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An Exploration of TREX1 Variants of Uncertain Significance and Their Potential Impact on Autoimmunity in Systemic Lupus Erythematosus and Aicardi-Goutieres Syndrome

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Poster Title: An exploration of *TREX1* variants of uncertain significance and their potential impact on autoimmunity in systemic lupus erythematosus and Aicardi-Goutieres syndrome

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Abstract:

TREX1 is a gene responsible for encoding a 3'-to-5' DNA exonuclease in human cells. Under normal conditions *TREX1* removes bases from the free 3' end to enhance DNA damage and prevent DNA end reannealing and rapid repair. Mutations in *TREX1*, which result in the absence of the 3'-to-5' DNA exonuclease and the intracellular accumulation of unneeded DNA and RNA, have been shown to trigger immune dysfunction leading to diseases such as systemic lupus erythematosus (SLE) and Aicardi-Goutières Syndrome (AGS). The goal of this study is to determine the potential impact of a *TREX1* missense mutation with uncertain clinical significance (VUS). This study relies heavily upon the evolutionary relatedness between humans (*Homo sapiens*) and nematodes (*Caenorhabditis elegans*) to examine conservation of *TREX1* VUS across species. Thirty *TREX1* variants associated with SLE and AGS were screened and analyzed for conservation in the *TREX1* nematode ortholog *W02F12.4*. These variants included those with pathogenic, likely pathogenic, likely benign, and uncertain clinical significance. Variant location and conservation along the *W02F12.4* gene was identified for all screened variants. Out of the 30 screened variants, two were found to be conserved in both *TREX1* and *W02F12.4*. These mutations were c.197A>G (p.Lys66Arg) and c.226G>T (p.Ala76Ser), both of which have uncertain clinical significance. Patient variant c.226G>T (p.Ala76Ser) was selected for further investigation due to its proximity with a likely pathogenic and pathogenic variant. PolyPhen-2 analysis predicted this VUS to be probably damaging with scores of 0.982 (HumDiv) and 0.953 (HumVar). DNA primers have been designed in preparation for the amplification of the specific VUS region within *W02F12.4* using polymerase chain reaction. Future experiments including RNA guide design and microinjection and use of CRISPR-Cas9 reagents for gene editing of *W02F12.4* to generate this VUS *C. elegans* model. This will allow us to support or refute the potential pathogenicity of c.226G>T (p.Ala76Ser) *in vivo* through phenotypic changes we observe in the mutant nematode compared to wildtype. This will help provide important insight into the structure and function of autoimmune-associated *TREX1* VUS being identified in patients.