Hu and colleagues investigated in this study whether TGFBR1*6A is associated with increased risk of osteosarcoma. They have assessed the presence of this polymorphism in a case control study of 168 Chinese patients with osteosarcoma and used 168 unaffected healthy blood donors matched for age and sex to the case population. They observe that the TGFBR1*6A genotype is associated with an increased risk of osteosarcoma in all three statistical models evaluated. They further assess if TGFBR1*6A is associated with specific clinical features and note that fewer patients with TGFBR1*6A have metastatic disease.

The findings of the study are significant in that the role of TGFBR1*6A in osteosarcoma is virtually unknown and this study provides evidence to suggest that the risk of osteosarcoma is increased in carriers of the TGFBR1*6A allele. The authors are, however inconsistent, in the reporting of their results and discussion. In the results section, they mention that the frequency of TGFBR1*6A genotypes is significantly decreased in patients with metastatic disease compared to those without metastatic disease. In the Discussion, they refer to “the increased risk distant metastasis of osteosarcoma in TGFBR1*6A variants…”. I suggest that the discussion section be re-worded and make it clearer.

The findings of decreased metastasis in patients with TGFBR1*6A is in contrast to in vitro experiments which show that TGFBR1*6A is associated with increased invasive properties. Whether this is a site specific or tumor specific effect is not known. If the authors have access to the tumor samples, it may be worthwhile to check for loss of homozygosity of TGFBR1 in the tumor samples. This may clarify whether the decreased frequency of TGFBR1*6A seen in samples with metastasis is associated with LOH at the TGFBR1 locus rather than a primary effect of TGFBR1*6A.

Overall, the manuscript will also need editing to improve the readability.