An Aicardi-Goutières Syndrome-Causative Point Mutation in *Adar1* Gene Invokes Multiorgan Inflammation and Late-Onset Encephalopathy in Mice

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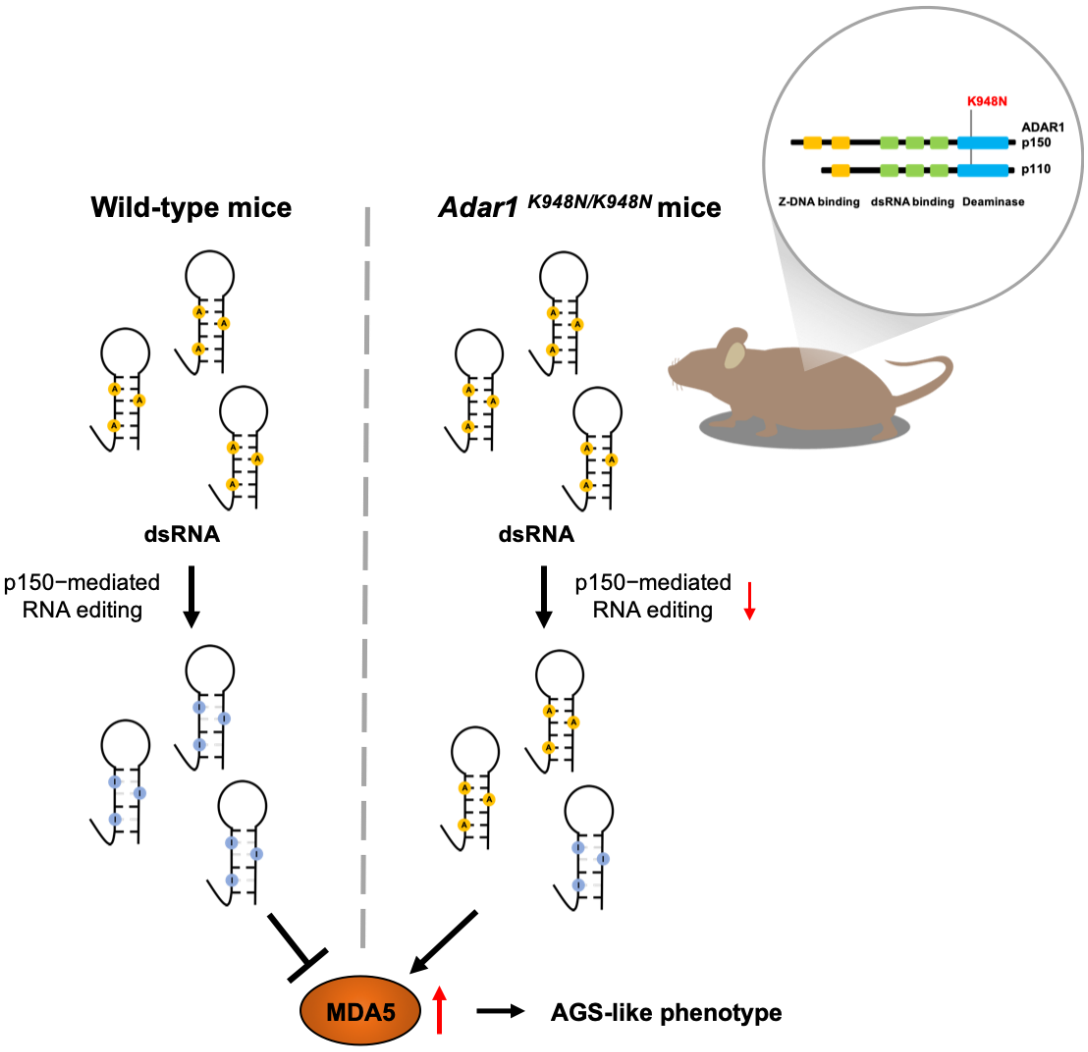
Aicardi−Goutières syndrome (AGS) is a congenital inflammatory disorder accompanied by overactivated type I IFN signaling and encephalopathy with leukodystrophy and intracranial calcification. To date, none of the mouse models carrying an AGS-causative mutation has mimicked such brain pathology. Here, we established a mutant mouse model carrying a K948N point mutation, corresponding to an AGS-causative K999N mutation, located in a deaminase domain of the *Adar1* gene that encodes an RNA editing enzyme. *Adar1*$^{K948N/K948N}$ mice displayed postnatal growth retardation. Hyperplasia of splenic white pulps with germinal centers and hepatic focal inflammation were observed from 2 mo of age. Inflammation developed in the lungs and heart with lymphocyte infiltration in an age-dependent manner. Furthermore, white matter abnormalities with astrocytosis and microgliosis were detected at 1 y of age. The increased expression of IFN-stimulated genes was detected in multiple organs, including the brain, from birth. In addition, single-nucleus RNA sequencing revealed that this elevated expression of IFN-stimulated genes was commonly observed in all neuronal subtypes, including neurons, oligodendrocytes, and astrocytes. We further showed that a K948N point mutation reduced the RNA editing activity of ADAR1 in vivo. The pathological abnormalities found in *Adar1*$^{K948N/K948N}$ mice were ameliorated by either the concurrent deletion of MDA5, a cytosolic sensor of unedited transcripts, or the sole expression of active ADAR1 p150, an isoform of ADAR1. Collectively, such data suggest that although the degree is mild, *Adar1*$^{K948N/K948N}$ mice mimic multiple AGS phenotypes, including encephalopathy, which is caused by reduced RNA editing activity of the ADAR1 p150 isoform.


K948N
ADAR1
p150
p110
Z-DNA binding
dsRNA binding
Deaminase
Wild-type mice
Adar1 K948N/K948N mice
dsRNA
dsRNA
p150−mediated
RNA editing
p150−mediated
RNA editing
MDA5
AGS-like phenotype