Endocr Rev, Vol. 34 (03_MeetingAbstracts): FP22-1

COMPLETE AROMATASE DEFICIENCY IN FOUR ADULT MEN: DETECTION OF A NOVEL MUTATION AND TWO KNOWN MUTATIONS IN THE CYP19A1 GENE

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INTRODUCTION. At present, only eight men with loss-of-function mutations in the *CYP19A1* gene have been described (1). We report the genetic study of four adult men with undetectable serum estrogens, unfused epiphyses, eunuchoid skeletal proportions, continuing linear growth, tall stature, *genu valgum*, osteoporosis, obesity and *achantosis nigricans*. Patient 1 (26-yrs/182cm) and 2 (28-yrs/187cm) are from Turkey, Patient 3 (44-yrs/185cm) and 4 (29-yrs/197cm) are two brothers from Jordan. All patients had a history of consanguinity (father and mother of each patient are cousins).

METHODS. All coding exons with their flanking intronic sequences of *CYP19A1* gene, amplified by PCR, were sequenced by ABI-Prism 3130 Genetic Analyzer and compared with known human *CYP19A1* gene sequences.

RESULTS. Patient 1 was homozygous for a point mutation in the first nucleotide of intron 3 (IVS3+1G>T); Patient 2 homozygous for a G>A mutation (c.1124 G>A) in exon IX resulting in protein missense mutation p.R375H. The two brothers (Patients 3 and 4) had a homozygous mutation in exon IV (c.434 G>A) leading to Arg to Gln substitution at position 115 (p.R115Q). All patients had impaired glucose tolerance, Patient 3 was diabetic, Patient 2 had a history of three forearm bone fractures after minimal trauma, Patient 1, 3, and 4 had impaired liver function. Patient 1 had documented GH-deficiency, all other patients had no evidence of GH hypersecretion.

CONCLUSIONS. The description of these new four aromatase-deficient men confirms the detrimental effects of congenital estrogen deficiency on glucose, liver and bone metabolism (particularly bone maturation and mineralization) (1). The homozygous missense mutation in exon IV (p.R115Q) (Patients 3 and 4) is novel: both aminoacids are basic, their different conformational structure probably leads to tertiary or quaternary distortion in protein structure. The other two known mutations are found in homozygosis for the first time. Clinical evidence of osteoporotic fractures is described for the first time and further emphasizes estrogen role on bone health in men and the need for fracture prevention in these patients (2). Thus, drugs preventing bone fractures could be considered as additional treatment other than estrogen replacement (3). Finally, tall stature with concomitant GH-deficiency or with low to normal GH secretion depends on unfused epiphyses that allows bone elongation resulting in eunuchoid skeletal proportions (4).

(1) Rochira V. & Carani C., Nat Rev Endocrinol 2009; 5:559-568. (2) Rochira V. et al., Bone 2007; 40:1662-1668. (3) Maffei L. et al., J Clin Endocrinol Metab 2004; 89:61-70. (4) Rochira V. et al., J Clin Endocrinol Metab 2010; 95:1626-1633.

Nothing to Disclose: EP, KMA, NK, KU, EK, CC, MS, MM, EV, VR

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