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AGTR2 in Brain Development and Function

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In the report by Huang and coworkers [Huang et al., 2005], the authors have tested four previously identified *AGTR2* gene alterations [Vervoort et al., 2002] in two presumed control groups: 673 adult males and 445 females tested for hereditary hemochromatosis (HH). They have also screened 608 males (presumably mentally retarded) and 616 female patients (presumably receiving carrier testing for fragile X and of normal intelligence), all negative for the *FMR1* expansion. Huang and coworkers identified the 395/402delT mutation in two of 673 HH male samples, one of 445 HH female samples, none of the *FMR1* negative males, and none of the *FMR1* negative females [Huang et al., 2005]. The authors consider this finding to be inconsistent with this mutation being pathogenic, even though it causes a frameshift and a truncated protein, which is deleterious in males, who carry only one copy of the gene. Without any clinical information, the assumption made by the authors that all the males and females submitted for hemochromatosis testing are likely cognitively normal is rather speculative. Several studies suggest that 1–3% of the population has some cognitive deficit and the prevalence of X-linked mental retardation (XLMR) has been estimated as approximately 1.8/1,000 males with a carrier frequency of 2.4/1,000 females [Herbst and Miller, 1980; Leonard and Wen, 2002]. Thus a possibility certainly exists that some individuals in the HH population have some degree of cognitive impairment (IQ <70). Since an alteration of the *AGTR2* gene may also cause a variable effect on the cognitive function in an individual, as seen in other cases of MR genes, it is important that any individual with an *AGTR2* alteration be assessed for cognitive function.

A second alteration, p.G21V, previously reported in MR patients [Vervoort et al., 2002; Ylisaukko-oja et al., 2004] as well as control samples [Erdmann et al., 2004], was also observed by Huang and coworkers in their test groups. However, the other two missense alterations, p.R324Q and p.I337V, reported by Vervoort et al. [2002] were not detected in any of the 2,334 individuals tested in their study. Such a finding is not uncommon for pathogenic alterations. An absence of a gene variant in MR or control samples points to the rarity of the variation in a population and confirms the importance of the choice of population (race, ethnicity, and geographical background) since allele frequency can differ between groups [Bienvenu et al., 2003]. Previously, three unrelated males with MR were found to have the p.R324G mutation [Vervoort et al., 2002]. Recently, we have screened 128 male patients with MR and seizures and identified one additional individual carrying the p.R324Q mutation. The results thus far demonstrate a significant difference in the frequency of the p.R324Q mutation in males with MR (4/1,318 total tested, assuming all 600 males tested for fragile X included in the report by

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Huang and coworkers have MR) when compared to control individuals (510 normal males in Vervoort et al., 2002, 673 HH males, and 445 HH females tested by Huang and coworkers) tested (0/1,628; 2,073 X chromosomes equivalent; $P < 0.05$ by Fisher's exact test). These findings point to a possible pathogenic nature of the mutation. Additional verification by functional approaches or extended population study is warranted to further support the suggestion that the p.R324Q mutation is disease associated.

Huang and coworkers also identified a 2-year old female patient with a *FMR1* expansion who was also heterozygous for the p.R324Q mutation (no information was given about the expansion length in this female) [Huang et al., 2005]. The presence of *FMR1* expansion makes it difficult to assess the status of the p.R324Q mutation. Assuming that the females submitted for fragile X diagnostic testing are all normal or have no family history of MR is also problematic. It is likely that some of these females may have had some cognitive deficit or have had a family history of neurological developmental delay or learning deficit and thus it would be difficult to make any conclusion from a positive finding in these females, especially for an X-linked recessive mutation.

The report by Huang and coworkers, although lacking several critical details, raises some important points and suggests even a truncating mutation in an X-linked gene may not be disease associated. This study further signifies the importance of the choice of a suitable control population when attempting a clinical interpretation of a sequence variation. The conclusions drawn by the authors that *AGTR2* mutations are an uncommon cause of XLMR, that *AGTR2* mutations other than those described in their article are responsible for XLMR, or that *AGTR2* mutations do not cause XLMR appear to over reach their data and require more rigorous study. A cohort of males with normal cognitive function should be tested before drawing such conclusions. Although the authors did not analyze the entire *AGTR2* gene in their MR population, their work certainly points out that the frequency of the *AGTR2* gene mutations may not be as high as was observed earlier [Vervoort et al., 2002]. A low frequency of an MR gene mutation in X-linked or autosomal MR cases is not unusual and have been observed in majority of MR genes cloned [Chelly and Mandel, 2001; Mandel and Chelly, 2004].

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