VITAMIN D METABOLIC PATHWAY RELATED GENE POLYMORPHISMS AND THE RISK OF GOUGEROT-SJÖGREN'S SYNDROME

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Background

- The global prevalence of vitamin D (vitD) deficiency appears to be increasing, and it has been linked to skeletal abnormalities, extra-skeletal diseases and other adverse outcomes. [1-2]
- The immunomodulatory effects of vitD have been extensively studied in the context of autoimmunity. Multiple studies have demonstrated Low levels of vitD in patients with Gougerot-Sjögren's syndrome (SS). [3]
- SS is one of the most common autoimmune disorders. Around 90% of cases are in females. Despite its impact on quality of life and physical function, no disease-modifying drugs have been approved. [4]

Objectives

- Study of potential variables involved in vitD deficiency in patients with SS.
- Investigate the possible association between genetic polymorphisms that affect key genes within the vitD metabolic pathway with SS through a case-control study.

Study Population

- A total of 153 subjects were included: 51 with SS matched in gender to 102 controls of similar ages (1 patient/2 controls).
- Recruited from the internal medicine departments of CHU Sahloul and CHU Hached Sousse.

Methods

- **Genotyping**(PCR-RFLP): We screened six key genes within the vitD metabolic pathway using **12** SNPs markers: DBP (rs 4588, rs 7041), CYP2R1 (rs2060793, rs10741657, rs12794714), NADSYN1 (rs12785878), CYP27B1 (rs 10877012), CYP24A1 (rs 6013897) et VDR (rs1544410, rs731236, rs7975232, rs2228570)
- **Statistical analysis:** SPSS v26 software

Results and discussion

Vitamin D and SS

- The concentration of vitD in patients was significantly lower compared to the controls (13,2[3-57,4] vs 17,65[3-76,4]ng/mL; p=0.038).
- The study of various environmental and biological factors revealed significant differences between controls and patients (p<0.05) in terms of sun exposure, HbA1C, insulin, total protein, alkaline phosphatase, cholesterol, phosphorus, and magnesium levels. All factors with p<0.25 were considered as potential confounding factors to which we adjusted all genotypic analysis.
- After adjusting for confounding factors, OR of SS associated to vitD deficiency was **1,44** (IC95% [1,03-5,75]; p=0,047).

Vitamin D and genotypes

- The genotypic and allelic distribution of the studied SNPs were in Hardy-Weinberg equilibrium.
- According to dominant model and after adjustment by binary logistic regression, we noted that there was a significant association of vitD deficiency for two SNPs (DPB-rs4588 and VDR-rs2228570): OR* of vitD deficiency associated with homozygote variant genotypes were **2.16** (IC95%:1.7-5.87; p<0.001)] and **2.19** (IC95%:1.15-7.3; p=0.024)] respectively.

SS and genotypes

- The study of adjusted OR for SS associated to the variant allele for the studied SNPs revealed that the variant alleles of DPB-rs4588 and VDR-rs1544410 were associated with a higher risk of SS, with OR* of **2.12** and **2.25**, respectively. Conversely, the variant allele of rs2228570 appears to have a protective effect, with an OR of **0.131.** (Table1)

Table 1: OR and CI of SS associated with various SNPs

SNP	Allele	IC [95%]	p	Adjusted OR*	IC	p
rs4588 -DBP	N	-		1	-	**0,014**
	V	[1,38-5,90]	0,006	2,12	[1,234-19,24]	
rs 1544410 -VDR	N	-		1	-	**0,013**
	V	[1,09-5,19]	0,02	2,25	[1,21-6,3]	
rs 2228570 -VDR	N	-		1	-	**0,021**
	V	[0,054-0,59]	0,004	0,13	[0,005-0,807]	

Conclusion

- Patients with vitD deficiency had **1.44** times the risk of developing SS compared to those with recommended levels which consolidate the incrimination of vitD as an environmental factor involved in the triggering of SS.
- Through the genetic study we found that:
  - ✓VDR-rs1544410 and especially DBP-rs4588 variant alleles seem to be candidate genetic markers for SS.
  - ✓DBP variant allele appear to be linked with both vitD deficiency and the onset of SS.
  - ✓VDR variant seems to be associated with the onset of SS, likely through a reduction of vitD activity and sensibility.

*vitD **supplementation**, especially for carriers of these variations, could help prevent SS which will be confirmed by an upcoming interventional study.*

References
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STBC Société Tunisienne de Biologie Clinique