NR1H3 p.Arg415Gln Is Not Associated to Multiple Sclerosis Risk

Abstract:
A recent study by Wang et al. (2016a) claims that the low-frequency variant NR1H3 p.Arg415Gln is sufficient to cause multiple sclerosis in certain individuals and determines a patient's likelihood of primary progressive disease. We sought to replicate this finding in the International MS Genetics Consortium (IMSGC) patient collection, which is 13-fold larger than the collection of Wang et al. (2016a), but we find no evidence that this variant is associated with either MS or disease subtype. Wang et al. (2016a)
also report a common variant association in the region, which we show captures the association the
IMSGC reported in 2013. Therefore, we conclude that the reported low-frequency association is a
false positive, likely generated by insufficient sample size. The claim of NR1H3 mutations describing a
Mendelian form of MS-of which no examples exist-can therefore not be substantiated by data. This
Matters Arising paper is in response to Wang et al. (2016a), published in Neuron. See also the related
Matters Arising paper by Minikel and MacArthur (2016) and the response by Wang et al. (2016b),
published in this issue.