



Clinical And Molecular Characterization Of 25-hydroxylase Deficiency In Saudi Patients

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BACKGROUND

Vitamin-D deficiency becomes a worldwide issue, and major cause of rickets in younger age groups. Multiple causes lead to vitamin-D deficiency in which nutritional causes contribute the major factor. The synthesis of bioactive vitamin-D requires hydroxylation at 1α and 25 positions by cytochrome-P450 in the kidney and liver, respectively. Recently, human CYP2R1 has been reported as a major factor for 25-hydroxylation, in which it contributes for the inherited forms of vitamin-D deficiency. Till now, 5 cases with CYP2R1 mutation were reported worldwide.

We have few cases with this hereditary condition, which was not well described in literature; we are going to report in this study.

METHODS

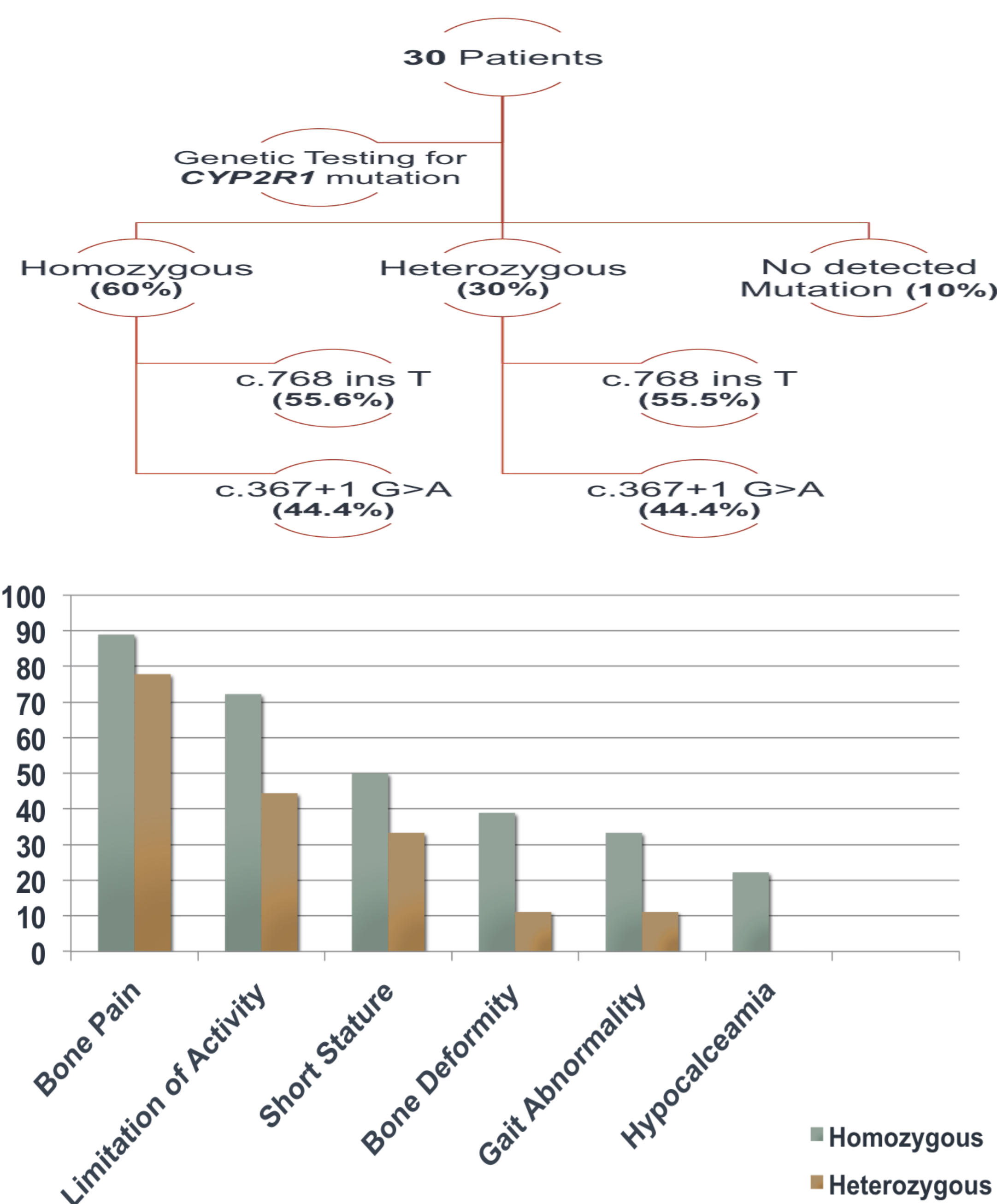
A retrospective cohort study conducted at King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia. That included 41 patients who presented with low vitamin D level (<50 nmol/L) and classical symptoms of vitamin-D deficiency who minimally responded to regular vitamin-D supplementation. We excluded patients who had nutritional or comorbidity factors. Medical charts of all patients were reviewed for demographic, clinical, laboratory and radiological data. Genetic testing for CYP2R1 mutations has been performed for all patients as part from routine diagnostic evaluation.

RESULTS

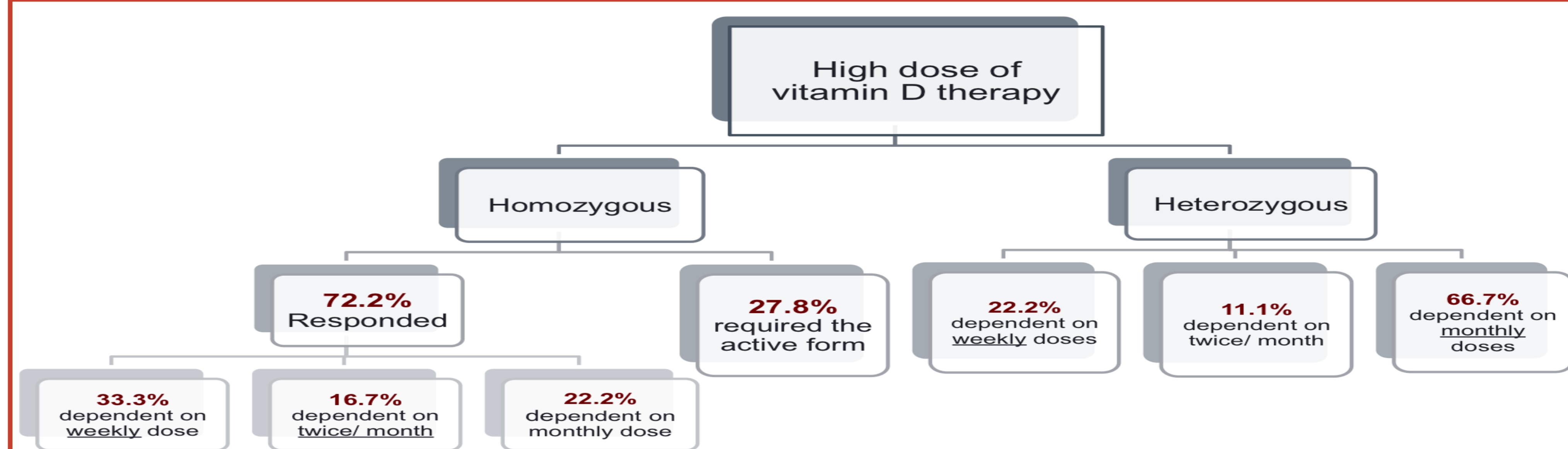
From the 41 patients, 11 patients (26.8%) gene test was done for them but lost follow up and 30 patients (73.2%) were included in the analysis. Of 30 patients, 11 were males and 19 females, with mean age of 6 years. All were found to have significant family history of vitamin-D deficiency. They presented with variable presentations, the most common presentation was bone pain (86.2%) and limitation of physical activity (58.6%), and the severe form including bone deformity (31%) and hypocalcaemic manifestations (17.2%). The genetic testing of all patients identified two different mutations: c.367+1,G>A (44.4%) and c.768,insT (55.6%), were 18 patients found to be homozygously affected, 9 patients were heterozygous carriers and 3 without detected mutation.

The patients with homozygous mutation found to have very low 25 OH vitamin-D levels compared patients with heterozygous mutation where their levels ranged between. Biochemical and radiological abnormalities were also detected in higher percentages with the homozygous group compared with heterozygous group. Most homozygous patients presented with moderate to severe symptoms, but there were few patients presenting with milder forms including bone pain only.

All these patients needed very high doses of vitamin-D (i.e. 50,000 -100,000 IU of vitamin D2 weekly), 72.2% of the homozygous group and all of the heterozygous groups were responsive (25 OH vitamin D was normal) but they showed regression after cessation of treatment. 27.8% of the homozygous group did not respond to high doses of vitamin D they were given 1,25hydroxy vitamin D (Calcitriol) and improved. Most of the responsive patients required maintenance therapy of high dose vitamin D, which vary in frequency from weekly; twice/month; and monthly doses.



	Homozygous	Heterozygous
Vitamin D level	Ranging between 6-25 nmol/L	Ranging between 10-40 nmol/L
Biochemical Abnormality	88.9%	44.4%
Radiological Abnormality	61.1%	22.2%



CONCLUSIONS

Our data identified high percentage of CYP2R1 related vitamin-D deficiency in the Saudi community. There was no clear genotype/phenotype correlation, with wide variety in disease expression and response to treatment in relation to either mutation or in the homozygous/heterozygous form. This result will help in diagnosing, treatment and prevention of similar cases in the future.

RECOMMENDATION

The molecular analysis of CYP2R1 can be considered for:

- Children with early symptoms of vitamin D deficiency, and associated rickets who have diminished or minimal response to regular therapy.
- Individuals with a strong family history of vitamin D deficiency.

Such patients need to be started on high dose of vitamin-D therapy, or the active form if there was no response.

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