

Supplementary Clinical Information

Patient 1 (P1) is a boy born to non-consanguineous parents in Morocco in 2009. He was admitted to hospital with cognitive and visual impairment with no history of prior illness, at the age of three years. Herpes encephalitis was suggested by MRI and confirmed by positive PCR results for HSV-1 DNA.

P2 is a girl born to non-consanguineous parents in Saudi Arabia in 2004. She was admitted to hospital with no history of prior illness, at the age of three months. Herpes encephalitis was suggested by MRI and confirmed by a positive PCR result for HSV-1.

P3 is a young adult born to non-consanguineous parents in the United States in 1992. He presented with HSE at the age of 20 years, with no skin manifestations and no history of HSV infection.

P4 is a man born to non-consanguineous parents in France in 1949. He was admitted to hospital at the age of 51 years with a fever, behavioral instability, and seizures. HSE was confirmed by MRI and a positive PCR result for HSV-1 DNA. P4 was hospitalized again at the age of 63 years, with a fever, loss of spatiotemporal orientation, lack of face recognition and incoherent speech. HSE was suggested by a positive PCR result for HSV-1 DNA.

P5 is a boy born in Portugal in 2011. He was admitted to hospital at the age of four months, with behavioral instability and left upper arm palsy. He had seizures and fell into a coma on the fifth day of illness. MRI suggested herpes encephalitis, and the diagnosis of HSV-1 encephalitis was confirmed on day 7.

At the time of HSE, the patients were seropositive for IgG antibodies against various other viruses, including varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein Barr virus (EBV), hepatitis A virus (HAV) and respiratory syncytial virus (RSV) for P1, CMV and parvovirus B19 for P2, VZV, CMV, HAV, parvovirus B19, influenza A virus, influenza B virus and RSV for P4,

and parvovirus B19 for P5. This suggests that they had been infected by the corresponding viruses without developing severe diseases. No abnormality was reported in the patients' laboratory peripheral blood cell immunophenotyping results.

Of the family members carrying the same *SNORA31* variant as the index case in each family, the mother of P1, the mother and brother of P2, and the mother of P5 tested positive for anti-HSV-1 IgG antibody in the blood, suggesting that they had been infected with HSV-1 in the past without developing HSE. The mother and brother of P3 tested negative for anti-HSV-1 IgG.