Recent studies suggest that many observed phenotypes, including common diseases, are complex and are likely governed by multiple loci and interaction between them. Uncovering such interactions will be critical to understanding of such complex traits. Here, we proposed a method that explores the hypothesis that such interacting loci might co-evolve acquiring allele specific compatibility to maintain their interaction. This allele specific compatibility between two loci might be compromised in meiotic crosses leading to phenotypic changes in progeny, which, in turn, can guide the detection of such interaction. Focusing on such cases we developed a computational method, LoCAp (Locus Compatibility Approach) to detect interactions between loci consistent with such a model. We then applied our approach to detect interactions related to yeast DNA repair phenotype. Our method pointed to the locus harboring Rad5 as a locus interaction hub for the response to DNA damaging agent. Our results are consistent with the results obtained by a recently developed Extreme QTL experimental technique. These findings not only indicate the importance of Rad5 but also serve as a proof of principle for exploring allele specific interaction compatibility in predicting interactions between genetic loci. (Received September 22, 2011)