

Age- and Sex-Related Interactions between Insulin-Like Growth Factor-I Promoter Polymorphisms and IGF-I Levels

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Abstract: The present study explored sex- and age-related interactions of IGF-I polymorphisms with IGF-I serum levels. In 2000 data on IGF-I promoter polymorphism and IGF-I level were available of 344 (mean age 36; 162 men) and 6 years later in 287 subjects (133 men). As the sample sizes of groups of subjects with IGF-I genotypes 192/192, 190/192, 192/194 and 192/196 were large enough to be analyzed, the relationship between these specific genotypes and IGF-I-level was determined. The results indicated that in women aged 36 IGF-I levels for genotype 190/192 (mean 29.24 nmol/l) were higher than those for genotypes 192/192 (mean 24.29), 192/194 (mean 24.61) and 192/196 (mean 23.93). Male IGF-I levels were decreased in 2006 compared to 2000 for genotypes 192/192 (mean decline – 3.67), 192/194 (mean decline – 1.61), 192/196 (mean decline – 4.18), but not for 190/192. Female IGF-I levels were decreased for genotypes 192/192 (mean decline – 1.85) and 190/192 (mean decline – 4.64), but not for 192/194 and 192/196. Thus females with genotype 190/192 have higher IGF-I levels, while females with genotypes 192/194 or 192/196 and males with genotype 190/192 do not show a decline of IGF-I level.

Keywords: IGF-I polymorphisms, genotype.

INTRODUCTION

Insulin-like growth factor-I (IGF-I) is a peptide hormone that is primarily secreted by the liver and is important for growth and development throughout the body. The secretion of IGF-I is mainly induced by growth hormone. Other factors influencing the serum level of IGF-I are nutritional status, the serum level of sex steroids and insulin and liver function. The level of IGF-I reaches a peak during puberty, and declines with age. IGF-I plays an important role in the regulation of cell proliferation, differentiation and apoptosis and has acute insulin-like metabolic effects [1]. Furthermore, IGF-I levels appear to be positively correlated to muscle mass, physical condition, the ratio of high-density lipoprotein to low-density lipoprotein, bone density, oxygen consumption and overall quality of life, and negatively to body fat [2,3]. IGF-I levels have also been shown to have a positive correlation with cognitive functioning [4]. Low IGF-I levels are associated with an increased risk of developing cardiovascular disease and diabetes, whereas high IGF-I levels in humans are associated with an increased risk of developing cancer [5-9].

In addition to the above mentioned factors that can influence IGF-I levels, it has been estimated that up to 60% of the variability has a genetic basis [10,11]. A genetic determinant

of the IGF-I level appears to be a polymorphism in the promoter region of the IGF-I gene, being a variable length cytosine-adenine (CA) repeat sequence, which has been investigated in the past years. The repeat lengths found previously vary from a minimum of 10 repeats to a maximum of 23 repeats [6,12]. The term 192 was used to signify the 19 CA repeats (192 bp) as reported by Weber and May [13] and labeled Z in their initial report. Other polymerase chain reaction (PCR) product sizes ranging from 188–198 were given a number designated by the length of the CA repeat [14]. The 192bp allele and the 194bp allele are the most common alleles and therefore considered the wild-types [6,9,15,16]. Studies on the IGF-I promoter polymorphism and IGF-I level have mainly focused on the 192bp allele. Systematic reviews by Fletcher *et al.* [6] and by Wagner *et al.* [12] describe how the influence of the polymorphism on the IGF-I level has been investigated in multiple studies, with variable outcomes; the first study by Rosen *et al.* [14] associated the 192/192 genotype with decreased IGF-I levels, while subsequent studies have shown an association of the 192bp allele with increased hormone levels [9,17], with lower IGF-I level [18], or have found no association at all [19-22]. Furthermore, Rietveld *et al.* [23] found that the expected age-related decline in IGF-I levels occurred in homozygotes 192/192, but not in heterozygotes and non-carriers of the 192bp allele. In these studies, groups were generally compared with other groups based on the number of 192bp alleles present: homozygotes (192/192) vs. heterozygotes (192/_) vs. non-carriers (_/_) or homozygotes vs. heterozygotes and non-carriers

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combined (192/_ and _/_) or carriers (192/192 and 192/_) vs. non-carriers.

As the present study is aimed to explore the other genotypes as well, more specific conclusions concerning differences in IGF-I levels between genotypes may be drawn.

Genetic influence on the IGF-I level is not only interesting because IGF-I levels are associated with certain types of cancer, diabetes mellitus and ischemic heart disease [6-9], but also because these diseases have been associated with the polymorphisms in the IGF-I gene itself, although conclusions have been controversial [6,9,12,24]. The influence of the polymorphism on the IGF-I level may be the source of a predisposition for these diseases.

The aim of this study is to describe the occurrence of polymorphisms in the IGF-I gene and genotypes of the different alleles. In addition, the present study explores the relationship between these genotypes and the IGF-I-level as well as the age-related decline of the IGF-I level in a general sample of Dutch men and women.

MATERIALS AND METHODOLOGY

Subjects

The subjects are participants of the Amsterdam Growth and Health Longitudinal Study (AGAHLs). In 1976 this study was started with a total inclusion of 698 subjects to gain an understanding of growth, development and health of children in puberty. Data concerning health, lifestyle and psychological factors have been collected and data collection is still being continued [25]. In 2000 a number of 375 subjects with an average age of 36 years (range 34-38, SD 0.74) still participated in the study. A remaining sample of 343 subjects participated in 2006, at the average age of 42 years (range 41-46, SD 0.65). Thus, the present study allows to examine IGF-I decline across a 6-year interval. The magnitude of IGF-I change per year has been estimated to be 2.1 ng/ml in men and 2.5 ng/ml in women aged between 40 and 50 years. The slopes summarizing the age-IGF-I relationship for two different studies appeared remarkably similar [26]. Although the estimated IGF-I decline of 12.6 ng/ml in males and 15 ng/ml in females across 6 years is moderate, the estimation appears to be so precise that this interval may still reveal structural differences between genotypes.

The distribution of the IGF-I polymorphisms in non-Caucasian subjects appears to be different than that in Caucasian subjects [6,27]. Furthermore, ethnic differences in circulating levels of IGF-I have been reported [27,28]. Therefore, the 13 subjects with a non-Caucasian ancestry were excluded.

Study Procedure

Genetic polymorphisms of the IGF-I-gene and IGF-I levels of 344 Caucasian subjects (162 men, 182 women) were determined in 2000 (Table 1). In 287 of these subjects (133 men, 154 women) a second assessment of IGF-I serum levels was done in 2006.

Genotyping

The genetic polymorphisms of the IGF-I-gene were determined as described previously [9]. In brief, DNA was isolated using standard methods. PCR was performed in a

final volume of 10 μ L containing 10 ng DNA, 10* Gold (Au) buffer (Perkins and Elmer), 200 M dNTP, 30 pmol of each primer, 3 mM MgCl₂, 0.5 U Ampli Tag Gold polymerase (Perkins and Elmer). The PCR program consisted of 30 cycles of 30 sec 95°C, 30 sec 55°C and 30 sec 72°C and additionally 5 min of denaturation at 95°C before the first cycle and an extension of 10 min. at 72°C after the last cycle. Forward primers were labeled with FAM¹² to determine the size of the PCR products by fragment analysis (ABI-Prism genetic analyzer with Genescan 2.1 software). The Genescan 350/500 Tamra was used as internal size standard within the fragment analysis [16].

IGF-I Serum Levels

IGF-I serum levels were measured using a commercially available assay (Chemiluminescent immunometric, Immulite 2500, DPC, Los Angeles, USA). The detection limit was 3.2 nmol/l. The intra and inter assay coefficient of variation were both 5% for the entire range.

Data Analysis

First, subjects with missing IGF-I values were removed. Then, IGF-I serum levels were compared between genotypes, sex and year of measurement (2000/2006). Data were analyzed using Linear Mixed Model with covariance type "unstructured" for repeated measures with Group (genotype) and Sex as independent factors and Year as repeated measurements factor [29]. Since it is known that the IGF-I level of men generally tends to be higher than that of women, sex was also included as independent factor. With respect to Group, pairwise comparisons of IGF-I levels in 2000 and those in 2006 were made separately for males and females. In addition, age-related changes in IGF-I levels were analyzed with pairwise comparisons of Year (2000/2006) for each genotype separately for males and females. All statistical tests were two-tailed. Significance level was set as $\alpha < 0.05$. To control for multiple testing the Benjamini-Hochberg correction was applied [30]. After the removal of subjects with a non-Caucasian ancestry and subjects with missing IGF-I values, data from 344 (2000) and 287 (2006) subjects were evaluable for the Mixed Linear Models Analysis. Only groups of subjects with genotypes 192/192, 190/192, 192/194 and 192/196 were found large enough to be analyzed taking sex differences into account ($n \geq 6$). The other genotypes were analyzed as one remaining group. This group consisted of 31 males and 26 females. (males: 176/192 ($n=1$), 188/192 ($n=7$), 188/194 ($n=1$), 188/196 ($n=2$), 190/190 ($n=1$), 190/194 ($n=4$), 190/196 ($n=1$), 190/198 ($n=1$), 192/198 ($n=2$), 194/194 ($n=3$), 194/196 ($n=8$); females: 176/194 ($n=1$), 176/196 ($n=1$), 188/192 ($n=2$), 188/194 ($n=3$), 188/196 ($n=1$), 190/194 ($n=1$), 190/196 ($n=2$), 190/198 ($n=1$), 192/198 ($n=4$), 194/194 ($n=5$), 194/196 ($n=4$), 194/198 ($n=1$)).

All analyses were performed using SPSS (version 16).

RESULTS

Genotypes

Seven different alleles were present in the study sample. The 192bp allele had the highest frequency (63.9%). A number of 303 subjects (88.1%) were carrier of the 192bp allele. Of these carriers, 137 were homozygote for this allele, and

166 heterozygote. The 194bp allele was present in 132 subjects (38.4%) of whom 8 were homozygote and 124 were heterozygote. The other alleles were found less frequently (Table 1). The distribution of genotypes was in Hardy-Weinberg equilibrium ($p = 0.17$).

Thus, homozygosity for 192bp had the highest prevalence and was observed in 137 subjects (39.8%). The combined presence of 192bp and 194bp (192/194) was the second most frequently observed genotype, followed by 192/196, 190/192, and 194/196 genotypes, respectively (Table 1).

Genotypes and IGF-I Level

Variation in IGF-I levels has been found to be associated with specific lifestyle factors. Particularly, IGF-I concentrations appeared to be inversely related to BMI and the use of postmenopausal estrogen formulations [31]. Therefore, with respect to our study sample, it is important to note that ANOVA separately performed for 2000 and 2006 in males and females indicated no difference in BMI between genotype groups. In addition, chi-square tests indicated that there was no difference in distribution of the use of oral contraceptives in 2000 and 2006 across female genotype groups (Table 2).

Linear Mixed Model Analysis with Group (genotype) and Sex as independent factors and Year (2000/2006) as repeated measurements factor indicated a significant interaction between Group, Sex and Year ($F(4,292) = 2.8, P < 0.05$).

To explore the meaning of this interaction, we further analyzed differences in IGF-I levels determined in 2000 separately for males and females and those determined in 2006 also separately for males and females. Finally, we analyzed changes in IGF-I levels over time separately for males and females. Mean IGF-I levels (nmol/l) \pm SD in 2000 and in 2006 in males and females with different genotypes are shown in Table 3.

IGF-I Levels in 2000

With respect to males, pairwise comparisons indicated no difference in IGF-I levels in 2000 between genotype groups. In contrast, with respect to females, pairwise comparisons showed that for females IGF-I levels in the 190/192 group (mean = 29.24) were significantly higher than those in the 192/192 group (mean = 24.29), as well as those in the 192/194 group (mean = 24.61) as those in the 192/196 group (mean = 23.93) ($P = 0.006, P = 0.013, \text{ and } P = 0.014$ respectively) (Fig. 1). IGF-I levels of the remaining group (mean = 28.42) were higher than those of the 192/192 group, as well as those of the 192/194 group, as those of the 192/196 group ($P = 0.002, P = 0.007$ and $P = 0.012$ respectively). All these effects were significant after application of the Benjamini-Hochberg correction for multiple testing (adjusted alpha = 0.03).

IGF-I Levels in 2006

With respect to IGF-I levels of males in 2006 pairwise comparisons indicated that IGF-I levels in the 192/194 group (mean = 25.76) tended to be higher than those of the 192/192 group (mean = 23.17 ($P = 0.087$)). In order to be significant after application of the Benjamini-Hochberg correction P

Table 1. Number of Subjects (and Percentages) with Specific Genotypes

Genotype	Number of Subjects (%)	Men	Women
176/192	1 (0.3)	1	0
176/194	1 (0.3)	0	1
176/196	1 (0.3)	0	1
188/192	9 (2.6)	7	2
188/194	4 (1.2)	1	3
188/196	3 (0.9)	2	1
190/190	1 (0.3)	1	0
190/192	19 (5.5)	7	12
190/194	5 (1.4)	4	1
190/196	3 (0.9)	1	2
190/198	2 (0.6)	1	1
192/192	137 (39.8)	62	75
192/194	101 (29.3)	50	51
192/196	30 (8.7)	12	18
192/198	6 (1.7)	2	4
194/194	8 (2.3)	3	5
194/196	12 (3.5)	8	4
194/198	1 (0.3)	0	1
total	344 (100)	162	182

should be less than the adjusted alpha = 0.005, meaning that this finding is likely the result of chance.

With respect to females, although the pattern of IGF-I levels was similar to that of 2000 pairwise comparisons indicated no difference in IGF-I levels in 2006 between genotype groups (Fig. 1).

IGF-I Level Differences between Age 36 and 42 Years

For the whole group of subjects, irrespective of Sex and Group, a significant decline in IGF-I levels was seen between the mean age of 36 and 42 years ($P < 0.0001$). In addition, there was no significant interaction between Sex and Year, indicating that the decline was similar in males as in females.

With respect to males, pairwise comparisons indicated that after correction with Benjamini-Hochberg (adjusted alpha = 0.03) IGF-I levels were decreased in 2006 compared to 2000 in subjects with genotypes 192/192 (mean decline - 3.67 nmol/l, $P < 0.0001$), 192/194 (mean decline - 1.61 nmol/l, $P = 0.005$), 192/196 (mean decline - 4.18 nmol/l $P = 0.02$), and were neither decreased in genotype 190/192 nor in the remaining group.

With respect to females, after correction with Benjamini-Hochberg (adjusted alpha = 0.03) IGF-I levels were significantly decreased in 2006 compared to 2000 in subjects with

genotypes 192/192 (mean decline -1.85 nmol/l, $P = 0.002$), 190/192 (mean decline -4.64 nmol/l, $P = 0.008$) and in subjects from the remaining group (mean decline -3.58 nmol/l, $P < 0.0001$), but not in 192/194 and 192/196.

DISCUSSION

This explorative study describes the distribution of the IGF-I promoter polymorphisms and examines the relationship between IGF-I promoter genotype and IGF-I level. The repeat lengths found previously vary from a minimum of 10 repeats to a maximum of 23 repeats [6,12]. As a consequence it is theoretically possible to find 14 different alleles. In our study sample consisting of Caucasian subjects seven different alleles were present. Mainly the 192bp and 194bp alleles were present in our sample. The allele frequency of the 192bp allele was 63.9%, which corresponds to the allele frequency reported in other Caucasian populations, estimated to be between 59% [14] and 70% [20]. In line with former reports, the allele frequency we found for the 194bp allele was 20.2% [9,14,20]. Although the occurrence of the other genotypes has been determined in other studies, they are most often referred to as 'others'. In agreement with findings of studies reported previously, homozygosity for 192bp had highest prevalence 39.8% [9,14,23,32] and heterozygotes 192/194 were observed in 29.3% [14]. We, however, have described the occurrence and the relationships with IGF-I levels of the other genotypes more specifically. In the present study also a remaining group was included in the analyses. As this group consisted of such a heterogeneous variety of genotypes with low frequencies, we considered it useless to take the results into account and therefore leave these out of the discussion.

With respect to females, we found significantly higher IGF-I levels for the 190/192 group compared to the 192/192, the 192/194 and the 192/196 genotypes. In studies that divided subjects into 'carriers' and 'non-carriers' of the 192bp allele, subjects with the 190/192 genotype were in the same group as subjects with 192/192 and 192/196 genotypes [20,27,33]. As a consequence, the comparison between carriers and non-carriers lacks specificity. In the same way the comparison of 'homozygotes' vs. 'heterozygotes and non-carriers' in other studies is not specific. Thus, in contrast to former studies we were able to show that the IGF-I level of

the 190/192 genotypes in females was higher than that of other genotypes.

The mean IGF-I levels found in our study were in the normal range (in both men and in women, aged 36 – 40 years: 11.2 – 35.7 nmol/l (P_5 - P_{95}); in men and women aged 41-51 years: 9.7 – 28.8 nmol/l (P_5 - P_{95})). Our results suggest that heterozygotes 190/192 in females had higher IGF-I levels than others. Therefore, differences in bone mineral density, body composition, lipid profile and brain functioning are likely to differ between genotypes, and between men and women. Moreover, several studies have investigated the relationship between the IGF-I promoter polymorphism and risk of specific disorders, e.g. breast cancer, bone mineral density, colorectal cancer, hereditary non-polyposis colorectal cancer, prostate cancer, type 2 diabetes, cardiovascular disease and polycystic ovary syndrome [7,9,12]. Most of these studies focused on the 192bp allele. Considering the results of the present study, it is more revealing to focus in females on the 190/192 genotype while examining the effect of the IGF-I promoter polymorphism on various disorders.

It has been postulated that decreasing levels of IGF-I may be partly responsible for effects of aging, as these are similar to IGF-I deficiency [2,34-37]. With respect to the expected decrease in IGF-I levels from 2000 to 2006 we found a reduction in IGF-I levels from 2000 to 2006 with respect to all four genotypes when sex was not taken into account. However, IGF-I decline appeared to be sex-specific as no significant decrease was found in males with genotype 190/192 and in females with genotypes 192/194 and 192/196. Rietveld *et al.* [23] found an age-related decline in IGF-I levels in homozygotes 192/192 but not in heterozygotes and non-carriers of the 192bp allele. There was no distinction made between males and females. With respect to females our results are similar, noting that due to infrequent occurrence no non-carriers of the 192bp allele were evaluated in our study. Rietveld *et al.* suggested that the IGF-I levels in heterozygotes and non-carriers are less growth hormone-dependent and more influenced by other factors such as liver function, nutrition and insulin levels, and show therefore no decline along with the growth hormone levels. In our study growth hormone levels were not measured and further studies are needed to test this hypothesis.

Table 2. Mean BMI Values(kg/m²) \pm SD and Number (and Percentage) of Oral Contraceptive Users within different Genotype Groups

Genotype	2000			2006		
	Male	Female		Male	Female	
	BMI	BMI	OC	BMI	BMI	OC
192/192	24.2 \pm 2.8	23.5 \pm 3.7	33 (44)	24.6 \pm 2.8	24.2 \pm 4.2	25 (33)
190/192	25.4 \pm 3.5	24.2 \pm 5.4	5 (42)	25.9 \pm 3.4	26.1 \pm 8.0	2 (17)
192/194	25.5 \pm 2.5	23.0 \pm 3.0	13 (25)	26.0 \pm 3.0	23.5 \pm 3.1	7 (14)
192/196	25.2 \pm 2.3	23.2 \pm 2.9	7 (39)	25.2 \pm 3.2	23.8 \pm 3.4	2 (11)
other	24.3 \pm 2.7	23.6 \pm 2.9	6 (46)	24.4 \pm 2.7	24.7 \pm 3.1	5 (38)

Table 3. Mean IGF-I Levels (nmol/l) \pm SD in 2000 and in 2006 in Males and Females with different Genotypes

Genotype	2000		2006	
	Male (n)	Female (n)	Male (n)	Female (n)
192/192	26.84 \pm 5.31 (62)	24.29 \pm 5.96 (75)	23.17 \pm 4.96 (49) [†]	22.44 \pm 5.70 (66) [†]
190/192	24.74 \pm 5.42 (7)	29.24 \pm 7.57 (12)*	22.63 \pm 5.77 (7)	24.60 \pm 7.41 (10) [†]
192/194	27.37 \pm 6.0 (50)	24.61 \pm 5.50 (51)	25.76 \pm 5.61 (44) [†]	23.55 \pm 4.70 (41)
192/196	27.35 \pm 3.90 (12)	23.93 \pm 3.99 (18)	23.17 \pm 4.61 (8) [†]	23.38 \pm 4.05 (15)
other	25.89 \pm 6.0 (31)	28.42 \pm 6.92 (26)*	24.94 \pm 6.19 (25)	24.84 \pm 5.73 (22) [†]
All	26.77 \pm 5.55 (162)	25.26 \pm 6.14(182)	24.33 \pm 5.50 (133) [†]	23.31 \pm 5.44 (154) [†]

* $P \leq 0.01$ vs female genotypes 192/192, 192/194, 192/196 [†] $P < 0.03$ vs 2000

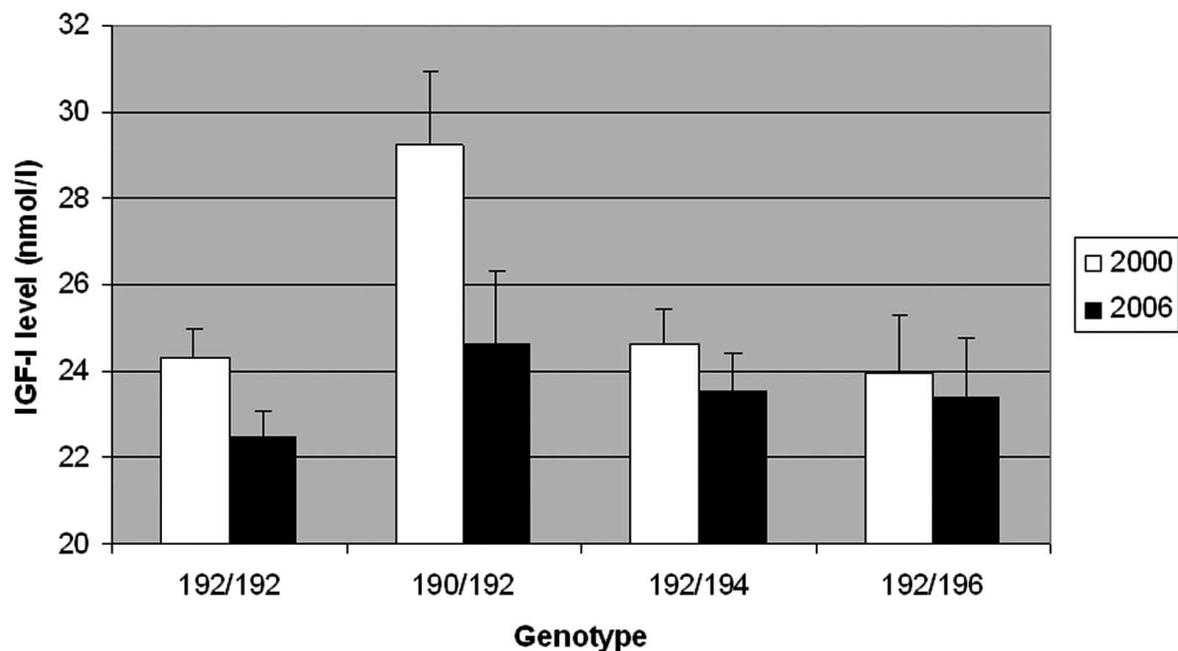


Fig. (1). Mean IGF-I levels (nmol/l) \pm SD in 2000 and in 2006 in females with different genotypes.

Our results suggest that IGF-I levels are influenced by IGF-I polymorphisms. Yet, the mechanism through which the IGF-I polymorphism influences the IGF-I level is still unclear. It may affect transcription or it may be in linkage disequilibrium with another functional variant. Although there are no regulatory elements close to the repeat region, it has been shown that CA elements are able to form unusual DNA conformations, such as Z-forms, that may modulate transcriptional activity [38]. Furthermore, since the replication fork pauses at the repeats with an increasing repeat length, the DNA becomes more unstable and is more prone to involve slippage events or doublestrand breaks [12,39].

It is important to note that the method used in the present study to determine genetic polymorphisms of the IGF-I-gene may have introduced errors in the classification of genotype. In a small case-control study comparing sizing analysis with direct DNA sequencing in analyzing CA repeats in the IGF-I gene a substantial discrepancy between the methods in de-

termining homozygous alleles was found. From this observed discrepancy the authors conclude that although DNA sizing analysis is the method of choice in analyzing short tandem repeat (STR) polymorphisms, laboratory analysis of dinucleotide STR may be unreliable in detecting small allelic differences [40]. Thus, our study results should be interpreted cautiously.

In addition, other polymorphisms in the IGF-I gene may contribute to IGF-I levels. Recently, data have been published on Single Nucleotide Polymorphisms (SNPs) within the IGF-I locus, or within evolutionarily conserved non-coding regions (ECRs) close to the IGF-I locus. Different SNPs, significantly associated with IGF-I levels have been found: rs35767 [41-43], rs6220 [41,44,45], rs1520220 [44-46] rs35765 [41], rs5742678, rs5742694 and rs2946834 [44], rs7965399 [43] and rs6214, rs5742612, rs5742614, rs5742-657, rs5742692, and rs3730204 [46]. Others found no significant associations between IGF-I tag SNPs and circulating

levels of IGF-I [47]. In this study we have not taken the possible influence of these polymorphisms on the IGF-I levels into account.

In conclusion, our population-based 6-year longitudinal study with Caucasian men and women studied at average ages of 36 and 42 years suggests that a genetic polymorphism in the promoter region of the IGF-I gene interacts with both sex and age in its IGF-I expression. In the general Caucasian population, the presence of the 190/192 genotype in females (as observed in 6.6% of women) seems associated with higher IGF-I levels. Furthermore, no age-related decline of the IGF-I levels was observed in males with genotype 190/192 and in females with genotypes 192/194 and 192/196. This may have consequences for tissues and metabolic factors on which IGF-I acts, e.g. for bone, lipids and brain. Further studies are needed to clarify the clinical implications of the observed genotype-related differences in (decline of) IGF-I levels.

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