Int J Legal Med (2005) 119: 179–180
DOI 10.1007/s00414-005-0525-0

LETTER TO THE EDITOR

Reinhard Szibor · Sandra Hering · Jeanett Edelmann

The HumARA genotype is linked to spinal and bulbar muscular dystrophy and some further disease risks and should no longer be used as a DNA marker for forensic purposes

Received: 22 September 2004 / Accepted: 3 January 2005 / Published online: 3 February 2005

Dear Sir,
We write this letter to announce that our group no longer considers HumARA to be a suitable DNA marker in forensic casework.

In several countries, such as Germany, forensic scientists follow the principle that forensic DNA testing should not disclose diseases or genetic risks. This principle is fully complied with STR typing strategies using the well established autosomale STRs, such as the CODIS markers, chromosome Y (ChrY) markers, mtDNA analysis and nearly all established chromosome X (ChrX) markers. ChrY and mtDNA typing may reveal some general information as to a person's ethnic origin; however this cannot be considered as an intervention into the person's privacy. TH01, VWA, FGA, HPRTB, etc. and the mt-D-loop polymorphism are physically linked to loci responsible for some inborn diseases; however, those forensically employed markers do not encode proteins and thus are believed not to be associated with characteristics that may impact on privacy of the individual. Of course, close physical linkage between a genetic marker and a pathogen mutation may produce a linkage disequilibrium. That means that carriers of a certain pathogen mutation may exhibit a biased allele distribution with regard to the linked forensic marker. However, allele associations are generally limited to a specific population, and cannot be generalised. This is even underlined by the fact that an allele association of the TH01 alleles and schizophrenia or bipolar disorders [11, 12, 17] could not be confirmed by other authors [1, 10]. Consequently, in almost all cases forensic typing is not connected with a predictive value for the development of genetic diseases or health risks. In this context the forensically established ARA trinucleotide repeat polymorphism can be considered to be a unique exception.

In forensic science X-chromosomal testing started with the development of HumARA and HumHPRTB markers [2, 4, 6, 7]. Desmarais et al. [2] used HumARA typing as a starting point for generating special formulae for applying ChrX typing to forensic practice. Hence, these markers are well established in forensic DNA typing. From the very beginning of HumARA testing it has been known that, in contrast to all other forensic DNA markers, the HumARA CAG repeat is located in a coding region (androgen receptor gene, exon 1). This means that the repeat codes for a polyglutamine tract. La Spada et al. [8] proved that X-linked spinal and bulbar muscular atrophy (SBMA) is attributable to a mutation at this locus. This disease occurs at trinucleotide repeat lengths longer than 43.

As SBMA is a very rare disease, the forensic community, including our group, has ignored this fact and used HumARA as a normal forensic marker for many years [3, 9, 13–16, 19–21].

Attentive studies of the literature have revealed the necessity to change this typing strategy.

Apart from the SBMA disease, HumARA typing can detect a number of further health risks, e.g. Tut et al. [18] found a fourfold increased risk of impaired spermatogenesis in patients with 28 or more glutamines in their androgen receptor (AR). Zitzmann et al. [22] investigated the interactions between the CAG polymorphism, serum levels of sex hormones, cardiovascular risk factors, and flow-mediated and nitrate-induced vasodilatation of the brachial artery. The number of CAG repeats had no significant correlation with serum concentrations of total or free tes-

R. Szibor (✉)
Institut für Rechtsmedizin,
Otto-von-Guericke-Universität Magdeburg,
Leipziger Strasse 44,
39120 Magdeburg, Germany
e-mail: reinhard.szibor@medizin.uni-magdeburg.de
Tel.: +49-391-6715812
Fax: +49-391-6715810

S. Hering
Institut für Rechtsmedizin,
Technische Universität Dresden,
Fetscherstraße 74,
01307 Dresden, Germany

J. Edelmann
Institut für Rechtsmedizin,
Universität Leipzig,
Johannisallee 28,
04103 Leipzig, Germany

tosterone; however this study revealed positive correlations of the number of CAG repeats with serum levels of high density lipoprotein (HDL) cholesterol and flow-mediated vasodilatation. The authors concluded that a low number of CAG repeats in the AR gene implies a greater chance for low levels of HDL cholesterol and reduced endothelial response to ischemia, which are both important risk factors for coronary heart disease. A thorough analysis of the AR gene mutation database [5] revealed that CAG repeat length variations are associated with risk for breast, endometrial, colorectal, and prostate cancer, as well as for male infertility. In contrast to the discussed phenomenon of the allele association based on physical linkage, the HumARA problem is of a causal nature. The relationship between HumARA alleles and SBMA as well as further disease risks is induced by the length of the polyglutamine tract in the AR. Bearing in mind that human chromosomes, including the ChrX, offer many thousands of STRs which are not burdened with ethical problems, we strongly recommend the forensic community to refrain from HumARA typing to prevent discreditation of forensic DNA testing. Notwithstanding this recommendation, HumARA can be further used for scientific purposes, i.e. as a marker to study ChrX marker recombination rates.

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