Human Paratuberculosis Foundation
Revised: January 2017
HumanPara.org
The following articles have been compiled to aid doctors, researchers, medical professions and patients in their research of how *Mycobacterium avium* subspecies *paratuberculosis* (MAP) relates to multiple sclerosis. Human Para will continue to add research studies as they become available.

**Research on MAP and Multiple Sclerosis in the Sardinian Population**

1. *Association of Mycobacterium avium subsp. paratuberculosis with multiple sclerosis in Sardinian patients.* (April 2011)
   50 Sardinian MS patients were tested for the presence of MAP DNA. 42% of the MS patients tested positive for MAP while only 12.5% of controls were positive. In regard to the presence of MAP in controls, researchers hypothesize that the Sardinian population may have been exposed to MAP, and the infection contained based on genetic differences. Anti-MAP antibodies were detected in 32% of MS patients but only 2% of controls. The researchers conclude that MAP may be one of the triggers of MS based on a molecular mimicry model in genetically susceptible individuals.

2. *Are Mycobacterium avium subsp. paratuberculosis and Epstein-Barr virus triggers of multiple sclerosis in Sardinia?* (August 2012)
   In this study of 119 Sardinian MS patients and 117 healthy controls, MAP and Epstein Barr virus DNA were detected in 27.5% and 17.3%, respectively, of the MS patients. Additionally, the researchers observed an extremely high immune response against a MAP protein that is comparable human mylin.

   The Sardinian population might be susceptible to developing autoimmune disease like MS due to mutations in the SLC11A1 gene, which is important in the immune response against intracellular bacteria such as MAP. The 100 MS patients tested had a significantly higher MAP antibody response and greater MAP DNA detection rates vs. 100 healthy controls. One specific mutation of the SLC11A1 gene was found to be associate with MS.

4. *A Sardinian Map for Multiple Sclerosis.* (September 2013)
   Several theories on why MAP may play a causal role in MS are discussed and a mechanism for how MAP triggers autoimmunity is hypothesized. One possible way MAP may trigger MS is by a molecular mimicry theory. (See above.) Another is a cross reaction of heat shock proteins. Heat shock proteins are produced by both MAP and host cells when under stress, which could cross react and trigger an autoimmune process. While the causative agent of MS remains to be determined, "MAP is one of the candidates that best suits the role of the environmental trigger."

5. *Mycobacterium avium subsp. paratuberculosis and multiple sclerosis in Sardinian patients: epidemiology and clinical features.* (October 2013)
   This study confirmed the association of MAP and MS in Sardinia. Of the 436 MS patients and 264 health controls, MAP DNA was detected in 68 MS patients and 6 controls. MAP antibodies were detected in 123 MS patients and 10 controls. MAP detection may be increased by MS treatments and steroids.
6. **Anti Mycobacterium avium subsp. paratuberculosis heat shock protein 70 antibodies in the sera of Sardinian patients with multiple sclerosis.** (December 2013)
Heat shock proteins are produced by both MAP and host cells when under stress, which could cross react and trigger an autoimmune process. In this cohort of 268 Sardinian MS patients and 231 controls, the MS patients had a significantly higher immune response to a specific heat shock protein found in both humans and MAP. (23% in MS vs. 6.5% in controls.) This indicates that MAP could play a role in MS.

7. **Epstein-Barr virus and Mycobacterium avium subsp. paratuberculosis peptides are cross recognized by anti-myelin basic protein antibodies in multiple sclerosis patients.** (May 2014)
Researchers searched for antibodies to an Epstein Barr virus protein and a MAP protein which are comparable to a protein found in myelin basic protein in Sardinian MS patients. They found that these antibodies are highly prevalent among MS patients vs. controls and that they cross react with the myelin protein. This supports the theory that MAP and EBV may trigger an autoimmune reaction in MS.

8. **Human interferon regulatory factor 5 homologous epitopes of Epstein-Barr virus and Mycobacterium avium subsp. paratuberculosis induce a specific humoral and cellular immune response in multiple sclerosis patients.** (July 2015)
Both Epstein-Barr and MAP epitopes (the part of the pathogen where an antibody attaches) elicit a consistent immune response in MS patients compared to controls. These epitopes were also able to induce a T-cell-mediated response in MS patients. These results indicate that EBV and MAP may play a role in MS.

9. **Immune response induced by Epstein–Barr virus and Mycobacterium avium subsp. paratuberculosis peptides in current and past infectious mononucleosis: a risk for multiple sclerosis.** (October 2015)
Epstein-Barr virus (EBV), the infectious cause of mononucleosis (mono), is associated with an increased multiple sclerosis risk. MAP is also thought to be involved in the pathogenesis of MS. 26 mono patients and 40 healthy controls were studied in Sardinia. The researchers found that both EBV and MAP proteins could induce an immune response independently in mono patients. They also induced a T-cell activation and production of TNF-α and interleukin 6, both which promote inflammation. The authors concluded that "EBV and MAP may be involved independently in the same causal process leading to MS in subjects with a history of mono."

10. **Combining HLA-DRB1-DQB1 and Mycobacterium Avium Subspecies Paratuberculosis (MAP) antibodies in Sardinian multiple sclerosis patients: associated or independent risk factors?** (August 2016)
Sardinians have a different genetic predisposition to multiple sclerosis than other populations. Here, researchers analyzed the human leukocyte antigen (HLA) variations of 531 Sardinian MS patients. HLA is the region of DNA responsible for regulating immune system. Certain versions of HLA are either protective of or predisposing to MS. Here, the researchers looked for MAP antibodies and whether the MS patient had a genetic predisposition to MS. While there was no association between the presence of MAP antibodies and a predisposition to MS, there was a
significantly lower presence of MAP antibodies in MS patients who had at least one the protective HLA gene. A protective HLA type may protect against MAP and MS.

**Additional research discussing the role of MAP in MS**

1. [Epstein_Barr_Virus_and_Mycobacterium_avium_subsp._paratuberculosis_peptides_are_recognized_in_sera_and_cerebrospinal_fluid_of_MS_patients](https://www.ncbi.nlm.nih.gov/pubmed/27319370) (March 2016)
   The researchers looked for antibodies to MAP and EBV in the blood and cerebral spinal fluid (CSF) of 43 MS patients. In both blood and CSF, an immune response was seen to EBV and MAP. The 33 control patients with other neurological disorders (not MS) did not show this response. Antibodies were also present to myelin basic protein (MBP). "The higher presence of antibodies against MBP and their MAP and EBV homologous in CSF during relapses suggests a possible role of the pathogens in enhancing inflammation."

   Both the Epstein-Barr virus (EBV) and MAP are thought to be potential pathogenic triggers in the onset of multiple sclerosis, and it has been hypothesized that pathogens such as MAP and EBV could act synergistically in genetically susceptible patients to cause disease. The researchers found that one MAP protein was highly reactive, and found in 30% of the 50 MS patients tested. When compared to the MS Map studies done by the Italian group, the researchers here noted that the antibody response to MAP may be altered between MS patients of different ethnic backgrounds. Also of note: MAP antibodies were just as prevalent in the group experiencing their first demyelinating episode as in the group with MS. Since there is currently no test to diagnose early MS, these results could be of clinical importance for future diagnostics.

3. [Serum_BAFF_levels,_Methypredsinolone_therapy,_Epstein-Barr_Virus_and_Mycobacterium_avium_subsp._paratuberculosis_infection_in_Multiple_Sclerosis_patients](https://www.ncbi.nlm.nih.gov/pubmed/27319370) (July 2016)
   Elevated B lymphocyte activating factor (BAFF) has been found in MS patients. BAFF plays a role in the maintenance of inflammation and has been indicated in the strength of antibody response to infectious agents. This study looked at BAFF levels and the presence of MAP antibodies, and found that lower BAFF levels were associated with higher MAP antibody response rates. This supports the hypotheses that higher BAFF levels could be associate with more stable disease.

4. [Soluble_BAFF_Level_Is_Not_Correlated_to_Mycobacterium_avium_Subspecies_Paratuberculosis_Antibodies_and_Increases_After_Interferon-β_Therapy_in_Multiple_Sclerosis_Patients](https://www.ncbi.nlm.nih.gov/pubmed/27319370) (Sept. 2016)
   This study looked at B lymphocyte activating factor (BAFF) levels in MS patients before and after interferon-β therapy and measured the MAP antibody response to see if it was related to increased BAFF levels. While the researchers found that interferon-β therapy increased BAFF levels, there was no change in the MAP antibody levels. Therefore, interferon-β therapy does not alter the immune response to MAP in MS patients.