***To the Editor:***

We have diagnosed a patient from Quebec with hyperimmunoglobulin M (hyper-IgM) syndrome resulting from a defect in activation-induced cytidine deaminase (AID). The patient's mutation proved to be identical to that of all other French Canadians with AID defects. This case illustrates the clinical nature of AID deficiency, and review of the relevant literature sheds light on what is being called the "French-Canadian AID mutation."

The patient was referred to our clinic at the age of 16 years. He had had chronic cervical lymphadenopathy since the age of 2 years and also had recurrent sinopulmonary infections consistent with bacterial pathogens. He had not experienced any severe viral or opportunistic infection. One paternal grandmother and one maternal grandmother were sisters. Examination revealed normal height and weight, cervical lymphadenopathy, a left middle-ear effusion, and bilateral lower-lobe expiratory crackles. A chest radiograph was suggestive of bronchiectasis. A complete blood count, complement levels, and T- and B-cell enumerations were normal. Levels of all antibodies were low except that of IgM, which was significantly elevated at 7.93 g/L (normal = 0.56–3.52). The result of a CD154 binding assay was normal. Sequencing of the *AID* gene demonstrated a homozygous C-to-T mutation at position 334, resulting in cysteine replacing arginine at position 112 of the protein. In every French-Canadian patient with AID deficiency (there have been 15 such patients if our patient is included) a homozygous R112C mutation has been found.[1] These findings are suggestive of a founder effect.

A founder effect can occur when a small group of people from one population separate and form a new population. An allele that had a rare frequency in the parent population may then have a higher frequency in the new population simply because one or more of the founders happened to carry the rare allele. If the new population remains isolated as it expands, as has been the case in parts of Quebec, and especially if there is inbreeding, as was the case in this patient's family, the founder allele is able to become homozygous, thus causing autosomal recessive diseases such as AID deficiency. The R112C mutation has never been reported in France, the country of the Quebec founders. This is not surprising because the mutation may have a low frequency in France, and in the absence of inbreeding, it may never manifest as disease. However, one cannot exclude the possibility that the R112C mutation did not exist in the Quebec founders but in fact occurred afterwards. Regardless, genotyping of polymorphisms surrounding R112C has demonstrated a single haplotype, and has thus confirmed that the mutation originated from a single individual. In 55 non-French Canadians with AID deficiency, this mutation was found only once[1–3]: a Japanese patient was heterozygous for R112C, the other AID gene having a premature stop codon. It is interesting to contemplate whether this patient had a French or French-Canadian ancestor or whether the Japanese mutation arose independently.

In summary, this case illustrates the typical clinical manifestations of hyper-IgM syndrome due to AID deficiency, which differ significantly from those of hyper-IgM syndrome due to CD154 deficiency: normal growth, the presence of lymphadenopathy, infections only of bacterial origin, and the lack of cytopenias. Our patient's AID mutation proved to be identical to that found in all other French Canadians with this disease, illustrating a mutation that is identical by descent.

*Emil Nashi, MD*
*Devi Banerjee, MD*
*Thomas Hudson, MD*
*Rhoda Kagan, MD*
McGill University, Montreal, Quebec

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## References

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