Table 3: Summary of DNA variants observed within the coding sequence of the *NRIP1* gene.

DNA variant*	Amino acid Substitution (change in codon)	dbSNP** accession number	Detection in Endometriotic tissue samples (40 chromosomes)	Detection in germline DNA derived from endometriosis patients (118 chromosomes)	Detection in controls (282 chromosomes)	Status
Nt c.512 G->A	None [Gly75] (ggg to gga)	rs2229741	15/40	57/118	129/282	Common polymorphism
Nt c.949 A->G	His221Arg (cat to cgt)	-	1/40	1/118	3/282	Common polymorphism
Nt c.1608 A->G	Ile441Val (ata to gta)	-	0/20	0/118	4/282	Common polymorphism
Nt c.1629 C->G	Arg448Gly (cga to gga)	rs2229742	9/40	16/118	19/282	Common polymorphism
Nt c.2695 C->T	Ser803Leu (tcg to ttg)	-	2/40	3/118	10/282	Common polymorphism
Nt c.3522 G->T	Val1079Phe (gtt to ttt)	-	1/40	1/118	0/282	Rare Variant/ Mutation

*In accordance with genbank number NM_003489.
** dbSNP: the Single Nucleotide Polymorphism Database at the National Centre for Biotechnology Information (NCBI) http://www.ncbi.nlm.nih.gov/

maximize the differences between case and control groups for each polymorphism. Genotypic distributions of polymorphisms analyzed are in accordance with the Hardy-Weinberg equilibrium law ($p > 0.15$), indicating no bias due to technical or stratification problems nor evolution-dependent genetic sweep/selection events (data not shown). Interestingly, our analysis revealed that *Arg448Gly* polymorphism appears to be weakly associated with endometriosis in our population (Odds ratio = 2.327, $p_{\text{allele positivity test}} = 0.027$). In contrast, no significant association could be achieved when comparing unselected versus super-control women, supporting the accuracy of the selected control panel ($p > 0.34$ for *Gly75Gly*, $p > 0.41$ for *Arg448Gly*, and $p > 0.1$ for *Ser804Leu*).

Overall, our results might support the role of *NRIP1* gene in endometriosis, although given the small sample size, we propose an extensive re-analysis by increasing the sample size to confirm our results.

Discussion

Endometriosis is a complex disease affecting 10–15% of women at reproductive age. Very few genes are known to be altered in this pathology. Molecular genetic analyses provide some evidence of genetic association in case-control studies analyzing *Estrogen Receptor 1* (*ESR1* OMIM 133430) and *Cytochrome P450, Family 19, Subfamily A, Polypeptide 1* (*CYP19* OMIM 107910) genes. Interestingly, both loci are involved in oestrogen mechanism of production and action [12,13]. In addition, other nuclear receptor genes, such as *Progesterone Receptor* (*PGR* OMIM 607311) and *Peroxisome Proliferative Activated Receptor, Gamma* (*PPARG* OMIM 601487) gene have been associated with endometriosis in other case-control studies [14,15]. The involvement in endometriosis of loci related to detoxification has been also studied and replicated [16-18].

Given these preliminary findings and the importance of steroid receptors in uterine physiology [19] and endometriosis pathogenesis [1,20], the biochemical pathways involved in steroids production, degradation or mechanisms of action appear to be strong candidates for endometriosis etiology and many other phenotypes related to human fertility.

Following this working hypothesis, targeting disruption of nuclear receptors and their regulators such as *nrip1* or *CCR4-NOT transcription complex, subunit 7* (*cnot7* GenBank AK009561) in animal models have provided direct evidence of the importance of nuclear receptor homeostasis in male and female reproduction [3,21-24].

Here we present the first structural analysis of the human *NRIP1* gene in relation to human disease. It is of interest to mention that the dbSNP includes 26 SNPs for *NRIP1* gene currently. Eighteen of these variants are located within the 3'untranslated region (3'UTR), this genomic region has not been covered in this study, and the remaining ones are coding SNPs. According to GenBank, only three SNPs in the 3'UTR region and two coding SNPs have been validated in population based studies including