**TPP2 mutation associated with sterile brain inflammation mimicking Multiple Sclerosis**

**Supplementary material**

**Additional clinical details of the index family**

Age at onset of disease for the MS1 ranges between 21 and 38 years. Both brothers developed symptoms at the age of 21 years. The disease course observed in the siblings is consistent with a benign relapsing-remitting MS even 27 (II.1) and 24 (II.2) years after the onset of clinical symptoms. The female sibling had a single neurological episode of demyelination and no further clinical relapses over the following 14 years. The expanded disability status scale (EDSS) was not more than 1.5 in any of the siblings.

The two brothers (II.1 and II.2) suffer in addition to their MS from psoriasis. Both parents are neurologically normal, and there is no report of MS in other close relatives.

None of the patients show any signs of developmental delay. They work full-time. All three patients have a university degree and have higher than average IQ. None of the family members carries the HLA-DRB1\*1501 risk allele.

**Clinical characteristics of T676I carriers**

**MSJ173:** T676I homozygous; sex: female; type of MS: relapsing remitting; age: 35a, disease onset: 23a; disease duration: 12a; last EDSS: 3 (2012); total number of attacks: 2 (last assessment: 2012); therapy: interferon ß; family history for MS: negative

**MSJ208:** T676I heterozygous; sex: male; type of MS: relapsing remitting; age: 44a, disease onset: 39a; disease duration: 5a; last EDSS: 5 (2016); total number of attacks: 5 (last assessment 2016); therapy: Interferon ß; family history for MS: negative.

**MSJ05:** T676I heterozygous; sex: female; type of MS: relapsing remitting; age: 28a, disease onset: 24a; disease duration: 4a; last EDSS: 1 (2016); total number of attacks: 1 (last assessment: 2016); therapy: n.a; family history for MS: negative.

**MSJ35:** T676I heterozygous; sex: female; type of MS: relapsing remitting; age: 25a, disease onset: 18a; disease duration: 6a; last EDSS: 10 (2014); total number of attacks: 10 (last assessment: 2014); therapy: n.a; family history for MS: positive, mother and a cousin are reported to have had MS

**Clinical characteristics of brain donors for immunohistochemistry analysis of TPP2**

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| **Case** | **Details** | **Sex** | **Age** | **Region of Interest** | **Disease duration (months)** | **Cause of death** |
| Control 1 | Controls | female | 36 | WM |   | aspiration |
| Control 2 | Controls | male | 46 | WM |   | pulmonary embolism |
| Control 3 | Controls | female | 45 | WM |   | pulmonary embolism |
| Control 4 | Controls | female | 47 | WM |   | Heart failure |
| Control 5 | Controls | male | 37 | WM |   | cardiovascular failure |
| Control 6 | Controls | female | 80 | WM |   | n.a. |
| Control 7 | Controls | female | 84 | WM |   | pulmonary embolism |
| Control 8 | Controls | female | 97 | WM |   | cardiovascular failure |
| Control 9 | Controls | female | 71 | WM |   | heart failure |
| Control 10 | Controls | male | 72 | WM |   | cardiovascular failure |
| Control 11 | Controls | female | 71 | WM |   | renal failure |
| Control 12 | Controls | female | 39 | WM |   | cervix Ca |
| Control 13 | Controls | female | 88 | WM |   | cardiovascular failure |
| Control 14 | Controls | male | 83 | WM |   | cardiovascular failure |
| Control 15 | Controls | male | 65 | WM |   | heart failure |
| Control 16 | Controls | male | 70 | WM |   | cardiovascular failure |
| MS 1 | AMS | female | 45 | NAWM,PPWM,Initial,EA/LA, Inactive | 0,2 | MS related |
| MS 2 | AMS | female | 34 | NAWM,PPWM,Initial,EA/LA, Inactive | 4 | MS related |
| MS 3 | AMS | male | 35 | NAWM,PPWM,Initial,EA/LA | 1,5 | MS related |
| MS 4 | AMS | female | 69 | NAWM,PPWM,Initial,EA/LA, Inactive | 2 | MS related |
| MS 5 | AMS | male | 45 | NAWM,PPWM,Initial,EA/LA, Inactive | 0,6 | MS related |
| MS 6 | RRMS | female | 40 | NAWM,PPWM,Initial,EA/LA | 120 | n.a. |
| MS 7 | SPMS | male | 41 | NAWM,PPWM,Initial,EA/LA, Inactive | 137 | cardiovascular failure |
| MS 8 | SPMS | female | 53 | NAWM,PPWM,Initial,EA/LA, Inactive | 241 | pneumonia |
| MS 9 | PPMS | female | 54 | NAWM,PPWM,Initial,EA/LA, Inactive | 72 | cardiovascular failure |
| MS 10 | SPMS | male | 34 | NAWM,PPWM,Initial,EA/LA, Inactive | 120 | n.a. |
| MS 11 | PPMS | female | 77 | NAWM,PPWM,Initial,EA/LA, Inactive | 168 | cardiovascular failure |
| MS 12 | PPMS | male | 67 | NAWM,PPWM,Initial,EA/LA, Inactive | 87 | cardiovascular failure |
| MS 13 | PPMS | Male | 55 | NAWM,PPWM,Initial,EA/LA, Inactive | 168 | pulmonary embolism |

The material included six cases of acute or relapsing MS (three female, three male; age at death range 34 to 69) and seven cases with primary or secondary progressive MS (four female, three male; age range 41 to 77). These cases were selected on the basis of a broad lesion spectrum, containing active and inactive lesions and slowly expanding lesions. For the control cohort we included 16 cases without neurological disease and absence of cerebral lesions (10 females, six males, age range at death 36 to 97). MS: multiple sclerosis, PPMS: primary progressive multiple sclerosis, SPMS: secondary progressive multiple sclerosis, RRMS: relapsing remitting multiple sclerosis, AMS: aggressive multiple sclerosis, NAWM: normal appearing white matter, PPWM: peri-plaque white matter, Initial: initial stages of multiple sclerosis, EA: early active lesion, LA: late active lesion