

Characterization of TREM2 Variants based on Quantitative Deficits and Maturation Defects

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TREM2, Maturation, Alzheimer's disease

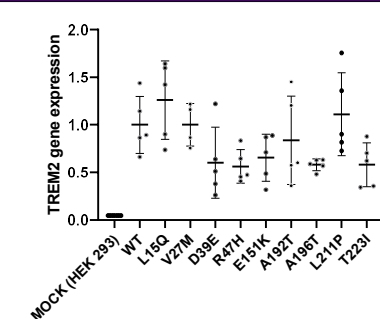
INTRODUCTION

Triggering Receptor Expressed on Myeloid Cells 2 (*TREM2*) is a pivotal receptor for maintaining immune and metabolic homeostasis in the brain. While *TREM2* was known to mediate amyloid-beta clearance, the impact of genetic variants on its post-translational processing remained poorly understood. In this study, we investigated the consequences of various Alzheimer's disease (AD)-related *TREM2* mutations, especially affecting protein maturation from the cytosol to cell membrane.

METHODS

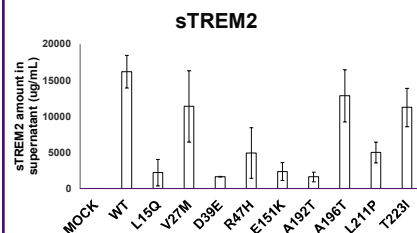
- Transfection:** *TREM2* wild-type (WT) and variants (L15Q, V27M, D39E, R47H, E151K, A192T, A196T, L211P, and T223I) were transfected into HEK293 cells with Lipofectamine technology.
- Confirmation Transfection:** Gene expressions were validated by RT-qPCR.
- TREM2 protein Analysis:** *TREM2* levels were quantified in the cytosol and solubilized membrane fractions through Western blot. Soluble *TREM2* (sTREM2) in the supernatant was measured by ELISA.
- Analysis:** All data was normalized by WT.

RESULT



Success of Transfection.

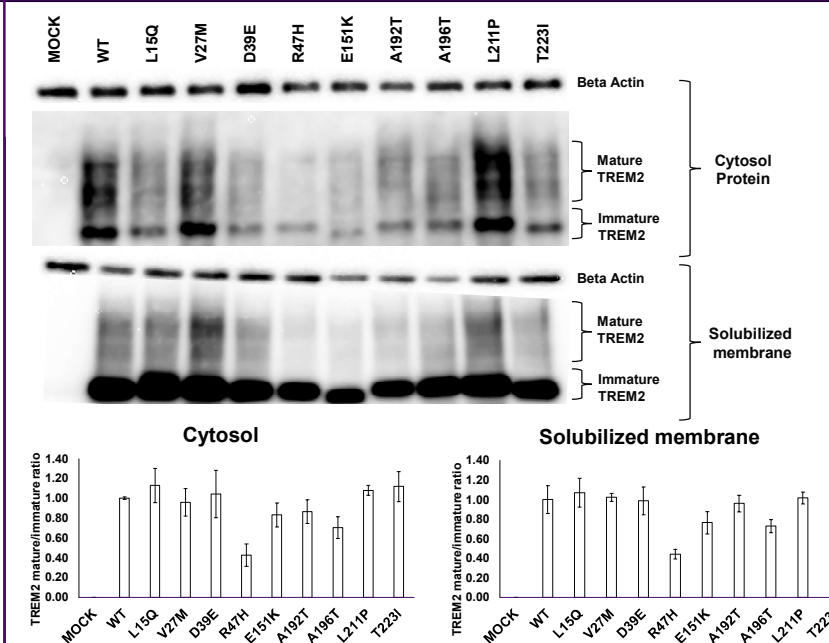
- All variants were successfully expressed, showing higher gene expression levels than the MOCK (non-transfection).



Decreasing sTREM2 in mutant.

- sTREM2 levels in the supernatant were decreased in all mutated cells than WT.

RESULT



Change of TREM2 protein maturation depending on mutation.

- To evaluate protein processing efficiency, the mature/immature ratio was analyzed in each fraction.
- In cytosol, the ratio decreased in R47H, E151K, A192T, and A196T, remained similar to WT in V27M and L211P, and increased in L15Q, D39E, and T223I.
- In the membrane fraction, which was the functional site of the receptor, the ratio exhibited a similar trend to that of cytosol.

CONCLUSIONS

Our findings demonstrated that *TREM2* mutations drove loss-of-function through mutation-specific mechanisms. The representative R47H variant, along with A192T and A196T, decreased both protein levels and maturation ratios, indicating a dual deficit in protein quantity and maturation efficiency. In contrast, L15Q, D39E, E151K, and T223I presented the reduced total protein levels, while maintaining similar maturation ratios to WT, suggesting a predominantly quantitative loss of function. Interestingly, V27M showed the increased total protein, but failed to reach the membrane proportionally, indicating a defect in the *TREM2* trafficking pathway. Lastly, L211P increased total protein with a maturation profile than WT. These diverse defects in protein processing likely impaired the neuroprotective functions, contributing to AD pathogenesis.

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