

ship between the CYP17 gene polymorphism and RA should be tested by further investigations of serum androgen levels.

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## References

1. HUANG J, USHIYAMA K, MORI K, HUKUDA S: Possible association of CYP17 gene polymorphism with the onset of rheumatoid arthritis. *Clin Exp Rheumatol* 1999; 17: 721-4.
2. CAREY AH, WATERWORTH D, PATEL K, *et al.*: Polycystic ovaries and premature male pattern baldness with one allele of the steroid metabolism gene CYP17. *Human Mol Genet* 1994; 3: 1873-6.
3. CUTOLO M: The role of the hypothalamus-pituitary-adrenocortical and gonadal axis in rheumatoid arthritis. *Clin Exp Rheumatol* 1998; 16: 3-6.
4. CUTOLO M, BALLEARI E, GIUSTI M, *et al.*: Sex hormones status in women suffering from rheumatoid arthritis. *J Rheumatol* 1986; 13: 1019-23.
5. ARNALICH F, BENITO-URBINA S, GONZALEZ GANCEDO P, DE MIQUEL E, GILON-BANOS J: Elévation des androgènes plasmatiques chez les femmes ménopausées atteintes de polyarthrite rhumatoïde. *Rev Rhum* 1990; 57: 509-12.
6. SPECTOR TD, PERRY LA, TUBB G, HUSKISSON EC: Androgen status of women with rheumatoid arthritis. *Br J Rheumatol* 1987; 26: 316-8.
7. SAMBROOK PN, EISMAN JA, CHAMPION GD, POCKOCK NA: Sex hormones status in postmenopausal women with rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 973-8.
8. FEHÉR KG, FEHÉR T, MERÉTEY K: Interrelationship between the immunological and steroid hormone parameters in rheumatoid arthritis. *Clin Exp Rheumatol* 1986; 87: 38-42.
9. DAUGHTON CM, WATSON MJ, WALKER DJ: Sex hormones in postmenopausal HLA-identical rheumatoid arthritis discordant sibling pairs. *J Rheumatol* 1992; 19: 1663-7.
10. CUTOLO M, ACCARDO S, BALLEARI E, SULLI A, SERIOLO B, GIUSTI M: Androgen status in postmenopausal patients with rheumatoid arthritis. *J Rheumatol* 1993; 20: 2163-4.
11. CUTOLO M, BALLEARI E, GIUSTI M, *et al.*: Preliminary results of serum androgen testing in men with rheumatoid arthritis. *Arthritis Rheum* 1984; 27: 958-9.
12. CUTOLO M, MASI AT: Do androgens influence the pathophysiology of rheumatoid arthritis? Facts and hypotheses. *J Rheumatol* 1998; 25: 1041-7.
13. CUTOLO M, PRETE C, WALKER J: Is stress a factor in the pathogenesis in autoimmune rheumatic diseases? *Clin Exp Rheumatol* 1999; 17: 515-8.

## Reply

Sirs,

Serum hormone measurements are subject to variation by many factors such as time of day, age, disease status, and prescribed medication, whereas the determination of genetic markers for steroidogenesis is not influenced by such variance.

We have demonstrated that the CYP17 gene polymorphism is associated with RA, especially in older age onset female RA, through sex hormone production (1). Parallel with our results, with a large sample using sibpair analysis methods, John *et al.* reported that the estrogen synthase (CYP19) locus was linked to RA and that this linkage was strongest in patients with onset at over 50 years old, when serum hormone levels decline (2). The functional activities of the CYP19 gene variants are unknown at the present. Furthermore, though both CYP17 and CYP19 are related to sex hormone synthesis, their genes are located in different chromosomes.

We have also demonstrated an association between both androgen and estrogen receptor gene polymorphisms and RA onset (3, 4). Shorter CAG repeats of the androgen receptor gene, presenting high levels of transactivation activity, are related to younger age onset male RA when serum androgen levels are higher (3). In addition, some intron variants of the estrogen receptor gene are related to the onset of female RA at a certain age period, probably depending on the serum levels of estrogens (4).

These findings suggest that RA is likely to occur in certain variations of hormonal status, which are induced by the interaction between sex-, age- dependent physiological sex hormone serum levels and the genetic background of the various sex hormone-related genes.

Overall, the results of our studies possibly explain the hypothesis of Cutolo *et al.*, which states that sex hormones, especially androgens, play an important role in the pathogenesis of RA.

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## References

1. HUANG J, USHIYAMA T, INOUE K, MORI K, HUKUDA S: Possible association of CYP17 gene polymorphisms with the onset of rheumatoid

- arthritis. *Clin Exp Rheumatol* 1999; 17: 721-4.
2. JOHN S, MYERSCOUGH A, EYRE S, *et al.*: Linkage of a marker in intron D of the estrogen synthase locus to rheumatoid arthritis. *Arthritis Rheum* 1999; 42: 1617-20.
3. KAWASAKI T, USHIYAMA T, UEYAMA H, *et al.*: Polymorphic CAG repeats of the androgen receptor gene and rheumatoid arthritis. *Ann Rheum Dis* 1999; 58: 500-2.
4. USHIYAMA T, MORI K, INOUE K, HUANG J, NISHIOKA J, HUKUDA S: Association of oestrogen receptor gene polymorphisms with age at onset of rheumatoid arthritis. *Ann Rheum Dis* 1999; 58: 7-10.

## Headache in SLE

Sirs,

We read the article by Amit *et al.* "Headache in systemic lupus erythematosus and its relation to other disease manifestations" in the July - August issue of the Journal (1) and found it of great interest. The authors described a large series of SLE patients with headache, which appears as a frequent symptom, and found a correlation to constitutional and musculoskeletal manifestations.

We would like to emphasize and highlight a rare but severe form of headache in SLE. We previously reported (2) on 3 girls with SLE who developed cerebral vein thrombosis (CVT). In one of them the diagnosis was delayed until severe hemorrhagic infarct occurred. The clue to the diagnosis in the 3 patients was severe, persistent, throbbing, unremitting headache, unresponsive to daily analgesic drugs. All 3 showed the presence of antiphospholipids antibodies. Radiological studies, CT, MRI, and MR venography confirmed the CVT. As Amit *et al.* concluded, headache in SLE is common, but rarely a higher index of suspicion for the unusual "lupus headache", should lead to intense investigations enabling early diagnosis and treatment.

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## References

1. AMIT A, MOLAD Y, LEVY O, WYSENBECK AJ: Headache in systemic lupus erythematosus and its relation to other disease manifestations. *Clin Exp Rheumatol* 1999; 17: 467-70.
2. UZIEL Y, LAXER RM, BLASER S, ANDREW M, SCHNEIDER R, SILVERMAN ED: Cerebral vein thrombosis in childhood systemic lupus erythematosus. *J Pediatr* 1995; 126: 722-7.