Author Response: PRIMPOL Mutation: Functional Study Does Not Always Reveal the Truth

Although the findings reported in this letter by Li and Zhang\(^1\) may challenge the conclusions of Zhao et al.\(^2\) who originally identified a possible link between the PRIMPOL gene and high myopia, it is erroneous and misleading to say that “functional study does not always reveal the truth.” In our recent article,\(^3\) we set out to establish if a point mutation (Y89D) in a novel human DNA primase-polymerase called PrimPol, identified by others to be potentially associated with high myopia, alters the activity of this polymerase or impacts on DNA replication. Our study clearly and unequivocally establishes that this mutation has a significant impact on the function of this enzyme. The mutant is a poorly processive polymerase, compared to wild-type PrimPol. DNA binding and enzyme kinetic analyses attributes this defect in processivity to a reduction in nucleotide and DNA binding.\(^3\) Examination of protein structural changes indicates that the Y89D mutation alters the enzymes secondary structure, making it less stable than the wild-type domain.\(^3\) Finally, in vivo studies reveal that overexpression of this Y89D variant of PrimPol in PRIMPOL\(^{-/-}\) deficient cells leads to a significant decrease in unperturbed DNA replication rates.\(^2\) Together, these functional studies reveal the “truth” that this mutation significantly alters the activities of human PrimPol. Whether this mutation has any bearing on the development of high myopia remains to be established, but accessing this potential link was not the subject of our report. There is no doubt that myopia is a complex genetic trait and in our report we state that any “link between reduced PrimPol polymerase activity and myopigenicity remains unclear” and “further work is required to establish if a direct link exists between replication stress and onset of high myopia.”\(^3\) In summary, it is clear from our functional studies that tyrosine 89 has an important role in the structural integrity of human PrimPol, but further cellular studies are now required to establish if a bona fide link exists between this PrimPol mutation and high myopia.

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