

Table S1. Values of two-sample Kolmogorov-Smirnov test comparing distribution of PrP oligomers across 14 fractions of brain homogenate separated by sucrose gradient centrifugation. Pairwise comparison was performed between groups of animals of indicated *APOE* genotype, which were inoculated with normal brain homogenate (NBH) or with 22L mouse adapted scrapie strain and killed at 23 weeks post inoculation.

	$\epsilon 2/\epsilon 2_{\text{NBH}}$	$\epsilon 3/\epsilon 3_{\text{NBH}}$	$\epsilon 4/\epsilon 4_{\text{NBH}}$	$Apoe^{-/-}_{22\text{L}}$	$\epsilon 2/\epsilon 2_{22\text{L}}$	$\epsilon 3/\epsilon 3_{22\text{L}}$	$\epsilon 4/\epsilon 4_{22\text{L}}$
$Apoe^{-/-}_{\text{NBH}}$	$p = 0.065$	$p = 0.078$	$p = 0.267$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
$\epsilon 2/\epsilon 2_{\text{NBH}}$		$p > 0.999$	$p > 0.999$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
$\epsilon 3/\epsilon 3_{\text{NBH}}$			$p > 0.999$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
$\epsilon 4/\epsilon 4_{\text{NBH}}$				$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
$Apoe^{-/-}_{22\text{L}}$					$p = 0.126$	$p = 0.274$	$p < 0.0001$
$\epsilon 2/\epsilon 2_{22\text{L}}$						$p < 0.01$	$p < 0.0001$
$\epsilon 3/\epsilon 3_{22\text{L}}$							$p < 0.0001$

Table S2. List of microglia marker genes significantly upregulated in 22L infected mice. Values represent fold increase relative to normal brain homogenate (NBH) inoculated controls for matching *APOE* genotype. Highly upregulated genes (≥ 10 -fold relative to NBH) are underscored. ns – not significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$ (Holm's-Sidak's post hoc test).

Gene Symbol	Encoded protein	$\varepsilon 2/\varepsilon 2$	$\varepsilon 3/\varepsilon 3$	$\varepsilon 4/\varepsilon 4$
<i>Aif1</i>	Allograft inflammatory factor 1	2.9****	2.4***	3.6****
<i>Csf1r</i>	Macrophage colony stimulating factor 1 receptor	2.0****	1.7**	2.3****
<i>Cst7</i>	Cystatin-F	<u>110.4****</u>	<u>51.1**</u>	<u>134.6****</u>
<i>P2ry12</i>	P2Y purinoceptor 12	1.8****	1.3*	1.7****
<i>Siglech</i>	Sialic acid binding Ig-like lectin H	2.2****	1.8***	2.5****
<i>Tmem119</i>	Transmembrane protein119	2.5****	1.7*	2.8****
<i>C1qa</i>	Complement C1q subcomponent subunit A	5.2****	4.1****	7.0****
<i>C1qb</i>	Complement C1q subcomponent subunit B	4.8****	3.5****	6.5****
<i>C1qc</i>	Complement C1q subcomponent subunit C	4.6****	3.5****	6.0****
<i>C4a/b</i>	Complement component 4a	7.8****	5.9****	<u>11.2****</u>
<i>C3ar1</i>	Complement C3a receptor 1	3.9****	3.6****	5.4****
<i>Csf3r</i>	Colony stimulating factor3 receptor	3.7****	2.8**	3.8****
<i>Csf1</i>	Colony stimulating factor 1	1.7****	1.6****	2.2****
<i>Ccl3</i>	C-C motif chemokine ligand 3	<u>15.3****</u>	<u>10.0***</u>	<u>18.3****</u>
<i>Axl</i>	AXL receptor tyrosine kinase	2.0****	1.7***	2.2****
<i>Cx3cr1</i>	CX3C motif chemokine receptor 1	2.4****	1.6**	2.4****
<i>Fcrls</i>	Fc receptor-like S, scavenger receptor	3.6****	2.5****	4.2****
<i>Clec7a</i>	C-type lectin domain family 7, member A	<u>22.5****</u>	<u>14.2****</u>	<u>23.0****</u>
<i>Mertk</i>	Tyrosine-protein kinase Mer	1.7***	1.6***	2****
<i>P2ry6</i>	P2Y purinoceptor 6	1.7*	1.5 ^{ns}	2.2***
<i>Stab1</i>	Stabilin 1	1.3 ^{ns}	1.1 ^{ns}	1.9****
<i>Trem2</i>	Triggering receptor expressed on myeloid cells 2	5.4****	3.4***	6.0****
<i>Tyrobp</i>	TYRO protein tyrosine kinase binding protein	4.5****	3.3***	5.1****

Table S3. List of astrocytic marker genes significantly upregulated in 22L infected mice. Values represent fold increase relative to normal brain homogenate (NBH) inoculated controls of matching *APOE* genotype. Highly upregulated genes (≥ 10 -fold relative to NBH) are underscored. ns – not significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$ (Holm's-Sidak's post hoc test).

Gene Symbol	Encoded protein	$\epsilon 2/\epsilon 2$	$\epsilon 3/\epsilon 3$	$\epsilon 4/\epsilon 4$
<i>Aldh1l1</i>	Aldehyde dehydrogenase 1 family, member L1	1.8****	1.5***	2.1****
<i>Aqp4</i>	Aquaporin 4	2.3****	1.9****	2.5****
<i>Gfap</i>	Glial fibrillary acidic protein	<u>14.7****</u>	<u>12.9****</u>	<u>23.7****</u>
<i>Serpina3n</i>	Serine protease inhibitor A3N	6.0*	4.1*	<u>15.7****</u>
<i>Slc1a3</i>	Solute carrier family 1 member 3	1.4****	1.3**	1.5****
<i>Sox9</i>	Transcription factor SOX-9	1.1 ^{ns}	1.1 ^{ns}	1.6*
<i>Vim</i>	Vimentin	2.4*	2.1*	3.7****
<i>H2-D1</i>	Histocompatibility 2, D region locus 1	5.6****	4.3****	6.9****
<i>H2-T23</i>	Histocompatibility 2, T region locus 23	2.3****	2.2****	3.0****
<i>Tap1</i>	Transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	5.6****	4.4****	5.1****
<i>Ccl12</i>	C-C motif chemokine ligand 12	<u>12.4****</u>	9.4****	<u>14.5****</u>
<i>Cd14</i>	Monocyte differentiation antigen CD14	3.6****	2.2*	3.6****
<i>Stat1</i>	Signal transducer and activator of transcription 1	4.2****	4.1****	4.7****
<i>Stat2</i>	Signal transducer and activator of transcription 2	1.9****	1.9****	2.3****
<i>Stat3</i>	Signal transducer and activator of transcription 3	1.6****	1.5****	1.8****
<i>Gbp2</i>	Guanylate binding protein 2	5.2****	4.9****	5.5****
<i>Psmb8</i>	Proteasome subunit, beta type 8	4.3****	3.2***	4.5****