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Identification of a p.Trp403* nonsense variant in PHEX causing X-linked hypophosphatemia by inhibiting p38 MAPK signaling

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Abstract

X-linked hypophosphatemia (XLH) is the most common hereditary rickets, caused by mutations in PHEX encoding the phosphate regulating endopeptidase homolog X-linked. Here, we report a nonsense variant in exon 11 of PHEX (c.1209G>A p.Trp403*) cosegregating with XLH in a Chinese family with a LOD score of 2.70. Real-time reverse transcription polymerase chain reaction analysis demonstrated that p.Trp403* variant did not cause nonsense-mediated mRNA decay (NMD), but significantly increased the expression level of FGF23 mRNA in the patients. Interestingly, p.Trp403* significantly reduced phosphorylation of p38 mitogen-activated protein kinase (MAPK) but not ERK1/2. Moreover, overexpression of FGF23 significantly decreased phosphorylation of p38 MAPK, whereas knockdown of FGF23 by siRNA significantly increased phosphorylation of p38 MAPK. These data suggest that p.Trp403* may not function via an NMD mechanism, and instead causes XLH via a novel signaling mechanism involving PHEX, FGF23, and p38 MAPK. This finding provides important insights into genetic and molecular mechanisms for the pathogenesis of XLH.

Result

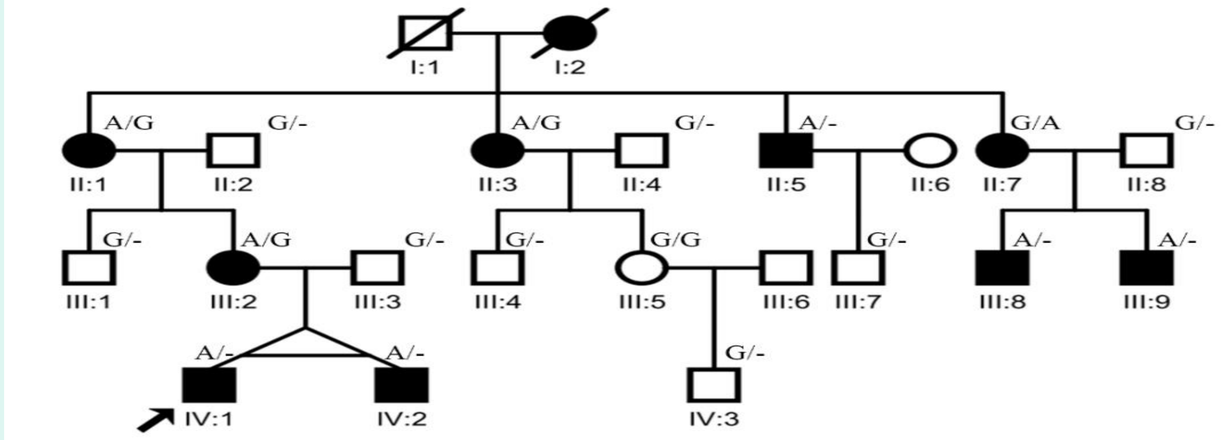


Figure 1. Pedigree structure of a Chinese family affected with XLH

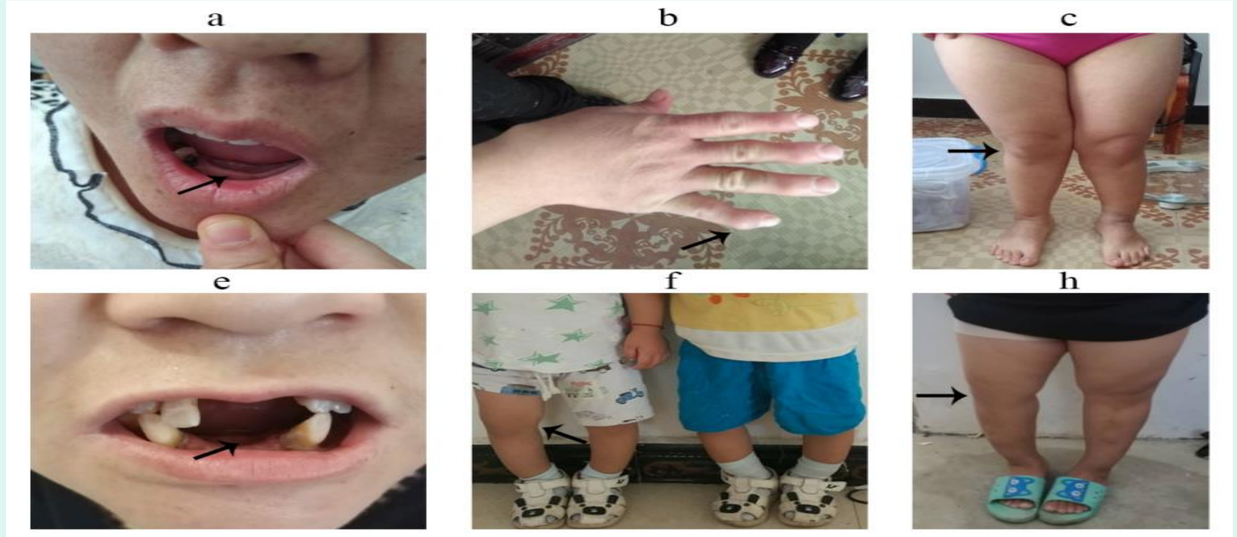
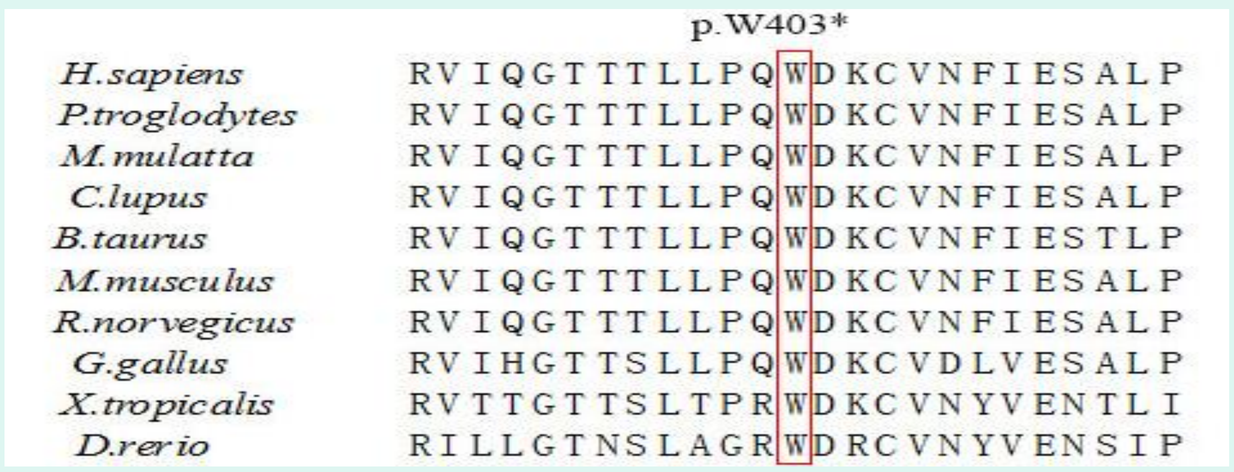
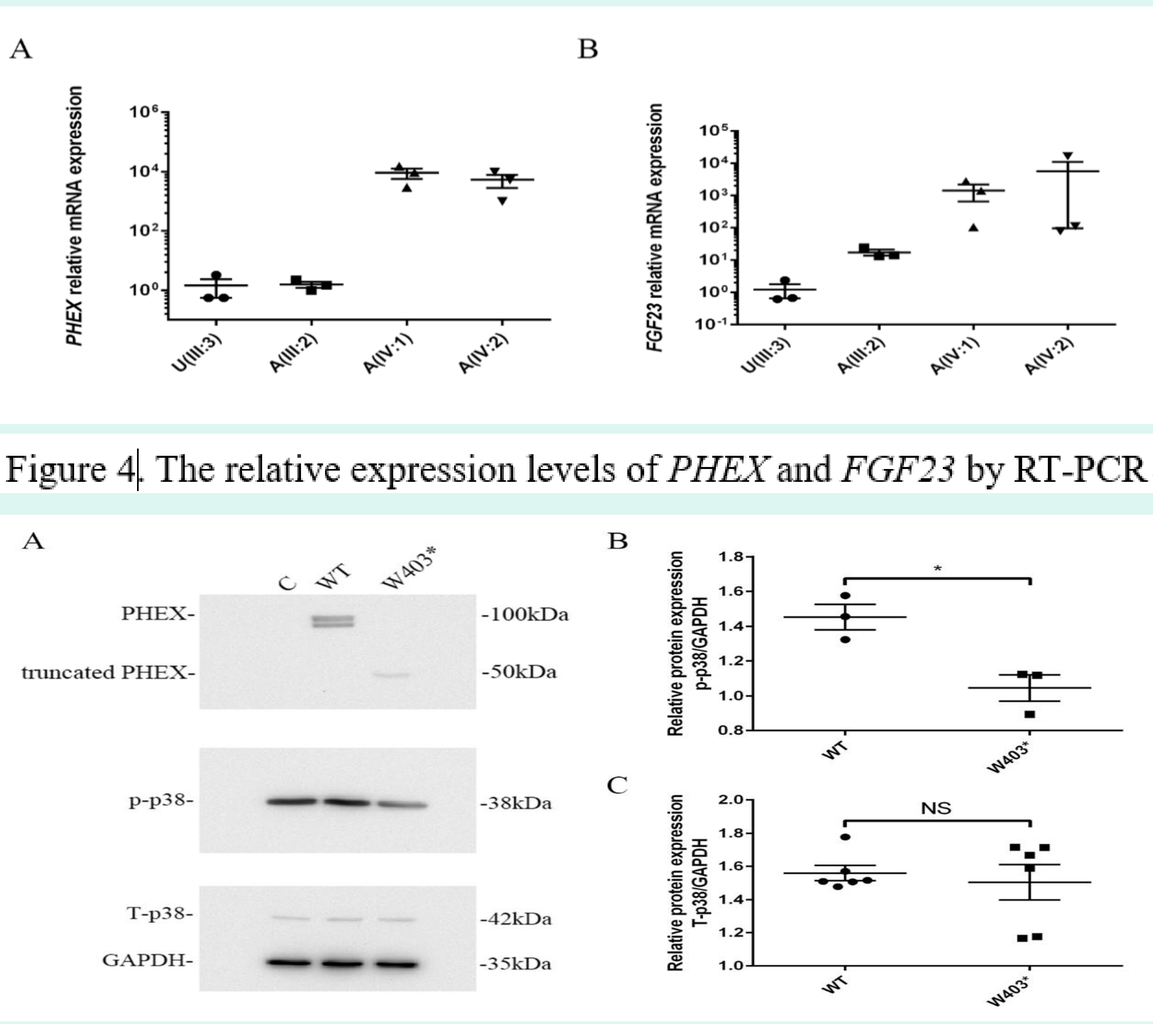


Figure 2. Clinical findings from the XLH patients from a large Chinese family



Fiugre 3. The evolutionary conservation of the 403 amino acid of PHEX



Conclusion

In conclusion, by characterizing a large Chinese family with XLH and a series of functional studies, we provide genetic and molecular evidence that the p.Trp403* nonsense variant in PHEX causes XLH. Moreover, we identified a novel molecular signaling pathway for the pathogenesis of XLH, which consists of a PHEX mutation, upregulation of FGF23, and inhibition of p38 MAPK activation. These results provide important insights into the genetic and molecular pathogenic mechanisms of XLH. Importantly, our data also implicate that an activating agent for p38 MAPK signaling may be developed into a potential therapeutic treatment strategy for patients with XLH.

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