The possible Middle East origin of the mutation for the limb/pelvis-hypoplasia/aplasia syndrome

Several reports have been published describing the newly recognised autosomal recessive limb/pelvis-hypoplasia/aplasia syndrome (LPHAS).¹⁻⁵ Raas-Rothschild *et al.*³ have speculated that the rare LPHAS gene has its origin in the Middle East, on the basis of both their report on three sibs of Iranian Jewish background and the report by Al-Awadi *et al.*¹ on two sibs of Arabic origin with the LPHAS phenotype. Farag *et al.*⁴ and Camera *et al.*⁵ however, have disputed this hypothesis on the grounds that two of the identified families have their origin outside the Middle East, one being Brazilian and the other Italian.

I still think there is a strong basis for the original suggestion by Raas-Rothschild *et al.*³ The very long coexistence of both Arabs and Jews in what is now known as the Middle East has been certified, if not by history, then by the holy scriptures. Also the historical Arabic interaction with peoples of both Italy and Spain (the presumed origin of the Latin American ancestors of the Brazilian family) in the Middle Ages suggests a possible Arabic genetic influence in these parts of the world. I discussed this idea with senior members of the Kuwait Medical Genetics Centre who were authors or co-authors of two of the published reports on LPHAS⁴ and it seems that they do not disagree with this suggestion. I would also be interested to know the opinion of authors from other countries in the light of these historical facts.

M A SABRY
Kuwait Medical Genetics Centre,
PO Box 35017, Al-Shaab 36051,
Kuwait

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- 2 Richiardi-Costa A. Profound limb deficiency, thoracic anomalies, unusual facies and normal intelligence: the Al Awadi syndrome. Report of a Brazilian patient. *Rev Brasil Genet* 1987; X:611-6.
- 3 Raas-Rothschild A, Goodman RM, Meyer S, *et al.* Pathological features and prenatal diagnosis in the newly recognised limb/pelvis-hypoplasia/aplasia syndrome. *J Med Genet* 1988;25:687-97.
- 4 Farag TI, Al-Awadi SA, Marafie MJ, *et al.* The newly recognised limb/pelvis-hypoplasia/aplasia syndrome: a report of a Bedouin patient and review. *J Med Genet* 1993;30:62-4.
- 5 Camera G, Ferraiolo G, Leo D, *et al.* Limb/pelvis-hypoplasia/aplasia syndrome (Al-Awadi/Raas-Rothschild syndrome): report of two Italian sibs and further confirmation of autosomal recessive inheritance. *J Med Genet* 1993; 30:65-9.

No association between dopamine D4 receptor polymorphism and manic depressive illness

Manic depressive illness (MD), also termed bipolar affective disorder, is a major psychiatric disorder characterised by severe

mood changes and a variable age of onset that afflicts an estimated 1% of the world's population.¹ Accumulated evidence from family, twin, and adoption studies has confirmed the involvement of genetic factors in MD. Lod scores suggesting linkage to the short arm of chromosome 11 have been reported using markers such as HRAS.² Moreover, genetic association between tyrosine hydroxylase, a gene localised in this region, and MD has also been reported.³ However, these initial reports have not been reproduced,^{4,5} this failure being attributed to various factors: genetic heterogeneity, diagnostic uncertainties, and a not well established mode of inheritance; in fact, it is possible that MD is inherited multifactorially. Linkage analysis is the most widely used strategy in the research of monogenic diseases, but in diseases with a complex mode of transmission, such as MD, linkage studies may be complicated by the factors indicated above. An alternative to the analysis of complex multifactorial diseases is the search for genetic association between alleles at a given locus and the disease phenotype.^{6,7}

The dopamine D4 receptor (DRD4) maps to 11p15.5, close to HRAS, and has a high affinity for the antipsychotic clozapine.⁸ Thus, DRD4 may be considered as a good candidate gene to confer susceptibility to MD. A functional polymorphism in this gene has recently been reported.⁹ We have searched for evidence of association between MD and this polymorphism located inside this gene in a sample from central Spain.

We tested 64 patients with bipolar affective disorder (25 males and 39 females), ascertained at random from admissions to the Psychiatric Service of the Hospital Ramón y Cajal, Madrid. All of them were diagnosed according to Research Diagnostic Criteria (RDC).¹⁰ Forty-six unrelated persons (24 males and 22 females) were tested as normal controls. All patients and controls were white, from Central Spain, and more than 40 years old.

A 48 base pair (bp) repeat polymorphism located in the putative third cytoplasmic loop region of DRD4 gene⁹ has been detected

by PCR amplification using the primers and conditions described by Nanko *et al.*¹¹ PCR products were resolved by vertical discontinuous non-denaturing polyacrylamide gel electrophoresis, and detected by silver staining.

Association between MD and the VNTR polymorphism was tested for statistical significance by the χ^2 test.

We found five alleles in our sample corresponding to two, three, four, seven, and eight repeats (figure). The table shows the allele frequencies obtained for controls and patients. The comparison, in a 2×5 contingency table of the distribution of alleles, between the controls and the patients showed no statistically significant differences ($\chi^2 = 2.9$, $df = 4$, $p = 0.57$). The data were analysed in a 2×2 contingency table comparing the frequencies of each allele versus the rest. This analysis also failed to show significant differences for any allelic frequencies between the two groups (data not shown).

The DRD4 polymorphism was chosen because DRD4 receptors with different repeat numbers have been shown to exhibit a different affinity for clozapine. Receptors with two or four repeats bound this atypical neuroleptic three to four times better than receptors with seven repeats.^{9,10} One possible explanation would be that the variation in the number of repeats has significant effects on the amino acid sequence and, probably, on the structure of the receptor. This may affect the conformation of the ligand binding site or the G protein interaction site or both.¹² However, Ross¹³ reported that the third cytoplasmic loop is dispensable for signal transduction. From our study we conclude that there is no association between this DRD4 polymorphism and MD. Our results are thus in line with the data reported by Ross,¹³ as no variant of this polymorphism is significantly more frequent in the subpopulation of patients. Furthermore, recent studies on schizophrenia^{11,14} and Parkinson's disease¹⁵ have also suggested a negative relationship between these diseases and this DRD4 polymorphism. Thus, so far there is no evidence for the involvement of the DRD4 gene in the

Alleles at the DRD4 locus according to the number of repeats. Lines 1-6 indicate different persons analysed. Fragment sizes in base pairs by migration relative to size standards.