Genotypic and Phenotypic Characterization of Turkish Patients with Vitamin D Dependent Rickets Type IA

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Background

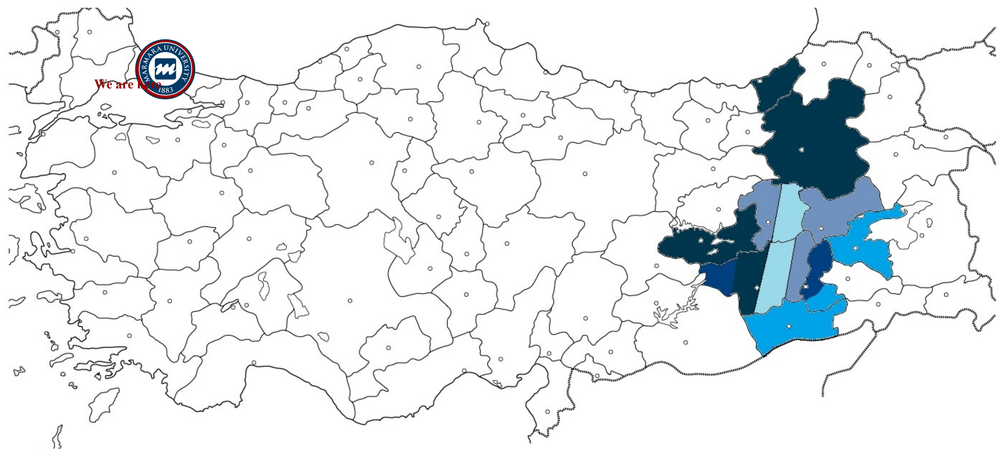
- Vitamin D Dependent Rickets Type IA (VDDR-IA)
  - Most common type of VDDR
  - Caused by mutations in *CYP27B1*
- **Aim:** Analyze the genotypic and phenotypic features of our VDDR-IA patients.

Methods

- The patients with a clinical diagnosis of VDDR-IA were enrolled and analyzed for *CYP27B1* gene mutations.

Results

- 12 (5 males) patients / 9 unrelated families
- Mean age of diagnosis : 3.48±4.00 (median: 1.1 ; min-max: 0.75-11.6) years
- nitially misdiagnosed as nutritional (n:7) or hypophosphatemic rickets (n:3)
- All had biochemical evidence suggestive of VDDR-IA
- Except one with hypocalcemia and hyperphosphatemia
  - Normal *GNAS* gene sequencing and Gsα levels
  - VDDR-IA was subsequently considered upon bone pain and the radiological findings of rickets on initial presentation
- Six patients had a history of high dose vitamin D intake (300000-1500000 IU)
  - One had toxic level of 25[OH]D (250ng/ml)
- All mutations reported in our patients represent previously reported regional founders, which potentially facilitate genetic testing in VDRR-IA patients with same geographical origin
- Patients with p.Phe443Profs*24 mutation which leads to a truncated protein without enzymatic activity presented to the clinic at an earlier age than the patients with p.Lys192Glu mutation (1.12±0.31 vs 10.13±1.40 years).



		N individuals (n family)
	Intron 1 : c.195+2T>G / p.65Q fs	22(13)[1,2,3,4]
	Exon 3 : c.574A>G / p.K192E	11(6)[3]
	Exon 4 : c.590G>A / p.197G>D	5(3)[3]
	Intron 7 : c.1215+2T>A /p.L380Afs*57	6(4)[2,4]
	Exon 8 : c.1325_1326 insCCCACCC/p.F443Pfs*24	14(10)[1,3,4]

Figure 1: Common *CYP27B1* mutations in Turkish population

1. Durmaz, Erdem, et al. "Clinical and genetic analysis of patients with vitamin D−dependent rickets type 1 A." Clinical endocrinology 77.3 (2012): 363-369.
2. Demir, Korcan, et al. "Novel CYP27B1 gene mutations in patients with vitamin D-dependent rickets type 1A." PLoS One 10.7 (2015): e0131376.
3. Tahir, Sophia, et al. "Genotype and phenotype characteristics in 22 patients with vitamin D-dependent rickets type I." Hormone research in paediatrics 85.5 (2016): 309-317.
4. Dursun, Fatma, et al. "Genetic and Clinical Characteristics of Patients with Vitamin D Dependent Rickets Type 1A." Journal of clinical research in pediatric endocrinology 11.1 (2019): 34.

Table 1: Clinical, laboratory, and genetic findings of patients at admission

		Presenting complaints	Sex	Age (yrs)	Ca (mg/dL) (8.8-10.8)	P (mg/dL) (4.5-5.5)	ALP (IU/L) (150-500)	PTH (pg/ml) (15-65)	25OHD (ng/ml) (20-100)	1.25OHD (pg/mL) (16-65)	*CYP271B* Mutation/ Pedigree of Patients
I	1	Delay in walking, hypocalcaemic seizure	F	1	5,10	3,80	1179,00	160,00	250	32	**Exon 8 :** c.1325_1326 insCCCACCC p.Phe443Profs*24
	2	Delay in walking	F	1	7,10	2,70	1352,00	873,00			
II	1*	Hypophosphatemic Rickets	M	8,6	9,60	3,90	219,00	121,00	30,5		
	2	History of VDDR sibling	F	0,9	6,40	2,70	1108,00	891,00	38,30	32,6	
III	1	Sweating, elevated serum ALP levels	M	1,1	8,40	2,90	1447,00	363,00	106.4	85,9	
IV	1	Delay in walking	M	1.75	7.9	2.3	9251	877.0	147.50	<8	
V	1	Bowed legs	F	10	8,60	2,30	2190,00	237,00	49,00	21	**Exon 3:** c.574 A>G. p.Lys192Glu
	2	Bowed legs, gait abnormality	M	11,6	9,00	3,05	1048,00	203,40	61,18	58,24	
VI	1	Leg pain	F	8.8	6,40	6,20	710,00	362,40	33,80		
VII	1	Hypocalcaemic seizure	F	1	4.8	2.4	858	482	24	47	Exon 3 cannot be amplified
VIII	1	Bowed legs	F	5,25	8,00	2,90	3585,00	1006,00	138.8		**Exon 7:** (polymorphism) c.1215 T>C. p.Asn405Asn **Intron 7:** c.1215+2 T>A. p.L380Afs*57
IX	1	Delay in walking	M	1.2	8.4	2.2	3324	586	43.16	49.23	**Exon 4:** c.590G>A. p.Gly197Asp

*Patient had been diagnosed previously with hypophosphatemic rickets at the age of 17 months at another clinic therefore were already on calcitriol and phosphorus replacement therapy. ** No consanguinity, parents originates from close villages

Table 2: Comparision of clinical and laboratory findings of two common mutation

	Exon 8 p.F443Pfs*24 (n = 13)	Exon 3 p.K192E (n = 8)	p
Age(yrs)	**1.02 ± 0.14**	**5.15 ± 1.54**	**0.002***
Height (SDS)	-2.13 ± 0.56	-0.74 ± 0.30	55
Ca (mg/dL)	7.3 ±0.4	7.4 ±0.5	0.98
P (mg/dL)	2.92±0.28	3.16±0.48	0.65
ALP (IU/L)	2590±710	1504±224	0.25
PTH (pg/ml)	508±88	415±69	0.47
25OHD (ng/ml)	105±17.8	57±9.5	53
1.25OHD(pg/mL)	17.3±9.7	39.6±18.6	348

*Mean ± SEM *p<0.005*

Conclusions

- Our results indicate a good genotype-phenotype correlation in patients with VDDR-IA and
- The patients with p.F443Pfs*24 mutaitons presents earlier than patients with p.K192E mutations
- We emphasized the importance of correct diagnosis in VDDR-IA for the proper management, and avoiding poor clinical outcomes.