COMT Gene Polymorphisms and Fibromyalgia

To the Director: We have read with interest the article by García Fructuoso et al[1] about the possible implication of the *COMT* gene in the susceptibility and the severity of fibromyalgia (FM). We do not share some aspects of the employed methodology and the relationship between these findings as well as the interpretations of the authors, and we wish to do the following commentary. The supposed relationship of the *COMT* gene polymorphism in multiple processes is a fact so thoroughly studied as discussed. In part, the origin of the absence of objective findings is simple: to establish an unequivocal relationship between a determined genotype and a phenotype, and the latter has to be concrete, well established and with the least possible amount of environmental interference. Obviously, FM and a series of psychiatric illneses,[2-4] in which a possible relationship with the Val158Met polymorphisms have been observed, are not characterized as being concrete, objective and free of environmental interference. These polymorphisms have even been observed in chronic fatigue syndrome[5] (with a percentage superior to 70% of patients that have generalized pain and more than 11 positive ACR trigger points) and in "healthy" people with an abnormal pain process,[6] smoking,[7] and alcoholism[8] as well. These are some of the reasons due to which, before investigating possible genetic associations with certain processes, we must delve deep into establishing with security that we are confronted with a unique illness and not with a variable group of symptoms that can have different causes. In this sense, the analysis of the comorbidites that the studied patients presented (depression or anxiety, stressful events, drug or alcohol consumption) could be explained as part of the observed findings. FM is one of the main causes o chronic generalized pain and, in spite of a recent study,[9] done in a large sample of patients with this symptom (the authors did not analyze the possible etiology of pain, something that constitutes a serious limitation), did not show any association between the Met/Met genotype and susceptibility to pain. What´s more, in the male patients sampled, the results suggested that it could have a discreet "protective" role when confronted with pain (Met/Met present, 29,4% vs Met/Met absent, 34.7%; *P*=.04), a result that is contrary to the observed in the article by García Fructuoso et al. The control sample employed in the study, defined as "110 healthy persons, of the same proportional age and gender (45-55 years), without pain or fatigue" is surprising because it is estimated that a third of the Spanish population in that demographic sector refers chronic pain[10] and, probably, a lesser percentage would refer fatigue. If we assume that the selection of these persons was done rigorously, the sample would not be representative of the normal "healthy" population, but rather of a concrete sector of the population "without pain or fatigue," implying an evident selection bias. Regarding the establishment of the severity of FM through FIQ, whose objective seems to be only judicial, as commented in the article, we consider that it could induce error because it employs subjective variables and, logically, the sum of subjectivities does not become an objective and annuls its value to establish or demonstrate a determined degree of limitation. In summary, even though the studies of genetic association are a invaluable tool for gaining knowledge into the pathogenesis of certain illnesses with clearly established phenotypes, in processes as complex as FM it is fundamental that the study of large samples that permit a subgroup analysis in which multiple co morbidities that, with great frequency, are present in these patients, as well as an exhaustive examination of their history in which documentation of existing past or present stressful episodes, drug consumption, addictive behavior, work situation, etc. Otherwise we cannot conclude we are faced with genetic association that, if true, could open new and interesting doors in research.

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