Reviewer #2: The study by Hachiya and colleagues focused on investigating the possible role of leukocyte immunoglobulin-like receptor A 3 (LILRA3) polymorphism deletion in the susceptibility and phenotype expression of SSc in Japanese relatively small population (n=378 in SSc patients and n=867 in healthy controls). Authors found there was no significant association with overall SSc patients but observed significant association of LILRA3 deletion with ATA+ SSc (n=88). This is the first study for genetic association of the LILRA3 gene polymorphism deletion with SSc. However, there is no replicated study in second population and no significantly high OR observed and sample size is very small.   
Genetic association studies provide a potentially powerful tool for identifying genetic variations that influence susceptibility to the diseases. However, there are numerous cases of associations that cannot be replicated afterwards, which have led to skepticism about genetic epidemiology studies of complex diseases. To discourage false-positive association hypotheses, several recommendations have been suggested: large sample sizes, small P values, a gene/allele with biologically/ physiologically meaningful sense, an association observed in both family- and population-based studies, replications in independent studies, and a high OR and/or attributable risk [Nature Genetics 22, 1 - 2 (1999) doi: 10.1038/8702]. Among these criteria, validation of a genetic association by replication might be the most important step to exclude false-positive associations. In statistical terms, independent replication decreases the chances of reporting an association if no association actually exists (type I error). Because gene association with disease is maybe because of: 1: by chance; 2: gene is functional; 3: LD (linkage disequilibrium) with functional locus; and 4: population structure. We need evidence shown that the study observation is not by chance or population structure.