**Supplementary results**

**TREM2 brain transcript-specific studies in AD and TREM2 mutation carriers**

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*TREM2 expression levels are not affected by disease status*

Using the quasi-mapping mode of Kallisto, we were able to estimate the log10TPM for the *TREM2* gene level and each of its isoforms, for each of the studies and comparison groups (Supplemental Figure1). The mean expression patterns among the different studies and comparison groups are shown in Supplemental Table1. The mean expression values in the Knight-ADRC study for the *TREM2* gene level in the different groups were 1.87 (SD: 0.21), 1.98 (SD: 0.27), 1.89 (SD: 0.23) and 1.97 (SD: 0.09) for control, cases, carriers Trem2-carriers and NHD-carriers respectively. In the case of MSBB-BM36 study, the means expression values were 1.92 (SD: 0.33), 2.06 (SD: 0.26) and 2.13 (SD: 0.31) for control, cases, carriers TREM2-carriers. In the MCBB study, the mean expression values were 2.64 (SD: 0.37), 2.74 (SD: 0.25) and 2.60 (SD: 0.31). In the last two studies, no data was available for NHD carriers.

The log10TPM count for each transcript was expressed relative to the canonical transcript ENST00000373113 (Figure1, Table 4). The mean expression value of ENST00000373113 was almost twice as high as the transcript ENST00000373122 and the soluble TREM2 transcript ENST00000338469 when combined in all the studies, in controls (p= 1.57×10-43, p= 2.61×10-35), cases (p= 1.86×10-79, p= 2.80×10-74) and in control + cases (p= 1.13×10-120, p= 4.76×10-107). This pattern was observed in each independent study for each comparison group. The mean expression value of transcript ENST00000338469, which encodes soluble *TREM2*, was higher than ENST00000373122 when all studies were combined (control: p=0.0090, case: p= 0.0095 and control + case: p= 0.0002) most of the significance of these p values was driven by MCBB.

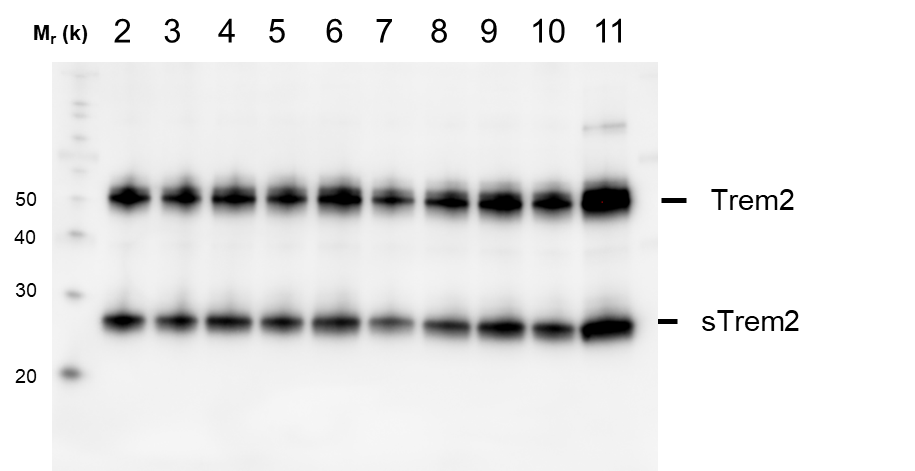
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| **Supplementary Table 1:** ***TREM2* mean expression levels for each transcript and in each study** | | | | |
| **Knight-ADRC** | | | | |
| **Transcript** | **Control**  **Mean (SD)** | **Cases**  **Mean (SD)** | **TREM2-carriers**  **Mean (SD)** | **NHD-carries**  **Mean (SD)** |
| TREM2 | 1.87 (0.21) | 1.98 (0.27) | 1.89 (0.23) | 1.97 (0.09) |
| ENST00000373113 | 1.74 (0.28) | 1.82 (0.37) | 1.76 (0.27) | 1.83 (0.18) |
| ENST00000373122 | 1.01 (0.27) | 1.14 (0.27) | 0.97 (0.30) | 1.18 (0.00) |
| ENST00000338469 | 0.95 (0.21) | 1.13 (0.25) | 1.04 (0.27) | 1.15(0.00) |
| **Mount Sinai Brain Bank-BM36** | | | | |
| TREM2 | 1.92 (0.33) | 2.06 (0.26) | 2.13(0.31) | NP |
| ENST00000373113 | 1.80 (0.36) | 1.97 (0.27) | 2.04 (0.34) | NP |
| ENST00000373122 | 1.06 (0.25) | 1.08 (0.25) | 1.06 (0.28) | NP |
| ENST00000338469 | 1.16 (0.33) | 1.18 (0.35) | 1.32 (0.31) | NP |
| **Mayo Clinic Brain Bank** | | | | |
| TREM2 | 2.64 (0.37) | 2.74 (0.25) | 2.60 (0.31) | NP |
| ENST00000373113 | 2.56 (0.38) | 2.65 (0.26) | 2.54 (0.26) | NP |
| ENST00000373122 | 1.48 (0.32) | 1.56 (0.34) | 1.31 (0.39) | NP |
| ENST00000338469 | 1.64 (0.46) | 1.66 (0.37) | 1.53 (0.40) | NP |
| Gene expression is showed in log10 Transcripts Per Million (log10TPM)  SD: Standard Deviation  NP. Not present | | | | |

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| **Supplementary Table 2: Knight-ADRC results from each comparison group.** | | | | |
|  | ***TREM2*** | **ENST00000373113**  **(canonical transcript)** | **ENST00000373122** | **ENST00000338469 (soluble TREM2)** |
| Control vs Case | 0.15/0.09 | 0.11/0.39 | 0.12/0.25 | **0.25/0.03** |
| Control vs  TREM2-carriers | 0.02/0.85 | 0.003/0.97 | -0.01/0.94 | -0.002/0.97 |
| Case vs  TREM2-carriers | -0.12/0.18 | -0.1/0.45 | **-0.23/0.03** | -0.07/0.47 |
| Control vs p.R47H | -0.01/0.96 | -0.09/0.69 | **-0.47/0.007** | 0.15/0.31 |
| Case vs p.R47H | -0.16/0.34 | -0.02/0.91 | -0.08/0.52 | -0.06/0.71 |
| Control vs p.R62H | -0.002/0.98 | -0.02/0.91 | -0.08/0.52 | -0.06/0.71 |
| Case vs p.R62H | -0.14/0.21 | -0.11/0.47 | -0.19/0.13 | -0.09/0.46 |

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| **Supplementary Table 3: Mount Sinai Brain Bank (MSBB) –BM36 results from each comparison group.** | | | | |
|  | ***TREM2*** | **ENST00000373113**  **(canonical transcript)** | **ENST00000373122** | **ENST00000338469 (soluble TREM2)** |
| Control vs Case | **0.16/0.001** | **0.19/0.001** | 0.05/0.45 | 0.10/0.18 |
| Control vs  TREM2-carriers | **0.22/0.03** | **0.25/0.02** | 0.03/0.84 | **0.25/0.04** |
| Case vs  TREM2-carriers | 0.06/0.34 | 0.06/0.38 | -0.02/0.83 | 0.15/0.11 |
| Control vs p.R47H | **0.26/0.03** | **0.27/0.05** | 0.03/0.87 | **0.29/0.04** |
| Case vs p.R47H | 0.09/0.28 | 0.06/0.52 | -0.003/0.98 | 0.19/0.13 |
| Control vs p.R62H | 0.23/0.17 | 0.33/0.09 | NA | 0.41/0.08 |
| Case vs p.R62H | 0.07/0.56 | 0.12/0.37 | NA | 0.25/0.23 |

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| **Supplementary Table 4: Mayo Clinic Brain Bank (MCBB) results from each comparison group** | | | | |
|  | ***TREM2*** | **ENST00000373113**  **(canonical transcript)** | **ENST00000373122** | **ENST00000338469 (soluble TREM2)** |
| Control vs Case | 0.005/0.93 | 0.004/0.95 | 0.07/0.23 | -0.10/0.19 |
| Control vs  TREM2-carriers | -0.07/0.63 | -0.05/0.73 | -0.17/0.23 | -0.17/0.37 |
| Case vs  TREM2-carriers | -0.14/0.17 | -0.12/0.25 | -0.27/0.07 | -0.13/0.36 |
| Control vs p.R62H | -0.14/0.43 | -0.11/0.53 | **-0.35/0.04** | -0.21/0.35 |
| Case vs p.R62H | -0.19/0.10 | -0.16/0.17 | **-0.44/0.01** | -0.16/0.34 |

Figure S1

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**Figure 1 Immuno precipitation sTREM2 in brain samples**