Supplementary Materials

Mechanism of the dual activities of CYP17A1 and binding to anti-prostate cancer drug abiraterone revealed by a novel V366M mutation causing 17,20 lyase deficiency.

Mónica Fernández-Cancio†, Núria Camats1,2,3, Christa E Flück2,3,†, Adam Zalewski2,3,†, Bernhard Dick‡, Brigitte M Frey‡, Raquel Monné§, Núria Torán§, Laura Audí†, and Amit V Pandey2,3*

1 Growth and Development Research Unit, Vall d’Hebron Research Institute (VHIR), Center for Biomedical Research on Rare Diseases (CIBERER), Instituto de Salud Carlos III, Autonomous University of Barcelona, Barcelona, Spain.
2 Pediatric Endocrinology Unit, Department of Paediatrics, University Children's Hospital Bern, Switzerland.
3 Department of Biomedical Research, University of Bern, Bern, Switzerland.
4 Department of Nephrology and Hypertension, University of Bern, Bern, Switzerland.
5 Pediatric Service, Hospital Joan XXIII, Tarragona, Spain.
6 Pathology Department, Hospital Universitari Vall d’Hebron, CIBERER, Barcelona, Spain.

†Co-first authors.
* Correspondence: amit@pandeylab.org; Tel.: +41-31-632-9637
**Supplementary Fig. 1:** Details of abiraterone interaction with the WT and V366M variant of CYP17A1. In the WT CYP17A1 abiraterone binds by forming a nitrogen-iron coordination with the central heme (a and c). In the V366M mutant, the larger methionine side chain protrudes towards the heme iron and creates a steric hindrance for the binding of abiraterone (b and d). As a result, abiraterone is ineffective towards the residual 17hydroxylation reaction of the mutant enzyme. Panels a and b show the ribbons diagram of the active site of CYP17A1 while panels c and d show the ligand interactions depicted by LIGPLOT analysis.
Supplementary Fig. 2: Details of 17OH-PREG interaction with the V366M variant of CYP17A1. There are differences in optimal binding poses for PREG/PROG and 17OH-PREG and while interaction with N202 seems to benefit in orienting the steroids for 17-hydroxylase reaction, this increases the distance between C17 and heme iron. The multiple additional interactions observed here for 17OH-PREG and V366M mutant of CYP17A1 indicate nonoptimal binding and explain the loss of 17,20 lyase activity.