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COMMENTARY

A polymorphic CA repeat in the promoter region of the insulin-like growth factor-I (IGF-I) gene

Ingrid Rietveld[1,2], Joop A.M.J.L. Janssen[1], Cornelia M. Van Duijn[2] & Steven W.J. Lamberts[1]
[1]*Department of Internal Medicine;* [2]*Department of Epidemiology and Biostatistics, Erasmus MC, Rotterdam, The Netherlands*

In this issue of EJEP, Kato et al. describe their genotype–phenotype analysis in a small study group comprising both Caucasian people and African–Americans. In their study group the most frequent allele of the polymorphism in the promoter region of the IGF-I gene contains 18 CA repeats in both ethnic groups and no homozygote carriers of the 19 CA repeat were found. In Whites the frequency of the 19 CA repeat was significantly higher compared to African Americans. No relation was found between the number of CA repeats and serum IGF-I levels among all the subjects combined or in the white or black subgroups separately. A positive relation was found between IGF-I levels and height and cigarette smoking, and as expected age tended to be inversely associated with serum IGF-I.

Several points need to be addressed. One issue is the allele that is most frequently present in the study population. The IGF-I gene, which is located on chromosome 12q, contains in the promoter region a micro-satellite comprising a variable length of a CA repeat sequence. Length of the repeat sequence ranges from 10 to 24, with the most frequent allele containing 19 CA repeats in six previous studies all involving Caucasian people [1–6]. In a previous study in African–Americans only the most frequent allele contained 18 CA repeats [7]. This suggests that during evolution there has been a shift towards longer alleles.

Kato et al. observe the 18 CA repeat allele as most frequent in both Caucasians and African–Americans and explain their different results by the small number of subjects studied (total study group 113 subjects consisting of 57 African–Americans and 56 Caucasian people), by population admixture and/or by the use of a different genotyping method. Studies in which more than 450 healthy subjects are studied regarding the IGF-I promoter polymorphism found an allele frequency of the 19 CA repeat allele between 55.5 and 88%, with a genotype frequency for homozygous carriers between 37.3 and 46.8% [3–7]. In large studies a more narrow range in frequency of homozygous carriers of the wild type allele is observed than in small studies. Small sized studies can therefore, regardless of the study design, be expected to deviate from the population characteristics.

Serum IGF-I levels differ between ethnic groups, so it is not strange to expect differences in IGF-I allele frequencies between ethnic groups. A shift towards longer alleles during evolution is suggested from the study from Kato et al. as well as that from Takacs et al. In this regard the observed shorter allele in African–Americans is in accordance that they represent an older race than Caucasians [7]. The fact that in Whites in the study from Kato also this allele is found to be the most frequent implies indirectly the involvement of older US populations. Hardy–Weinberg equilibrium, tested by χ^2 statistics was not rejected, but this could be due to chance because of the small study group.

Automated DNA sequencing of all samples was done in order to determine the length of CA repeats. Methods relying on gel electrophoresis may not be sensitive enough to distinguish heterozygous alleles with differences of one repeat. However, more recent studies using an autosequencer described the 19 CA repeat allele in Caucasian people as the most frequent [3, 4]. Also determination of the IGF-I genotypes should be checked by at least two different investigators, because the software sometimes misclassifies homozygote carriers if the size of the peak-height of background noise is higher than the peak-height of the PCR product.

Another reason for the different outcome could be the selection of the controls. The controls in the study by Kato et al. were selected from an on-going hospital-based case–control study for prostate and breast cancer. All controls participated in the screening program for prostate cancer or visited the Breast Clinic but were not found to have malignant lesions. People participating in the screening programme or visiting the Breast Clinic may have complaints which could be related to prostate or breast cancer. Because the controls do not represent a population-based study group, differences in allele frequencies could have occurred.

Another outcome from this selection is a clear deviation of the observed mean IGF-I levels from normal values. The highest mean is found in the youngest age group (six subjects in the age range from 22 to 39 years of age), and is 146.6 ng/ml (= 146.6 ug/L) where the normal reference range in this age group is 114–492 ug/L [8]. The other IGF-I levels are also lower than expected for their age. Low serum IGF-I levels are thought to be a consequence of growth hormone deficiency, malnutrition, liver

dysfunction or ageing, but also certain diseases reflect low serum IGF-I levels [9, 10].

Several studies examined the relationship between serum IGF-I levels and osteoporosis and cardiovascular diseases [1, 11, 12]. Serum IGF-I levels seem to correlate well with bone mineral density and could therefore be related to osteoporosis [1, 13]. In cardiovascular diseases, low serum IGF-I after acute myocardial infarction has been associated with bad survival [11]. The question remains whether the subjects studied by Kato et al. really represent a healthy population. Another problem is that different types of specimen differ in their mean IGF-I levels. Commercially available kits from Medgenix and DSL state that measurements in plasma result in lower IGF-I levels compared to those in serum. Also a significantly higher mean IGF-I level was observed in serum compared to EDTA plasma and heparin plasma (157.5 ± 45.6 vs. 137.8 ± 42.5 and 141.3 ± 39.3; $p < 0.001$) [14]. The reason for the relatively low IGF-I levels in the present selected study group could therefore be diverse. However, we do not have enough information to find out its cause.

Kato et al. found no consistent trend in plasma IGF-I levels by age and no relation was observed between IGF-I alleles and IGF-I levels. Serum total IGF-I levels have been measured in healthy infants, children, adolescents and adults [15–18]. Levels increase fast during the first year of life, followed by a linear increase from early childhood into adolescence [15, 16]. During puberty a steep increase is seen to approximately 500 ug/L and after reaching it's maximum level, IGF-I levels decline with age toward prepubertal levels in adults (approximately 300 ug/L), followed by a further slow decrease until 70 years of age [15–17]. Lack of overall association between age and IGF-I levels in the present study could also be due to the small sample size and a wide age-range resulting in low numbers of subjects present in the age categories.

Several previous studies have been directed at the potential functionality of this polymorphism. Results so far have been conflicting. Vaessen et al. observed a higher serum total IGF-I level in homozygote carriers of the 19 CA repeat allele compared to non-carriers of this most frequent allele [4]. Frayling et al. described the opposite effect: low serum IGF-I levels were observed in homozygote carriers of the wild type allele compared to non-carriers of the 19 CA repeat allele [3]. Other studies did not find a relation between this polymorphism and IGF-I levels [5].

In conclusion, ethnicity, size of the study group and the genotyping method used by Kato et al. might have blurred the precise association between the polymorphism studied and its functional consequences.

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Address for correspondence: Dr J.A.M.J.L. Janssen, Department of Internal Medicine, Room D-436, Erasmus MC, Dr Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands
Phone: +31-10-463-9222; Fax: +31-10-463-3268
E-mail: janssen@inw3.azr.nl