The hypoxia-inducible-factors (HIFs) are responsible for cellular adaptations to low oxygen stress by activating transcriptional programs such as erythropoiesis and angiogenesis. Because these programs are related to tumor growth and progression, HIFs have become attractive targets for cancer therapy. To function as oxygen-sensitive regulatory subunits, HIF2α must form a heterodimer with the aryl hydrocarbon receptor nuclear translocator (ARNT). Both HIF and ARNT proteins have a basic-helix-loop-helix (bHLH) domain for DNA reading in their amino-termini, followed by two tandem Per-ARNT-Sim (PAS) domain, namely PAS-A and PAS-B, for HIF-ARNT dimerization, and transactivation domains (TAD) in their carboxyl-termini. According to the recently solved HIF2α-ARNT dimer structure (not covering their TADs), there are six domain-domain interfaces including HIF2α’s bHLH with ARNT’s bHLH, HIF2α’s PAS-A with ARNT’s PAS-A, HIF2α’s PAS-B with ARNT’s PAS-A, HIF2α’s PAS-B with ARNT’s PAS-B, HIF2α’s PAS-A with HIF2α’s PAS-B, and HIF2α’s PAS-B with HIF2α’s PAS-B. Structural comparison shows that HIF2α’s bHLH, PAS-A, and PAS-B domains are compactly interconnected; whereas ARNT’s bHLH, PAS-A, and PAS-B domains are linked by long flexible loops to grant structural adaptability to dimerize different bHLH-PAS proteins members. Lately, co-immunoprecipitation experiments have shown that R171A and/or V192D on HIF2α’s PAS-A domain impair HIF2α-ARNT dimerization. Herein we applied molecular dynamics simulations to investigate the structural and dynamic impact brought by these mutations. Our results conclude that these mutated amino residues, located in HIF2α’s PAS-A with HIF2α’s PAS-B interface, change the relative orientation and motion of PAS-A and PAS-B and therefore these two PAS domains are not recognizable by ARNT.