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Whole exome sequencing in patients with Primary Generalized Glucocorticoid Resistance, who did not have mutations in the *NR3C1* gene

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Background: Primary Generalized Glucocorticoid Resistance (PGGR) is a rare, familial or sporadic condition, characterized by generalized, partial tissue insensitivity to glucocorticoids. The molecular basis of this condition has been ascribed to mutations in the *NR3C1* (human glucocorticoid receptor, hGR) gene, which impair the molecular mechanisms of hGR action and decrease tissue sensitivity to glucocorticoids. However, a considerable number of patients with PGGR do not have mutations in the *NR3C1* gene.

Objective and Hypotheses: Using whole exome sequencing, we investigated whether other genes are implicated in the pathogenesis of PGGR.

Patients and Methods: Eleven adult patients (age range: 18-48 years; 6 males, 5 females) with PGGR, who did not have mutations in the *NR3C1* following Sanger sequencing, and two patients with PGGR harbouring two mutations (one missense mutation and a 5 bp deletion) of the *NR3C1* gene (positive controls) underwent whole exome sequencing on an Ion Proton platform (ThermoFisher Scientific USA).

Results: Each exome sequence revealed the presence of approximately 55000 variants. Using a cut off value of 100 reads/variant, a total number of **507** non synonymous and frameshift mutations were detected in all patients (**Fig.1**). These mutations corresponded to **390** genes involved in **5 different pathways** (**Fig.2**), one of which was that of steroid hormone biosynthesis (***CYP1B1, CYP3A7, AKR1C4, UGT2A3; Fig.3***). The mutations detected in these four genes were shown to be known polymorphisms and were present in all 13 samples. One mutation of the ***UGT2A3*** gene was detected in only one patient, the **c.1480T>G p.Phe494Val** and was reported as damaging, possibly damaging and polymorphism by three *in silico* tools.

Nineteen of the 390 genes were found to be regulated directly by *TP53* possibly indicating the presence of a cascade. One mutation of the *GP6* gene present in all patients was not annotated. The presence of mutations in the genes ***HSP90AA1, NCOA1, SMARCA4, NCOA2, JUN, UBC, CREBBP, NFKB1, RELA*** and ***NCOA3*** (functional partners of the *NR3C1* after searching the STRING database; **Fig.4**) was examined and no pathogenic variants were detected.

No *NR3C1* mutation was detected in any of the patients, whereas the mutations previously identified by Sanger sequencing were also detected by exome sequencing.

Patients ID	# SNPs
P1	5327
P2	6361
P3	5744
P4	5372
P5	5505
P6	4441
P7	5370
P8	6525
P9	5417
P10	3855
P11	3827
P12	3348
P13	3689

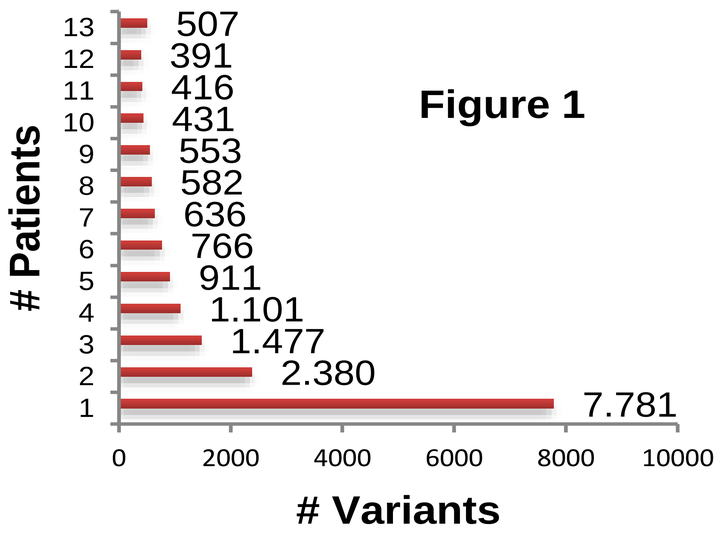

Figure 1

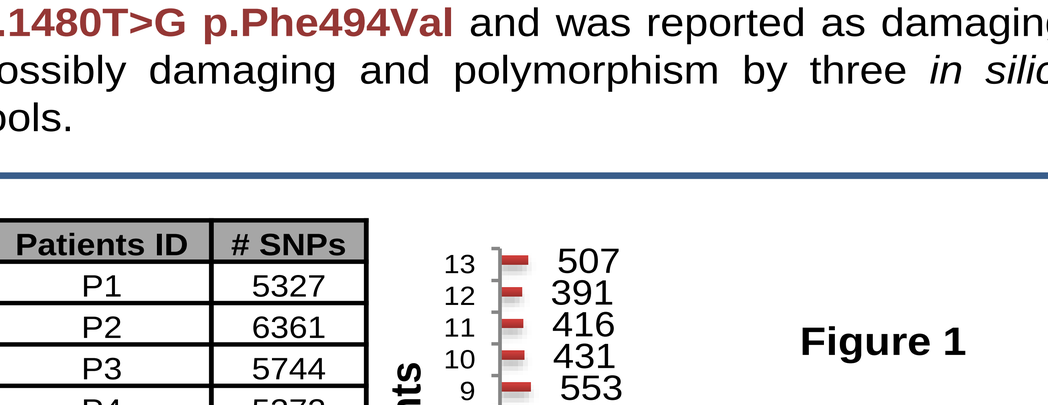

Figure 2

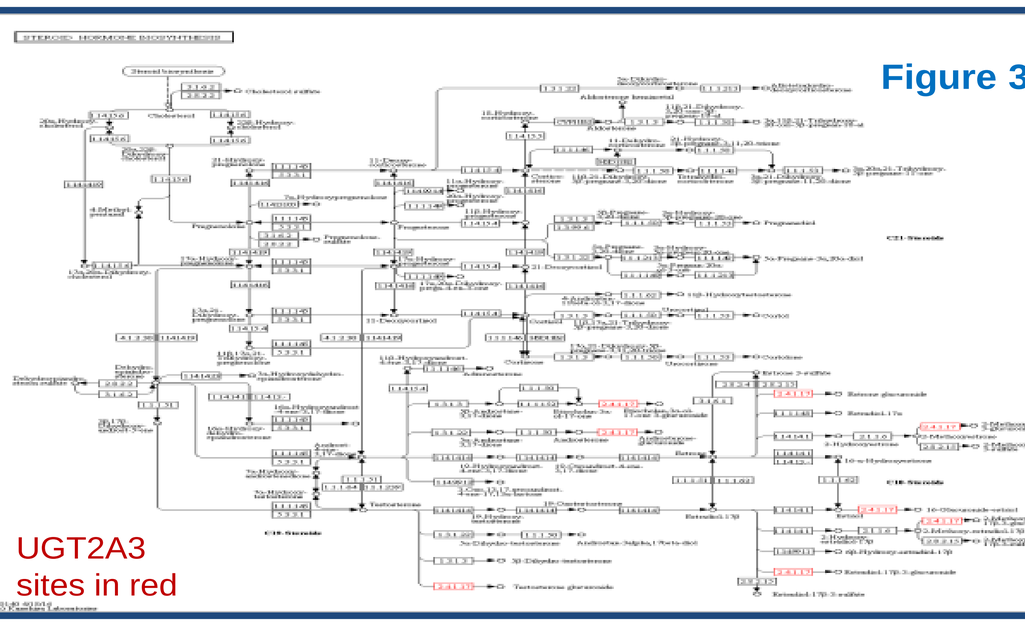

Figure 3

UGT2A3 sites in red

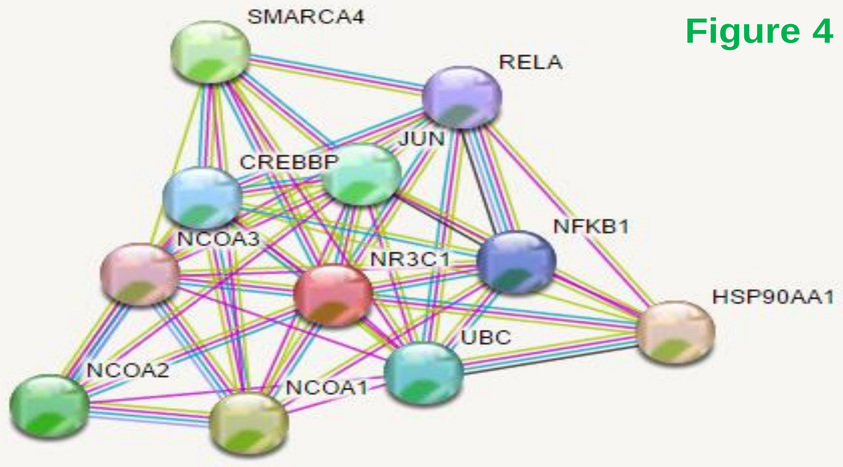

Figure 4

Conclusions: Whole exome sequencing may allow us to expand the spectrum of genes associated with PGGR. Further bioinformatic analysis is required to establish pathogenic variants in genes related to this condition.

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