to mammals.[5,6] Gene duplication has played a significant role in the evolution of IL-1 family genes.[5] However, some IL-1 family genes do not have substantial sequence conservation or strong chromosomal proximity with other genes of the family, suggesting more ancestral gene evolution.[5] Neofunctionalization of the duplicated and newly evolved genes has contributed significantly to the diverse functions of IL-1 molecules.[5,6] Indeed, several studies suggest additional roles for IL-1 gene-encoded proteins beyond their involvement in immunity and inflammation.[2,3]

The inflammation-related role of IL-1 family molecules in brain functions has been extensively studied, although mainly in animal models and in disease conditions.[7] Likewise, most of the human studies were also performed on disease samples.[8] Consequently, the role of IL-1 family molecules in the normal human brain, when inflammation is absent, is still largely unknown. Analysis of IL-1 family gene expression in the normal human brain is the first step towards the understanding of their brain-specific physiological role, which is the necessary basis for a knowledge-based understanding of their contribution to disease.

In this study, we have analyzed RNA-seq expression data of different healthy brain regions of male and female donors aged 8 post-conception-weeks to 79 years old. The data were retrieved from three different databases, and normalized before analysis. The analysis of variance identified factors associated with the dynamic expression patterns of IL-1 family genes in different brain areas. Using correlation analysis, we investigated the relationship between IL-1 family genes, and between IL-1 family genes and other co-expressed genes. Gene functional enrichment and motif enrichment of the correlated genes were used to infer the possible brain-specific physiological regulatory functions of the IL-1 family genes.

MATERIALS AND METHODS

Retrieval of human brain expression data

Brain gene expression data and donor descriptions were retrieved from version 8 of Genotype-Tissue Expression (GTEx) portal,[9] the Human Protein Atlas (HPA)[10,11] and the BrainSpan (www.brainspan.org) between August 10 to August 25, 2024. Data from spinal cord were also retrieved.

Sample processing and gene expression normalization

To ensure that only healthy samples were used in the GTEx data, donors who died from illness, with categories 0, 3 and 4 of GTEx death classification 4-point hardy scale, were excluded. The average TPM (transcripts per million) value of all replicates were computed for each tissue. BrainSpan expression values in RPKM (reads per kilobase of transcript per million reads mapped) were converted to TPM using previously reported procedure.[12] HPA used protein-coding genes as reference, while GTEx and BrainSpan used all genes, including noncoding RNAs and pseudogenes. We employed the normalization approach used by HPA (https://www.proteinatlas.org/) to unify the expression levels across databases. Briefly, raw TPM values were first converted to protein-coding gene TPM. The resulting values were then normalized using the trimmed mean of M (TMM) normalization method.[13] Gene expression normalization was done for all genes, before focusing on IL-1 family gene. The expression levels were $\log_2$-transformed with 0.1 added to approximate normal distribution.

Gene expression clustering with principal component analysis (PCA) and heatmaps

PCA were performed using *prcomp* in R statistical package. The normalized expression data were scaled to the center. Sample PCA were computed separately for all genes and for IL-1 family genes only.

Analysis of variance (ANOVA) for expression of the IL-1 family genes

ANOVA was performed using ordinary least squares (ols) implemented in Python statistical models (*statsmodels*), and applied separately to GTEx and BrainSpan data with detailed donor description to minimize the impacts of batch effect. The model was built using expression levels with age, gender,

brain region and interactions as factors. ANOVA was then performed using a linear model. The statistical significance was set at 0.05.

Analysis of the relationship between IL-1 cytokines and their related receptors

The relationship between the cytokines and their cognate receptors was analyzed by correlation analysis using Pearson's correlation. We identified the most positively correlated IL-1 family gene and known target (cytokine or receptor) across different brain regions. The receptors for *IL1A*, *IL1B* and *IL1RN*-encoded cytokines are encoded by *IL1R1* and *IL1R2*. The receptors for *IL18* and *IL37* are *IL18R1* and *IL18BP*. The receptor for *IL33* is *IL1RL1*, and the receptors for *IL36A*, *B*, *G* and *RN* is *IL1RL2*. *IL1RAP* encodes the accessory receptor chain that interacts with the receptors encoded by *IL1R1*, *IL1R2*, *IL1RL1* and *IL1RL2*, while *IL18RAP* encodes the accessory receptor chain that interacts with the receptor encoded by *IL18R1*. *SIGIRR* is hypothesized to interact with *IL1R1*, *IL1RL1* and *IL1RL2*, while the cytokine *IL1F10* is hypothesized to bind to the receptors *IL1RL2*, *IL1R1* and *IL1RAPL1*.

Gene expression correlation with age and regression analysis

Donor age was unified to post-conception-week (pcw) units, with the gestation time set to 40 weeks. The conversion for age in month was (age×4.35) +40, and (age×52.143) +40 for age in year. The resulting age was then $\log_2$-transformed to approximate normal distribution. Log_2-transformed adjusted age and TPM expression were used to compute expression correlation for each brain region. Regression analysis was done using *lineregress* implemented in Python's scipy.

Correlated gene expression and concordance analysis

Correlation analysis was computed at two stages using Pearson's correlation method. The first stage focused on the analysis of IL-1 family genes in different brain regions using the GTEx database. The second stage used all RNA-seq data from the three databases from all regions to extract biologically relevant insights. For a given IL-1 family gene, positively correlated genes were defined as genes having > 0.5 correlation coefficient, while negatively correlated genes were defined as genes having < -0.5 correlation coefficient (p value < 0.05). Correlated gene expression concordance between two IL-1 family genes was assessed based on the intersection between positively and negatively correlated gene sets in the two genes. For concordant gene pair, positively correlated gene sets of the two IL-1 family genes intersect, and the negatively correlated gene sets also intersect. For discordant gene pair, genes positively correlated to one IL-1 family gene intersect with genes negatively correlated to the other IL-1 family genes.

Gene enrichment analysis

Gene enrichment analysis was performed using enrichR.[14] For each IL-1 family gene, positively and negatively correlated gene sets were analyzed separately. When more correlated genes were found, the top 1,000 most correlated genes were used for enrichment analysis. Gene enrichment analysis was done independently for cellular components, biological processes, transcription factors and microRNAs using GO_Cellular_Component_2023, GO_Biological_Process_2023, ENCODE_and_ChEA_Consensus_TFs_from_ChIP-X and miRTarBase_2017 databases, respectively. An adjusted p value < 0.05 was set as significance threshold. When more than 10 significant terms were found, the bar plot or dot plot was plotted for the top 10 terms. To identify the most frequent terms, the top five terms for each of the IL-1 family genes were extracted for each enrichment database. Bar plots showing terms enriched in more than one gene were visualized.

Transcription factor (TF) motif enrichment analysis

TF motif enrichment of the correlated genes was performed using homer.[15] Homer's findMotifs.pl parameters were "-start -500 -end 1 -len 8,20". The top enriched known motifs were identified. The significance threshold was an adjusted p value < 0.05.

Statistical analysis and visualization

Statistical analysis was computed using R or scipy in Python. Gene enrichment and motif enrichment significance were computed in enrichR and homer, respectively. ANOVA p value was computed in Python's *statsmodels*. Heatmaps were visualized using pheatmap in *R*. Other plots were made using matplotlib and seaborn packages in Python.

RESULTS

Heterogenous IL-1 gene expression dynamics in the brain

We retrieved RNA-seq data from three databases: HPA (https://www.proteinatlas.org/), BrainSpan (https://www.brainspan.org/) and GTEx (https://www.gtexportal.org/). The HPA dataset included RNA-seq data from 194 human brain and spinal cord subregions. BrainSpan data included 579 RNA-seq data across different ages, gender and brain regions. A total of 1,987 GTEx brain and spinal cord RNA-seq data of healthy donors was analyzed, averaged to obtain 251 unique samples from different ages, gender and regions. In total, gene expression data were obtained for 1,022 data sets from the three databases (Tables S1-S2).

We first performed clustering analysis. PCA using TPM expression values showed that samples from the same database tended to cluster and separated from samples from other databases (Figure S1A). The expression levels were unified and normalized using the HPA normalization approach (see Materials and Methods), but samples from the same database still tended to cluster together and separate from samples from other databases (Figure 1), suggesting incomplete removal of the batch effect. However, PCA clustering pattern based on IL-1 family genes (Figure 1B) was different from the PCA pattern of all genes (Figure 1A). Specifically, IL-1 family gene PCA showed that HPA and GTEx data clustered together, while BrainSpan data had some unique samples and other samples that clustered with samples from other databases. Notably, BrainSpan included samples from fetal and younger donors (see, in Figure 1C, the expression data for the ganglionic eminence, only present during fetal development), while GTEx and HPA data were mostly from adult samples, suggesting that the clustering reveals potentially real biological signals.

IL-1 family gene expression was heterogenous, with highly expressed genes like *SIGIRR*, *IL33* and *IL1RAPL1*, while the expression of some genes like *IL36A, IL36B, IL36G, IL36RN* and *IL1F10* was almost undetectable (Figure 1C). For the expressed genes, differences across databases and brain regions were observed. Indeed, expression ranking of IL-1 genes showed that the ranks in HPA (Figure S1B), BrainSpan (Figure S1C) and GTEx (Figure S1D) were not the same, revealing potential donor differences. Notably, across all databases, most of the highly expressed IL-1 genes were receptors, while the majority of the cytokines had low or undetectable expression (Figures 1C & Figures S1B-D). The expression levels of the different IL-1 family genes in the HPA (Figure S2), BrainSpan (Figure S3) and GTEx databases (Figure S4) often did not reflect the canonical ligand-receptor pairing. For example, *IL36A, B, G* and *RN* expression was practically undetectable in the normal brain, whereas their receptors *(IL1RL2* and the accessory protein *IL1RAP*) were reasonably expressed. Interestingly, some genes had uniform expression in some regions, and high donor-to-donor variability in other regions. For example, *IL33* HPA expression in the midbrain was quite uniform, with low variance, while its expression in hypothalamus had larger variance (Figure S3). The differences across databases and heterogeneity across different brain regions suggest that the expression of IL-1 family genes in the healthy human brain is potentially regulated by a series of factors/biological signals.

Factors associated with IL-1 family gene expression in the brain

ANOVA was applied to GTEx data to assess the influence of age, gender and brain region. The region was the most significant factor influencing expression levels (Figures 1A& 2A, Figure S4). As an example, expression of the three orphan receptor genes *SIGIRR*, *IL1RAPL1* and *IL1RAPL2* shows high region-dependent heterogeneity, with low expression in the cerebellum, and variable expression in the spinal cord (high for *SIGIRR* and *IL1RAPL1*, and low for *IL1RAPL2*) (Figure S4). *SIGIRR* expression varied across regions, with up to four-fold difference between the median expression in the cerebellar hemisphere and cervical C1 of the spinal cord (Figure 2B). Similarly, *IL1RL2* expression varied across brain regions, with very high expression in the cortex and much lower in the cerebellar hemisphere (Figure 2C). The expression of many genes was also affected by age. Examples are *IL1RAPL2* and *IL1RL2*, which tended to lower expression in older donors (Figure 2D). Interestingly, the interaction between donor age and gender seemed to affect the expression of specific genes (Figure 2A). For example, the gender difference in *IL1B* expression levels seemed to be dependent on age, with higher male expression observed in age groups 20-29 and 30-39 years and higher female expression at 70–79 years (Figure 2E).

To better investigate the effect of age on the expression levels of IL-1 family genes, we performed the ANOVA analysis on the BrainSpan data, with

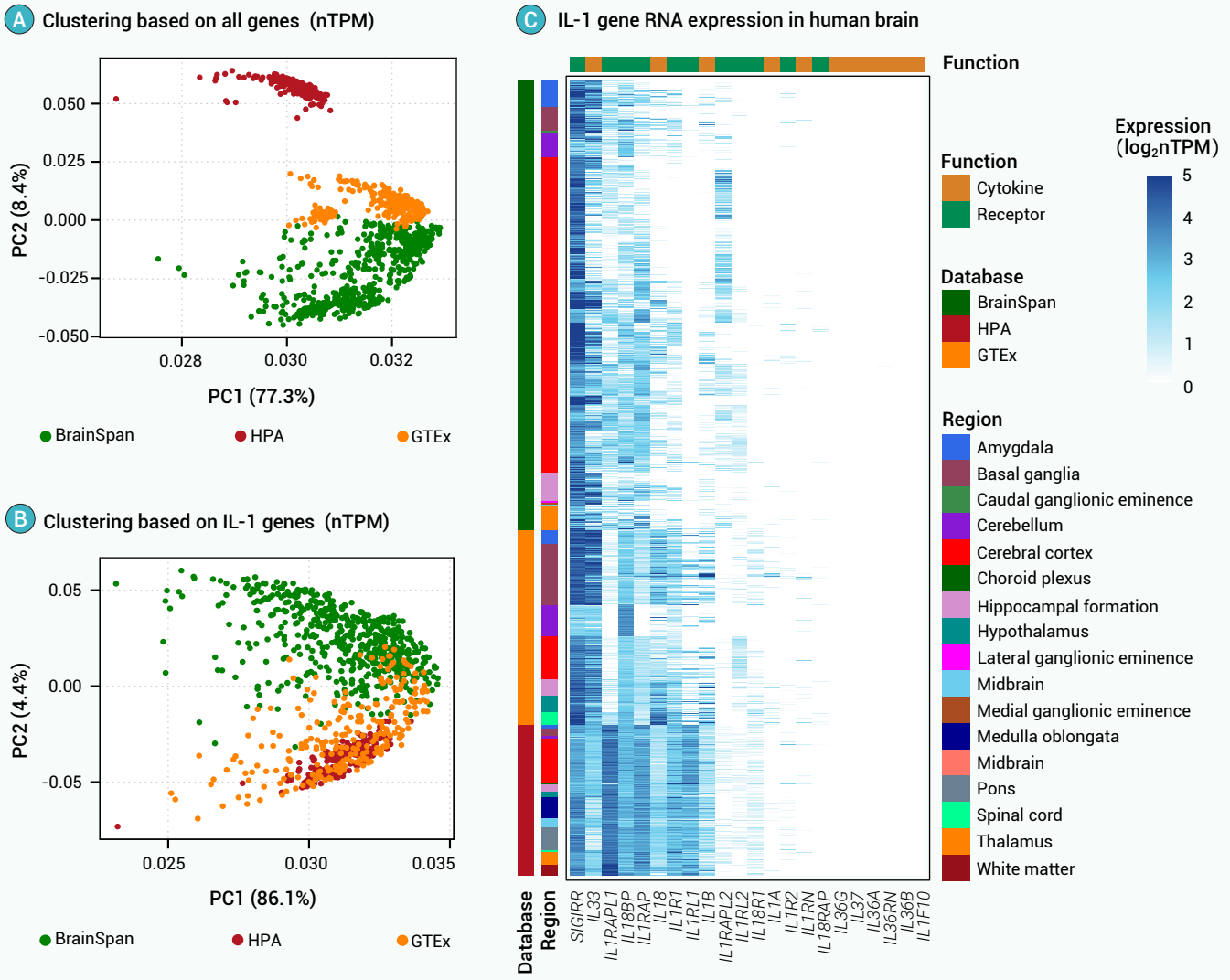

Figure 1. Dynamics of IL-1 family gene expression across different human brain regions (A) Principal component analysis showing the clustering of samples based on the expression of all protein-coding genes from the three databases (BrainSpan, HPA and GTEx). Spinal cord samples are included in the HPA and GTEx databases. Each point represents a specific region from different databases. (B) Principal component analysis showing the clustering of samples based on the expression of IL-1 family genes from the three databases. (C) Heatmap showing the expression levels of the IL-1 family genes across different databases and brain regions. The genes are ranked based on the expression levels. Normalized TPM (nTPM) values were used.

donors ranging from the fetal stage (8 post-conception weeks) up to 40 years. The results indeed showed an age-dependent variation of the expression level of many IL-1 family genes (Figure 2F). It is interesting to note that this age-related effect was evident in only two evolutionarily old cytokines, *IL1B* and *IL18* (presents in all vertebrates and not restricted to mammals) and to some extent in *IL33*, while it was observed for all the receptors (which are also not restricted to mammals). For receptors like *IL1RAPL1* and *IL1RL2*, the lowest expression was found at age 2-4 years (Figure 2G). Conversely, *SIGIRR* expression at age 2-4 years was higher than in other postnatal age groups, and the highest expression was in the fetal brain. When the correlation analysis was conducted independently for each brain region, IL-1 family genes with age-correlated expression were identified (Figure S5A). As an example, age correlation was positive for *IL1R2* in the dorsolateral prefrontal cortex (Pearson's coefficient = 0.8) and negative for *SIGIRR* in posteroventral (inferior) parietal cortex (Pearson's coefficient = -0.72) (Figure 2H). Even for the same gene, the patterns of correlation with age may be different across regions. For example, age correlation of *IL1RL2* was negative in the cerebellar cortex (Pearson's coefficient = -0.62) (Figures S5A-B) but positive in the orbital frontal cortex (Pearson's coefficient = 0.76) (Figures S5A & C). Other examples of IL-1 genes negatively correlated with age are *IL1RAPL2* in areas M1 and 4 in the primary motor cortex (Pearson's coefficient = -0.62) (Figures S5A & D), and *SIGIRR* in the striate cortex area V1/17 of the primary visual cortex (Pearson's coefficient = -0.68) (Figures S5A & E). Age-gender interaction was also found in the BrainSpan data. The strongest effect was found for *IL18*, *IL1R1*, *IL1R2* and *IL18RAP* expression (Figure 2F). Relatively weaker but significant effect was also found for *IL1RAP*, *IL1RAPL2*, *IL1RL2* and *IL18R1*. Taking *IL1RAPL2* as an example, female donors had slightly higher expression at the fetal stage and at 19-40 years, while no obvious differences could be detected in age groups 2-4 and 5-18 years (Figure 2I).

IL-1 family gene expression reveals unique co-expression patterns in the human brain

To check whether canonical cytokine-receptor interactions can occur in healthy human brain, we analyzed the GTEx database. We specifically checked if the expression of the IL-1 cytokine genes was correlated to the expression of the canonical target receptors. Although we found that some IL-1 family genes positively correlated with their targets (brown dots in Figure 3), the canonical targets were not the most correlated genes in any investigated

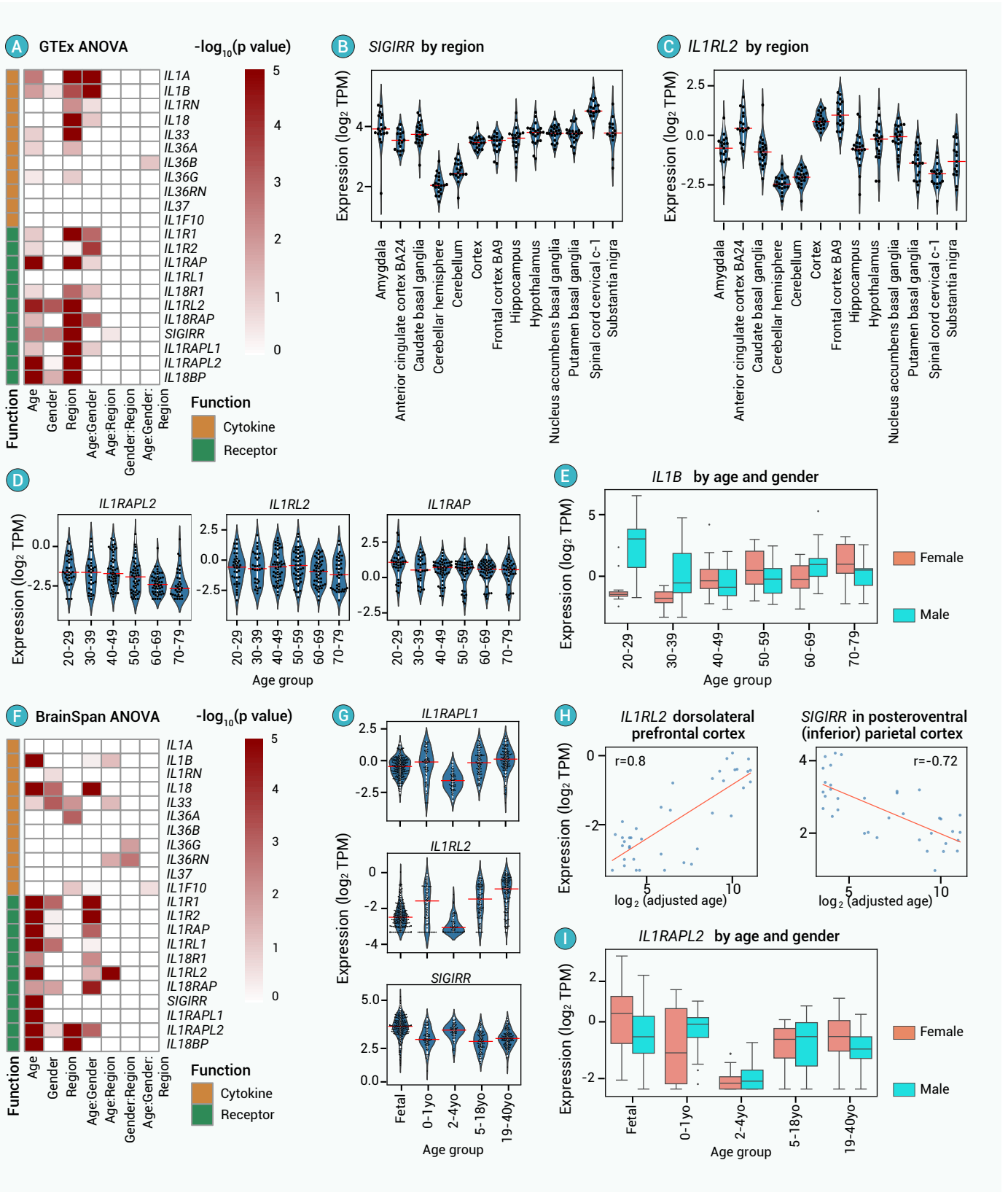

Figure 2. Assessment of factors affecting the expression levels of IL-1 family genes in the human brain (A) Analysis of variance (ANOVA) for IL-1 family gene expression in the GTEx database. ANOVA was performed for independent and interacting terms. (B-C) Expression levels of *SIGIRR* (B) and *IL1RL2* (C) across human brain and spinal cord regions. (D) *IL1RAPL2*, *IL1RL2* and *IL1RAP* gene expression levels across age groups. (E) Age and gender interaction in the expression of *IL1B*. GTEx database was used for panels A-E. (F) Analysis of variance (ANOVA) for IL-1 family gene expression in the BrainSpan database. ANOVA was performed for independent and interacting terms. (G) *IL1RAPL1*, *IL1RL2* and *SIGIRR* expression levels across age groups. (H) *IL1RL2* expression level is positively correlated with adjusted age in the dorsolateral prefrontal cortex, while *SIGIRR* expression level is negatively correlated with the adjusted age in the posteroventral (inferior) parietal cortex. Each blue dot represents a sample, the red line is the regression line, while r is the Pearson's correlation coefficient. (I) Interaction between age and gender in the expression levels of *IL1RAPL2*. The BrainSpan database was used for panels F-I. For violin plots in panels B, C, D, and G, each dot represents a sample, the middle red line shows the median, and the white vertical line inside the violin shows the interquartile range. For box plots in panels E and I, the box shows the interquartile range, the line inside the box shows the median, the whiskers show 1.5x interquartile range, while dots represent outliers.

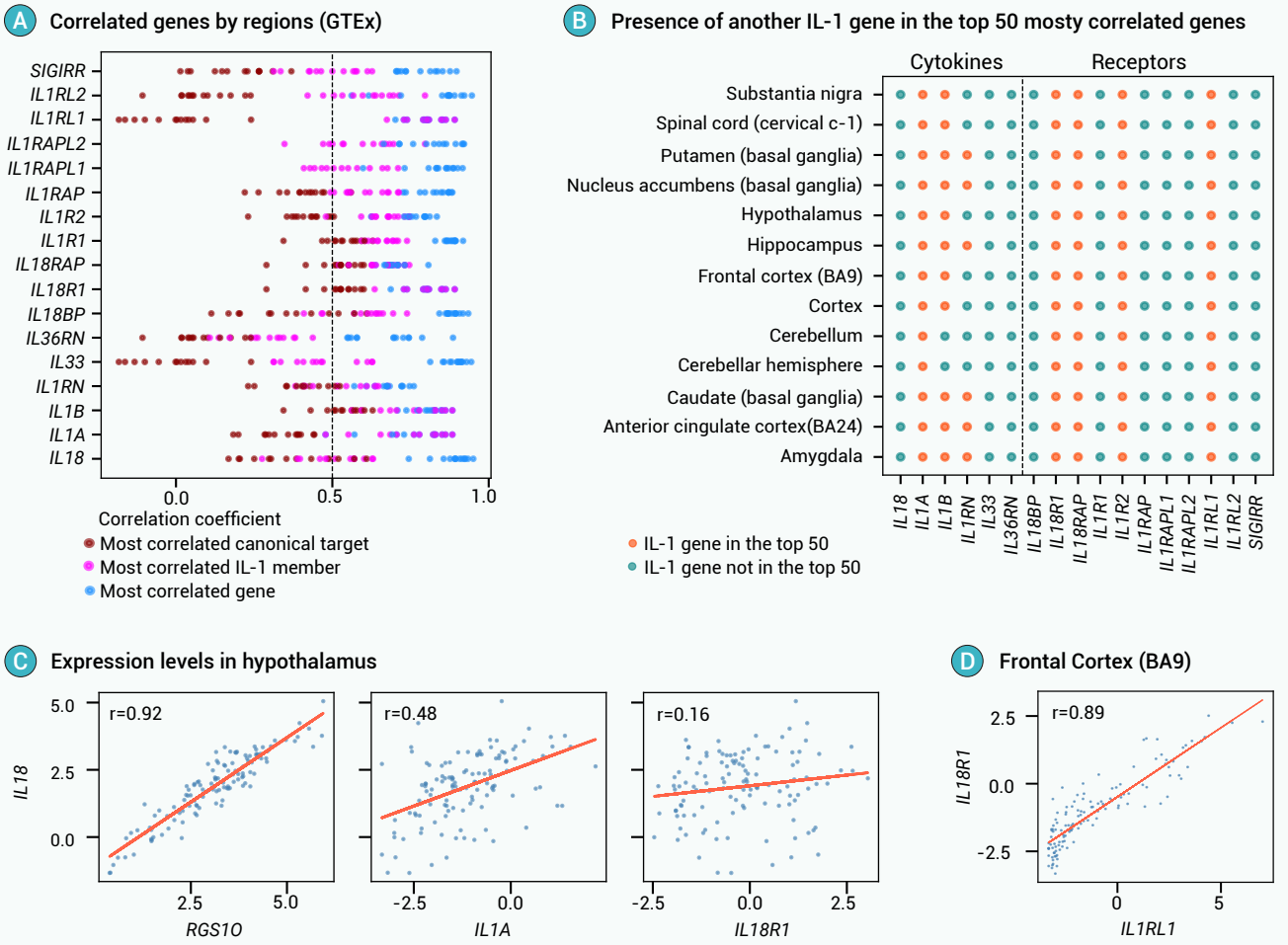

Figure 3. Correlated expression of IL-1 family genes across different brain regions (A) Expression correlation of IL-1 family genes across different brain and spinal cord areas. Each dot represents the correlation coefficient of the most correlated gene in a specific region. The most correlated canonical target gene, IL-1 family gene and any gene are shown in different colors. (B) The presence of other IL-1 family member genes in the top 50 most correlated genes to each IL-1 family gene in specific regions. (C) Correlation of *IL18* with *RGS10* (the most correlated gene), *IL1A* (the most correlated IL-1 member gene) and *IL18R1* (the most correlated canonical receptor) in human hypothalamus. (D) Correlation between *IL18R1* and *IL1RL1* in the frontal cortex. The GTEx database was used for all panels. For panels C and D, each blue dot represents a sample, the red line is the regression line, and r is Pearson's correlation coefficient.

brain region (Figure S6). Some IL-1 family genes were highly correlated with other IL-1 family genes that are not their target (pink dots in Figure 3A). For example, *IL1A* and *IL1B*, and *IL1RL1* and *IL18R1* were highly correlated between them but did not correlate with their target receptors (*IL1R1* for *IL1A* and *IL1B*, *IL1RAP* for *IL1RL1*, and *IL18RAP* for *IL18R1*) or cytokines (*IL33* for *IL1RL1*, and *IL18* for *IL18RAP*) (Figures 3A & S6). Indeed, we observed that for the majority of IL-1 genes the most correlated genes across different brain regions did not belong to the IL-1 family (blue dots in Figure 3A), while no IL-1 gene target (receptor/cytokine) was found in the top 50 most correlated genes. For some IL-1 genes, no other genes of the IL-1 family were even present in the top 50 most correlated genes (Figure 3B). When correlations were found, they were not between cognate ligands and receptors. For example, the most correlated IL-1 gene to *IL18* was *IL1A* (correlation coefficient = 0.48), while the canonical receptor *IL18R1* had very low correlation (correlation coefficient = 0.16) (Figure 3C). Similarly, the most correlated gene to *IL18R1* was not its canonical ligand *IL18*, but another receptor, *IL1RL1* (Figure 3D). Thus, the infrequent occurrence of co-expression of cytokines and their cognate receptors in the brain suggests that receptors and cytokines may have non-canonical and/or potentially non-immune functions in healthy conditions. In addition, this suggests a possible interaction with other genes to perform brain-specific functions. For example, the most correlated gene to *IL18* in the hypothalamus is *RGS10* (Pearson's correlation coefficient = 0.92) (Figure 3C), which encodes a neuroprotective G-protein signaling regulator.[16]

IL-1 family gene expression correlates with specific gene sets

We took advantage of the large number and heterogeneity of samples from the three databases to infer the relationship between IL-1 family genes and other co-expressed genes and their potential functions.[17] The PCA, based on the normalized expression from the three databases, shows four clusters of IL-1 family genes (Figure 4A). Cluster 1 contains all the genes encoding IL-1 and IL-18-related cytokines and receptors. Cluster 2 contains the genes encoding IL-33, all IL-36 molecules, the IL-37 and IL-38 (*IL1F10*) cytokines, and the orphan receptor IL-1R8 (*SIGIRR*). Cluster 3 includes *IL1RAPL1*, *IL1RL2* and *IL1RAP*, while cluster 4 contains only *IL1RAPL2*.

As previously done with region-specific analysis, we observed that the most correlated gene was never the canonical target (Figure S7), and that no IL-1 family gene had its target receptor or cytokine in the top 50 most correlated genes. These results further support the notion that IL-1 family gene interaction modules in the human brain are different from those underlying classical innate immune and inflammatory activities.

We also performed the clustering analysis based on the gene expression correlations. Consistent with the PCA, correlation heatmap revealed four clusters of IL-1 family genes (Figure S8A). *IL18R1* expression positively correlated with *IL1R1* and *IL1RL1* (Figure 4B). On the other hand, *IL1RAPL2* negatively correlated with most of the other IL-1 family genes, in particular ligands and receptors of the IL-1 (*IL1A*, *IL1B*, *IL1RN*, *IL1R1*, *IL1R2*), IL-18 (*IL18*, *IL18R1*, *IL18RAP*, *IL18BP*) and IL-33 systems (*IL33*, *IL1RL1*). Conversely,

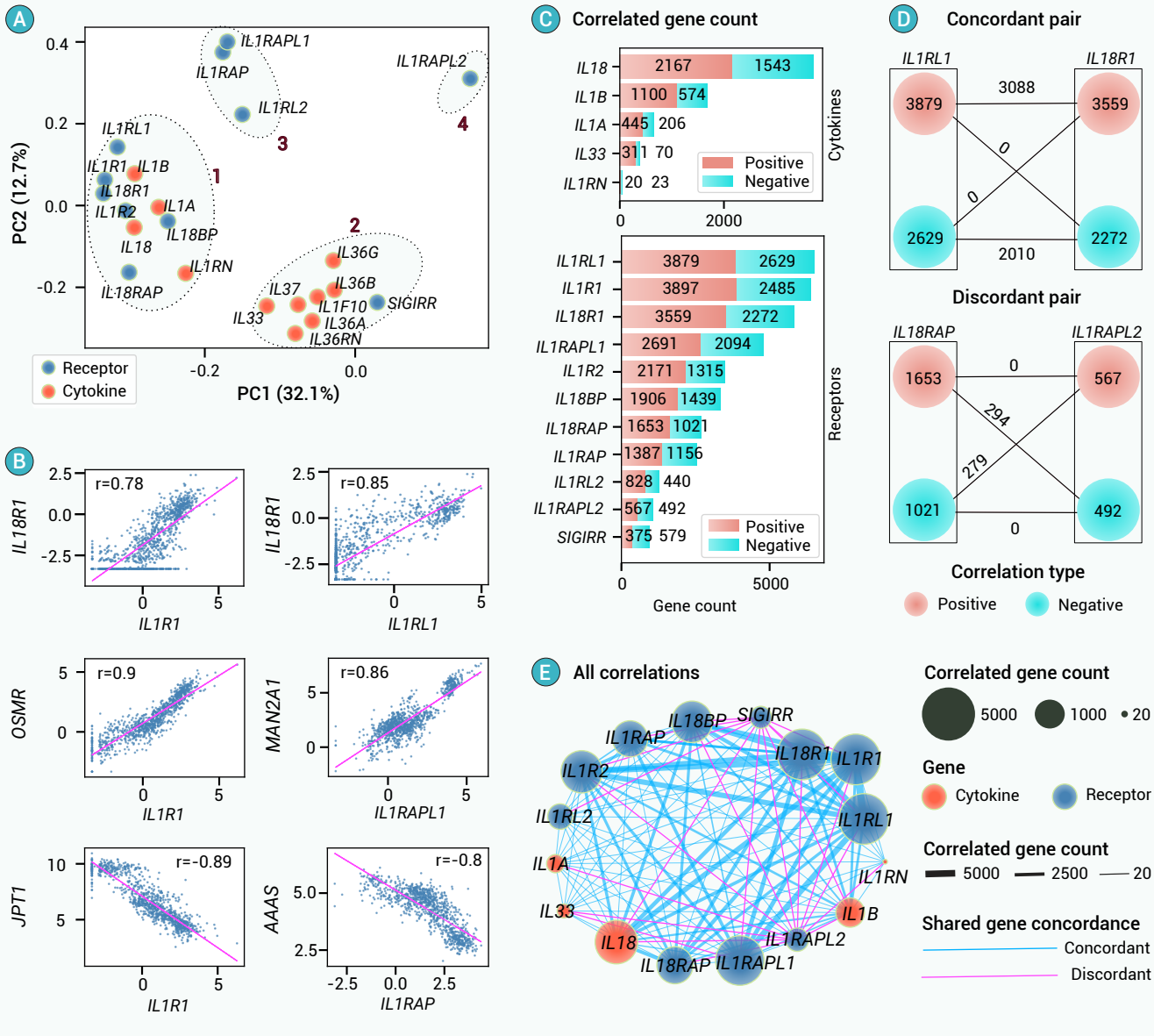

Figure 4. Co-expression analysis of IL-1 genes in the human brain (A) Principal component analysis showing the clustering of IL-1 family genes. (B) Gene expression correlations for selected gene pairs. Each blue dot represents a sample; the red line is the regression line, and r is the Pearson's correlation coefficient. (C) Numbers of correlated genes for each IL-1 gene. Correlated genes were defined by 0.5 absolute correlation coefficient and Pearson's correlation statistical significance of 0.05. (D) Correlated gene concordance for selected IL-1 gene pairs. The total number of correlated genes is shown in circles while the numbers of shared genes are shown on the connecting lines. (E) Gene networks showing the concordance of the gene expression correlations across IL-1 genes. The circle size corresponds to the number of correlated genes. The line color and width correspond to the type of concordance and the number of shared genes, respectively.

IL1RAPL2 showed a moderately positive correlation with *IL1RAP*, *IL1RL2* and *IL1RAPL1* (Figures S8A-B), suggesting a possible downregulatory role. Similarly, *SIGIRR* was found to negatively correlate with a number of IL-1 family genes.

Brain-expressed IL-1 family genes were highly correlated with many other genes. For example, high positive correlations were found between *IL1R1* and *OSMR*, encoding a component of the receptors for the cytokines OSM and IL-31 (Pearson's correlation coefficient = 0.9),[18] and between *IL1RAPL1* and *MAN2A1*, encoding mannosidase alpha class 2A member 1 (Pearson's correlation coefficient = 0.86). Conversely, high negative correlations were found between *IL1R1* and *JPT1*, encoding Jupiter microtubule-associated homolog 1 (Pearson's correlation coefficient = −0.89), and between *IL1RAP* and *AAAS*, encoding Aladin WD repeat nucleoporin (Pearson's correlation coefficient = −0.8) (Figure 4B). Interestingly, the correlated genes have been reported as having immune-related and/or brain-related functions.[18-21]

We investigated the frequency of correlated genes (Figure 4C). Generally, receptors tended to have more correlated genes than cytokines. The largest number of correlated genes (6,508) were found in *IL1RL1*. Among the cytokines, *IL18* had the largest number of correlated genes (3,710). At variance with other IL-1 family genes, *SIGIRR* had significantly more negatively than positively correlated genes (Chi-square p value = 3.98×10^{-11}), highlighting the role of *SIGIRR* as a negative regulator.[1-3]

Next, we checked if different IL-1 family genes are correlated with the same gene set. We defined concordant pair as two IL-1 family genes in which intersections were found for positive or negative gene sets. These gene pairs are likely to perform related functions. Examples of IL-1 genes with concordant intersection were *IL1RL1* and *IL18R1* with 3,088 genes found to be positively correlated to the two genes, and 2,010 genes negatively correlated to both (Figure 4D). Other examples of concordant pairs were *IL1R1-IL1RAPL1* and *IL18-IL1R2* (Figure S8C). For discordant pairs, positively correlated genes to one IL-1 family gene were found in the negatively correlated genes to the other IL-1 family gene. These gene pairs are likely to perform antagonistic functions. For example, 294 genes were found to be positively correlated to *IL18RAP* but negatively correlated to *IL1RAPL2*, and 279 genes were found to be negatively correlated to *IL18RAP* but positively correlated to *IL1RAPL2*

(Figure 4D). Another example of discordant pair includes *IL1RAPL1* and *IL1R1* (Figure S8C). The general view of the gene concordance is shown in the network (Figure 4E) and dot plot (Figure S8D). Generally, more genes were found in the concordant gene pairs. The majority of discordant gene pairs involved *IL1RAPL2* and *SIGIRR*, reflecting their negative correlations with other genes (Figure S8A), and further suggesting that these genes might perform unique roles in the human brain.

Enrichment analysis offers insights into potential functions of IL-1 family genes in the brain

While functional investigations are required for a clear definition of the physiological role of these genes in the brain, the analysis of co-expressed genes may give important insights into their potential functions.[17,17] Enrichment analysis of positively correlated genes using Biological Process Gene Ontology (GO) terms confirmed that many IL-1 family genes are involved in immune-related functions (Figure 5A & Table S3). In particular, positive regulation of cytokine production (GO:0001819) was found in the top 5 enriched GO terms for IL-1-related cytokine and receptor genes (*IL1A, IL1B, IL1R1, IL1R2*) and for IL-18-related genes (*IL18, IL18R1, IL18RAP*) (Figure 5A). Interestingly, these genes were mostly clustered together in the PCA (Figure 4A). Notably, besides immune functions, several brain-specific GO terms were also enriched in the positively correlated genes of several IL-1 family genes. In particular, terms related to sensory perception (Sensory perception of smell, GO:0007608; Sensory perception of chemical stimulus, GO:0007606; Detection of chemical stimulus in smell sensory perception, GO:0050911; Detection of chemical stimulus in sensory perception, GO:0050907) were enriched in the positively correlated genes of *IL1RAP, IL1RAPL1* and *IL1RL1* (Figure 5B). Interestingly, *IL1RL1*-positively correlated genes were also enriched in immune-related terms like regulation of type II interferon production (GO:0032649). Also, *IL1RL2*- and *IL1RAPL2*-positively correlated genes were enriched in terms related to nervous system development and synaptic organization and transmission (Figure 5B), suggesting brain-specific functions. *IL33*-positively correlated genes were enriched in fatty acid catabolism and oxidation (GO:0009062, GO:0006635, GO:0098916) and other GO terms related to amino acid metabolism (Figure 5B). Conversely, *SIGIRR*-positively correlated genes were enriched in a wide range of more basic biological processes involved in protein synthesis, such as translation (GO:0006412), macromolecule biosynthetic process (GO:0009059), gene expression (GO:0010467) and peptide biosynthetic process (GO:0043043) (Figure 5B).

To check if these observations were brain-specific or universal, we performed similar analysis in other tissues of the GTEx database, excluding the brain. Interestingly, most of the genes were enriched in immune-related functions in non-brain tissues, in addition to the well-known role in skin development/repair (Figure S9A). Specifically, *IL1RAP* and *SIGIRR* had immune-related functions, at variance with the brain results (Figure S9B). Thus, the correlation of *IL1RAP* with sensory smell perception and *SIGIRR* with protein biosynthesis appears to be brain-specific. Conversely, *IL1RAPL1* was found to be enriched in nervous system-related functions even outside the brain, although the correlation was mainly related to nerve and synapse development rather than sensory perception (Figure S9B). It should be noted that, unlike other IL-1 family genes whose brain expression was lower than in other tissues, *IL1RAPL1* was found to have higher expression in the brain (Figure S9C), suggesting a brain-biased expression.

The enrichment analysis of genes negatively correlated with IL-1 family genes showed that mRNA splicing via spliceosome (G0:0000398) and mRNA processing (G0:0006397) were the most enriched GO terms (Figure S10A & Table S4). Examples of genes with such negative correlation include *IL1RL2* and *IL1RAPL1* (Figure S10B). Genes negatively correlated with *IL1RAPL2* were enriched in fatty acid metabolic processes specifically in the brain (Figure S10B), suggesting a possible involvement of *IL1RAPL2* in downregulating fatty acid oxidation, a metabolic activity that is high in quiescent neuronal stem cells and decreases during stem cell proliferation in adult neurogenesis.[22] Genes negatively correlated with *SIGIRR* were enriched in various protein signaling processes and vesicle transport/recycling (Figure S10B). In particular, some brain-related transport functions, such as synaptic vesicle recycling (GO:0036465) and calcium ion-regulated exocytosis of neurotransmitter (GO:0048791), were significantly enriched in *SIGIRR*-negatively correlated gene.

Another way to infer gene functions is to consider the cellular components in which the correlated genes are enriched.[23] Secretory granule membrane (GO:0030667) was the most represented term, found in the top 5 terms for positively correlated genes of seven IL-1 family genes (Figure 5C & Table S4). Coincidentally, the same set of IL-1 family genes with potential cytokine regulatory/activation functions (Figure 5A) was positively correlated with genes localized to secretory granule membrane (Figure 5C). As an example, *IL1R2*-positively correlated genes were found to be enriched in secretory granule membrane and other granules (Figure S11A & Table S5). Consistent with biological process results, *IL1RL2* and *IL1RAPL2* were enriched in different nervous system components such as neuron projections (GO:0043005), axon (GO:0030424) and dendrites (GO:0030425) (Figure S11A). Interestingly, *SIGIRR*-negatively correlated genes were found to be enriched in neuron projection (GO:0043005) and synapses (also including GO:0048788) (Figure S11B & Table S6), highlighting potential brain-related functions.

Regulatory mechanisms of co-expressed genes

We performed transcription factor (TF) enrichment of the genes correlated to IL-1 genes. Positively correlated genes tended to be associated with the IRF8 transcription factor in eight IL-1 family genes (Figure 6 & Table S7), including all genes with enriched cytokine regulatory/activation-related functions, suggesting an IRF8-dependent regulation of immune responses.[24] Both the TF enrichment (Figure 6B) and TF motif overrepresentation (Figure 6C) showed that IRF8 was enriched in *IL18*-positively correlated genes. Similarly, both the TF enrichment (Figure 6D) and TF motif overrepresentation (Figure 6E) showed that *IL1RL2*-positively correlated genes were associated with REST/NRSF (RE1-silencing transcription factor/neuron-restrictive silencer factor), an important regulator of neuronal development, integrity and functions.[25] This is in line with the observed association with biological processes of synaptic transmission (Figure 5B) and neuronal cellular components (neuron projections, dendrites, axons; Figures 5C & S11A). It should be noted that an association with REST/NRSF was also found in genes positively correlated with *IL1RAPL2* (Table S7), which shares with *IL1RL2* a similar association with synaptic processes and neuronal components (Figures 5B-C & S11A). We also observed a number of TFs enriched in genes that were negatively correlated to IL-1 family genes (Table S8). Interestingly, some of the TFs, such as TAF1, MAX and MYC, which are enriched in negatively correlated genes, have been reported or suspected to have brain-related functions.[26-28] Specific TF motifs were enriched in the promoters of negatively and positively correlated genes (Tables S9-10).

As possible mechanism of post-transcriptional regulation, we examined the enrichment of miRNAs in correlated genes. Although enrichment in some miRNAs was found in positively correlated genes (Table S11), enrichments were mainly found in negatively correlated genes (Table S12). Notably, hsa-miR-615-3p was in the top five enriched miRNAs for twelve IL-1 family genes (Figure 6F). While hsa-miR-16-5p was the top enriched miRNA in *IL1RL1* negatively correlated genes (Figure 6G), the most enriched term in genes negatively correlated with *IL1A* was hsa-miR-615-3p (Figure 6H). Interestingly, while hsa-miR-16-5p has been reported in neuronal repair in rats,[29] hsa-miR-615-3p was observed to be upregulated in the frontal cortex of Huntington's disease patients.[30]

DISCUSSION AND CONCLUSIONS

IL-1 cytokines and receptors are important for immune and inflammatory responses.[1-3] By integrating data from three databases, we showed that numerous IL-1 family cytokines and receptors are heterogeneously expressed in the healthy human brain, in the absence of ongoing immune/inflammatory events. Some IL-1 family genes are highly expressed across multiple brain regions, while others are practically undetectable. Interestingly, most of the highly expressed IL-1 family genes are receptors, whereas *IL33*, *IL18* and *IL1B* are the only substantially expressed cytokines in the healthy human brain. Importantly, the cytokines and their cognate receptors were not the most correlated genes, suggesting potentially different, immune-unrelated functions for the IL-1 genes in the healthy human brain.

An important question is why certain IL-1 family genes are expressed in physiological conditions. A hypothesis is that a constant (homeostatic) supply of certain IL-1 genes/cytokines is required to be on standby in case of brain infections. Indeed, our results showed that numerous IL-1 genes positively correlate with other immune genes, suggesting immune-related functions. Thus, the substantial mRNA levels observed for several of these genes may be a strategy to ensure rapid translation and efficient defensive reaction upon infection. However, such strategy would be energy-intensive.[31] In addition,

Figure 5. Gene ontology enrichment analysis for potential functions of positively correlated genes (A) Frequency bar plot showing the number of IL-1 genes for which the indicated biological process GO term is in the top five enriched term in the positively correlated genes. (B) Biological process gene ontology enrichment for the genes positively correlated with *IL1RAP*, *IL1RAPL1*, *IL1RL1*, *IL1RAPL2*, *IL33* and *SIGIRR*. (C) Frequency bar plot showing the number of IL-1 genes for which the listed cellular component GO term is in the top five enriched terms in the positively correlated genes.

HPA[10] showed the actual translation of some IL-1 family genes in some brain regions in physiological, non-inflammatory conditions, suggesting that the protein products might indeed perform brain-related functions. Thus, the co-expression with some immune genes would not necessarily reflect immune-related roles, but it suggests that both the IL-1 genes and the co-expressed immune-related genes could be involved in brain-specific functions.

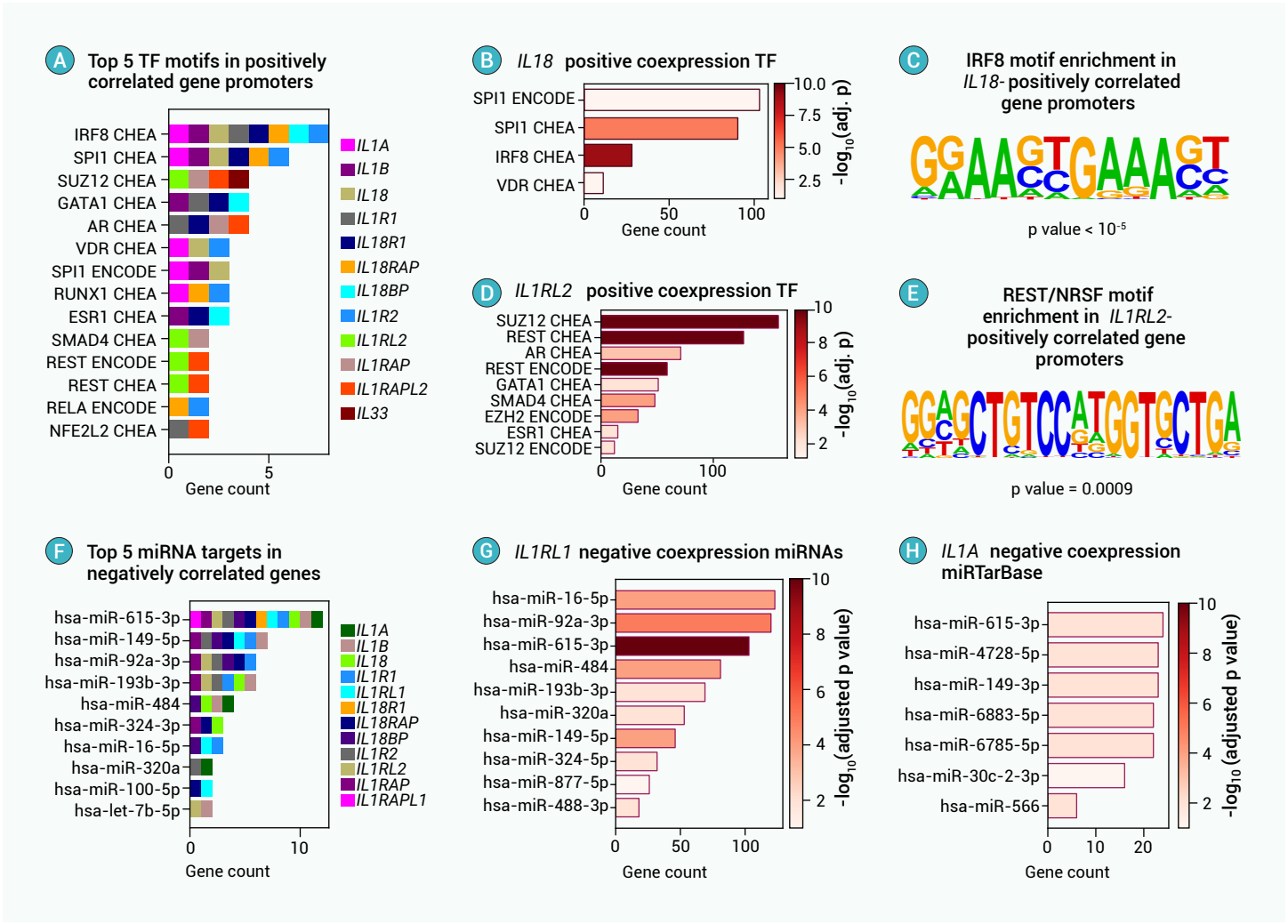

Figure 6. Transcription factor and miRNA enrichment analysis highlights the potential expression regulation of correlated genes (A) Frequency bar plot showing the number of IL-1 genes for which the indicated transcription factor (TF) is in the top five enriched term in the positively correlated genes. (B) TF enrichment for the genes positively correlated with *IL18*. (C) IRF8 motif is enriched in *IL18*-positively correlated genes. (D) TF enrichment for the genes positively correlated with *IL1RL2*. (E) REST-NRSF motif is enriched in *IL1RL2*-positively correlated genes. For y-axis in panels A, B and D, both TF and the database are shown (ENCODE: Encyclopedia of DNA Elements; CHEA: ChIP-X Enrichment Analysis). (F) Frequency bar plot showing the number of IL-1 genes for which the indicated miRNA is in the top five enriched term in the negatively correlated genes. (G) miRNA enrichment for the genes negatively correlated with *IL1RL1*. (H) miRNA enrichment for the genes negatively correlated with *IL1A*.

Gene enrichment analysis of correlated genes shows that certain brain-related functional terms are enriched. For example, *IL1RAPL2* is co-expressed with genes involved in neuronal development and synapses, and negatively correlates with genes involved in fatty acid oxidation, suggesting promotion of adult neurogenesis. This supports the potential role of this gene in brain development, consistent with previous functional and genome-wide association studies that linked the gene to mental development disorder, and suggests that *IL1RAPL2* is indeed involved in brain-related functions.[32] *IL1RL1*, *IL1RAP* and *IL1RAPL1* were found to be co-expressed with genes that perform smell and chemical signal perception functions. Interestingly, *IL1RL1* was linked with novel odors in a rat model.[33] The expression patterns of *SIGIRR* show a brain-specific positive correlation with genes involved in translation, transcription and peptide biosynthetic processes. This correlation only occurs in the brain, while the majority of other IL-1 genes inversely correlate with such processes in the brain. Conversely, *SIGIRR* negatively correlates with genes associated with brain functions such as neuron projections, axons, dendrites and synapses. It is interesting to note that *SIGIRR* dysregulation was reported in patients with major depressive disorder,[34] suggesting brain-related functions.

The brain expression patterns, and the regulatory, functional and cellular component enrichment analysis of the co-expressed genes suggest that IL-1 family genes could be broadly divided into four functional categories (Figure 4A). Cluster 1 genes correlate with immune genes in the brain (Figure 5A). Whether they are actually on standby against infections or they interact with immune-related genes to perform brain-specific functions requires further investigation and functional validation. Interestingly, although some of the IL-1 genes are highly correlated with other IL-1 family genes, the correlation with the canonical cytokines or receptors was limited, suggesting that the activities of the genes in the brain may differ from the canonical immune functions. Cluster 2 genes include lowly expressed genes (*IL36A*, *IL36B*, *IL36G*, *IL36RN*, *IL37*, *IL1F10*), and highly expressed *SIGIRR* and *IL33*. The latter two genes are correlated with genes that perform important functions like translation and fatty acid oxidation, a correlation that only occurs in the brain. Genes in clusters 3 and 4 are associated with genes that perform brain-specific functions (Figures 5B-C).

In summary, this study shows that many genes of the IL-1 family are expressed in the healthy human brain in homeostatic conditions and hypothesizes that they could be involved in brain-specific functions rather than immune/inflammatory activities. While some cytokines (*IL1A*, *IL1B*, *IL1RN*, *IL18*) could have immune-related functions in the healthy brain, poor co-expression between cytokines and their cognate receptors and significant co-expression with genes involved in non-immune mechanisms suggest potentially brain-specific non-inflammatory functions. Thus, this study suggests the possibility that several members of the IL-1 family (such as the cytokine *IL33* and the receptors *IL1RAP*, *IL1RL1*, *IL1RL2*, *IL1RAPL1*, *IL1RAPL2* and *SIGIRR*) may have non-immune non-inflammatory homeostatic functions in the human CNS, and that these factors may perform CNS-specific activities important in neurodevelopment and neurotransmission.

We can hypothesize that these molecules have a dual function in the CNS, a non-immune neurotransmission-related function in physiological conditions,

and an immune/inflammatory role when overexpressed in disease conditions. In several diseases, such as inflammatory and degenerative conditions, a substantial production and immune/inflammatory activity have been described for IL-1-related molecules,[8] which would necessarily overshadow any physiological function. Thus, reliable functional studies are still necessary for validating the hypothesis of a human brain-specific role of IL-1 molecules in physiological and homeostatic conditions without disease triggers. Very little if any information on the physiological role of these molecules in the human brain is currently available, besides the limited information inferred from diseases based on genetic mutations (e.g., the mutations/deletions in the *IL1RAPL2* gene that are associated to X-linked mental retardation).[32] Mouse and rat models have provided some evidence,[7] which however needs validation in the human system, given the substantial differences between the human and rodent brain. It is expected that important developments and reliable information will be obtained in the future by applying single cell spatial transcriptomics and proteomics to specific brain areas, so as to detect the occurrence of single brain-specific activities and the contribution of the different IL-1-related molecules to each of them. Despite the limitations due to the lack of functional validation in the human brain, this study provides an important foundation upon which future functional experiments and validation studies could be built.

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AUTHOR CONTRIBUTIONS

Isaac Adeyemi Babarinde contributed to the conception of the work, performed the database search and acquisition, analysis and interpretation of data, and wrote the manuscript. Diana Boraschi contributed to the conception of the work, critical interpretation of results and manuscript writing. Both authors approved the final version.

DECLARATION OF INTERESTS

Diana Boraschi serves as co-Editor-in-Chief of The Innovation Life and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. Isaac Adeyemi Babarinde declares no competing interests.

DATA AND CODE AVAILABILITY

Original data are from public databases. Codes are available from the corresponding author upon reasonable request.

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-life.2026.100183