A founder mutation in P450 reductase from Argentina causes virilization in 46,XY patients.

Introduction

Cytochrome P450 oxidoreductase (POR) deficiency results in defective steroid production. Mutations in POR cause ambiguous genitalia in both 46,XX and 46,XY patients & adrenal insufficiency with/without bone malformations. A novel homozygous variant c.262G>A/G88S in POR was found in four patients in Argentina and no common ancestors have been found between the families. All patients had elevated basal ACTH, 17-OH-Prog & Prog and normal cortisol with no response to ACTH, and low androstenedione and testosterone. We aimed to perform functional analysis of novel G88S variant in POR in 46,XY patients.

Results

A novel homozygous variant c.262G>A/G88S in POR was found in all four patients and no common ancestors have been found between the families. We found severe effects of G88S mutation on binding of co-factors and activities with different substrates.

Discussion and conclusion

The G88S mutation in POR severely decreased the efficiency in reduction of small molecules. The cytochrome c reduction showed a loss of 97% of its activity compared to WT POR. The Rezasaurin assay showed a decrease of 95%. In the case of the MITT reduction assay, we observed not only a severe loss of activity (a decrease of > 74%) but also a remarkably lower affinity for the substrate.

We assessed how the G88S variation in POR affects the activity of four major drug-metabolizing enzymes CYP3A4, CYP3A5, CYP2C9, and CYP2C19.

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