Characterization of the GNAQ promoter and association of increased Gq expression with cardiac hypertrophy in humans

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Aims
Transgenic mice with cardiac overexpression of Gq develop cardiac hypertrophy, apoptosis, and heart failure. Similar mechanisms may contribute to human left ventricular hypertrophy (LVH). However, mechanisms regulating transcription of the human GNAQ gene encoding the Gq protein are unknown and single-nucleotide polymorphisms have not been reported.

Methods and results
We delineated essential elements for transcription in the human GNAQ promoter using reporter assays and showed promoter induction by serum and angiotensin II. Sequencing of the whole promoter revealed a common (minor allele frequency 0.48) dinucleotide polymorphism at position -694/695, resulting in an exchange of two adjacent nucleotides (TT → GC). The GC allele had increased transcription factor binding and was associated with enhanced transcriptional activation by serum or angiotensin II, resulting in enhanced Gq expression and intracellular signalling. Genotyping a population-based survey (n = 1204) revealed a higher prevalence of LVH in individuals with the GC/GC genotype [odds ratio (OR) 4.07; 95% CI 1.63–10.16; P = 0.003], this effect being more pronounced in women (OR 5.52; P = 0.005).

Conclusion
A novel polymorphism in the Gq promoter region is associated with enhanced promoter activity, Gq expression, intracellular signal transduction, and increased prevalence of LVH, particularly in women.

Keywords
G proteins • Polymorphism • Hypertrophy

Introduction
Cardiac hypertrophy is an adaptive response to pressure or volume stress, mutations of sarcomeric (or other) proteins, or loss of contractile mass due to infarction. Although initially compensatory for an increased workload, cardiac hypertrophy eventually facilitates heart failure, arrhythmias, and sudden cardiac death.1,2 Cardiac hypertrophy is characterized by reactivation of the foetal gene programme with increased protein synthesis and cell size.3,4 Various signalling events are important for the development and decompensation of hypertrophy, including those linked with activation of the heterotrimeric G-protein Gq, which transduces signals of angiotensin II, norepinephrine, and other neurohormones. Insight into Gq signalling as a determinant of hypertrophy and failure is derived from studies of cultured cardiomyocytes and manipulation of the mouse genome: activation of...
Gq-coupled angiotensin II or α1-adrenergic receptors, or overexpression of Gq, caused hypertrophy, whereas inhibition of Gq prevented norepinephrine-stimulated hypertrophy. Moreover, Gq overexpression induces apoptosis after cardiac stress and contributes to heart failure in vivo. Accordingly, combined cardiac-specific ablation or inhibition of Gq and the functionally similar G11 prevents hypertrophy in response to pressure overload, whereas a modest increase in Gq results in spontaneous hypertrophy with depressed contractility. Recent studies suggest pro-survival features and dose-dependency of Gq signalling in cardiac hypertrophy.

The GNAQ gene, which encodes the Gq protein, is located on chromosome 9q21. Data on transcriptional regulation GNAQ are lacking, possibly due to the extreme GC content (80%) of the 5′ untranslated sequence which hampers amplification. Here, we characterize the 5′ untranslated region of GNAQ and define functional consequences of altered promoter activity.

**Methods**

**DNA genotyping**

DNA was extracted from blood by standard techniques. For determination of GNAQ TT (−695/−694)GC genotypes, PCR was performed with the primers Gq_Se4 and Gq_AS4 (all primer sequences and positions are available on Supplementary material online, Table S1) using a lowdown PCR technique including 5% DMSO. PCR products were restricted with 4U NoI (NEB, Beverly, USA), separated on 2.5% agarose gels, and visualized under UV illumination. The G(−168)A and G(−173)A polymorphisms were determined by Pyrosequencing using primers Gq_Se5 and biotinylated Gq_AS3.

**Rapid amplification of 5′-cDNA ends**

Human heart Marathon-Ready cDNA (BD Biosciences, Heidelberg, Germany) was amplified by PCR using the adaptor primer AP1 and cDNA-specific primer Gq_Se7. The PCR product was diluted 1:50 and then subjected to nested PCR with primers AP2 and Gq_Se3 using the same protocol. PCR products were subcloned into pGEM T-easy vector (Promega, Mannheim, Germany) and nine independent clones were sequenced (GATC, Konstanz, Germany).

**Reporter constructs**

GNAQ promoter fragments were PCR-amplified from human genomic DNA using primer pairs Gq_Se3/Gq_AS4 (888 nt). PCR products were cloned into pGEM T-easy vector (Promega, Mannheim, Germany), sequenced, and subcloned into pSEAP Basic (BD Biosciences) using the unique EcoRI site. 5′ deletion mutants were generated by restriction digests of the larger fragments.

**Transient transfections and secreted alkaline phosphatase assay**

Human embryonic kidney (HEK293) and rat aortic smooth muscle cells (A-10) were routinely maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% (HEK293) or 20% (A-10) foetal bovine serum and 100 U/mL penicillin and 100 μg/mL streptomycin in a 5% CO2 atmosphere at 37 °C. HEK293 cells were transfected using lipofectamine 2000 (Invitrogen, Karlsruhe, Germany) with 4 μg of the GNAQ-alkaline phosphatase reporter constructs. A-10 cells were transfected by FuGene 6 transfection reagent 3:1 (Roche, Mannheim, Germany) with 1 μg of the GNAQ-alkaline phosphatase reporter constructs. Reporter gene activity was determined with the secreted alkaline phosphatase (SEAP) reporter system 2 (BD Biosciences; see Supplementary material online).

**Ca2+ measurement**

Twelve primary cultures of human skin fibroblasts obtained as described were used for these experiments. Fibroblasts from passages 5–15 were grown to confluence, passaged at a ratio of 1:0.8 2 days before the experiment, and growth-arrested for 24 h. Washed cells were then incubated with 3 μM fura 2-AM for 1 h at 37 °C and washed again. With 100 nM bradykinin, 2.5–5.0 × 10^6 cells were stimulated, and [Ca2+]i was measured in a spectrofluorometer (Perkin Elmer Corp., Norwalk, USA) as described.

**Human cardiac tissue samples**

Right atrial appendages were obtained during installation of the cardopulmonary bypass from 95 patients undergoing coronary artery bypass grafting. Immediately after excision, specimens were transferred into carbogentrated Tyrode-solution, quickly frozen in liquid nitrogen, and stored at −80 °C. Full informed consent was obtained from all patients.

**Gq expression analysis**

Gq mRNA in HEK cells and human atrial specimens was measured by real-time PCR as described (see Supplementary material online).

**Electrophoretic mobility shift assay**

The DIG Gel Shift System (Roche Applied Sciences, Mannheim, Germany) was utilized with digoxigenin (DIG)-labelled double-stranded oligonucleotides which were derived either from PCR with primers Gq_EMSA_S/Gq_EMSA_AS resulting in an 86 nt product or from synthesized oligonucleotides (34 nt). Oligonucleotides were DIG-labelled and probes were incubated with 10 μg nuclear extracts for 15 min at room temperature followed by Sp1-antibody incubation for supershift assays and non-denaturating 4–6% polyacrylamide gelelectrophoresis. DNA–protein complexes were electrophoblotted to positively charged nylon membranes (Roche Applied Sciences) and band shifts were visualized according to the user’s manual.

**Subjects**

To obtain DNA from healthy subjects (as ascertained by questionnaire), the European Caucasian population cohort (n = 187, aged 18–60) was recruited at the Department for Transfusion Medicine, University Hospital Essen. The subjects of this study participated in the echocardiographic substudy (total n = 1674) of the third MONICA (MONItoring of trends and determinants in CArdiovascular disease) Augsburg survey, which is now continued in the framework of KORA (Cooperative Health Research in the Augsburg Area). The third survey represents a gender and age-stratified random sample of all German residents of the Augsburg area and consists of individuals 25–74 years of age, with about 300 subjects for each 10 year increment. All individuals are white Caucasians. Details have been described previously.

Written informed consent was obtained from all subjects, and a local Ethics Committee approved the study protocol. Hypertension was defined as a blood pressure ≥ 140/90 mmHg or the intake of antihypertensive medication. Two-dimensional guided M-mode echocardiograms, recorded on a strip-chart paper at 50 mm/s, were...
obtained by two expert investigators using the Sonos 1500 (Hewlett Packard Inc.) with a 2.5 or a 3.5 MHz transducer. To reduce interobserver variability, all M-mode tracings were analysed by a single cardiologist who was blinded for clinical and biochemical data. Measurements for M-mode-guided calculation of the left ventricular mass (LVM) were taken just below the tip of the mitral valve. Only high-quality tracings with optimal visualizations of endocardial and epicardial surfaces throughout the cardiac cycle were used, resulting in exclusion of 16% of potential subjects. Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters and septal wall (SWT) and posterior wall (PWT) thicknesses were measured as recommended by the American Society of Echocardiography.20 LVM was calculated using the formula 0.8 x 1.04 [(LVEDD + SWT + PWT)³ – (LVEDD)³] + 0.6. LVM²1 was indexed to body surface area (LVMI = LVM/BSA) and to height (LVMI = LVM/height). Left ventricular hypertrophy (LVH) was defined as LVMI > 134 g/m² in men and LVMI > 110 g/m² in women.19,20 We constructed Bland–Altman plots from 144 duplicate readings. These subjects were participants from the study sample who volunteered for a blinded duplicate examination. The mean relative differences in LVM were 0.6% with a 2 SD range of 14.7%. For the present analysis, complete echocardiographic data and genotyping data were available in 1204 individuals.

Statistical analysis
To determine whether the genotypes of the GC(−695/−694)TT polymorphism deviated from Hardy–Weinberg equilibrium, actual and predicted genotype counts were compared by a χ² goodness-of-fit test with 1 degree of freedom. Data from reporter assays were analysed using Student’s paired t-test. Genotype-dependent mRNA expression analysis was done using two-way analysis of variance (ANOVA), with Bonferroni correction for multiple testing. The baseline characteristics in the MONICA/KORA survey were compared between genotype groups, using ANOVA for continuous traits and χ² test for categorical data. On the basis of the experimental evidence, we focused our primary analyses on the clinical relevant phenotype of LVH and tested the genotype for association with this phenotype by using a logistic regression model with LVH (presence vs. absence of LVH) as dependent variable, and genotype, age, BMI, SBP, antihypertensive medications, and gender as explanatory variables. These covariates were chosen because they are clinically relevant covariates for LV mass.1 Odds ratios (ORs) and 95% Wald confidence intervals are reported. This primary analysis was tested on a 5% significance level. In secondary analyses, we tested LVM and the different components of LV mass (wall thickness, LVEDD) as continuous traits for association with the genotype in order to elucidate what drives the association with LVM. LV mass measurements according to genotypes were compared using multiple linear regression adjusting for relevant covariates [age, BMI, SBP, antihypertensive medications, and gender (combined group)], assuming an additive genetic model. The distribution of LVM did not deviate from the assumption of normality according to the Kolmogoroff–Smirnov test (SAS Proc Univariate). The Hosmer–Lemeshow test showed no indication of poor model fit (SAS PROC Logist). As these were secondary analyses and as the different traits are not independent of each other (see equation for LV mass given in the previous section), the P-values of these analyses should be considered descriptive. Likewise, P-values of the tests comparing the baseline characteristics according to the genotypes should be considered descriptive. All statistical tests performed are two-sided. Exclusion of patients with myocardial infarction (1.8%) or additional consideration of daily-life physical activity (questionnaire) did not change the results.

Results
Characterization of the human GNAQ promoter
The nucleotide sequence of the genomic DNA upstream of the human Gq cDNA translation start site is shown in Figure 1A (GenBank accession number AL160278). The lack of consensus TATA or CCAAT elements is compatible with transcription from multiple start sites,22 and rapid amplification of 5′-cDNA ends of a human heart cDNA library showed that the 5′-end of cDNAs was −214 nt in four clones, −181 nt in four clones, and −173 nt in one clone. Thus, nt −214 and nt −181 appear to be the main GNAQ transcription start sites in the human heart (Figure 1A). The −214 nt start site also matches precisely the consensus for a transcriptional initiator element (YYA + 1NWWY22) and was, therefore, assigned as +1. No additional in-frame ATGs were present in the 5′ untranslated sequences (Figure 1A).

Subsequently, 5′ flanking sequences linked to a SEAP reporter gene were transiently expressed in HEK293 and A-10 cells. The −798 to +899 promoter construct directed a high level of SEAP expression which was significantly reduced in the restricted constructs (Figure 1B). Thus, essential regulatory elements of the GNAQ promoter are located within nt −798 and nt −511. Because of the high-GC content of the promoter (79.1%), we assessed the impact of inhibiting transcription factor binding to GC-rich elements by mithramycin A.24 In HEK293 cells, mithramycin A reduced Gq mRNA expression in a concentration-dependent manner (Figure 1C), whereas β-actin expression remained largely unchanged. Hence, transcription factors such as Sp-1, which bind to GC-rich elements, are essential regulators of Gq transcription.

To investigate whether the Gq promoter is inducible by exogenous stimulation, we transfected serum-starved HEK293 cells, which endogenously express AT1− but not α1-adrenoreceptors,25 with −798/+899-SEAP and stimulated them with serum and angiotensin II. Reporter activity was increased three-fold by serum and two-fold by 10 nM angiotensin II (P < 0.001; Figure 1D).

Identification of novel single-nucleotide polymorphisms in the GNAQ promoter
We sequenced PCR templates (nt −798 to +899 promoter region) from a multi-ethnic cohort of 50 unrelated healthy blood donors. Three novel polymorphisms were identified: G(−168)A, G(−173)A, and TT(−695/−694)GC, the latter always resulting in an exchange of two adjacent nucleotides. Allele frequencies were determined by genotyping 187 white Caucasians (Essen, Germany). Allele frequencies of the G(−173)A and G(−168)A polymorphisms were rare (allele frequency of <0.05) and not further analysed, whereas the allele frequency of the TT(−695/−694)GC polymorphism (hereafter termed TT > GC) was 0.48 in Caucasians. Importantly, this polymorphism is located within the region of high promoter activity (Figure 2A), and the TT > GC exchange generates a putative Sp-1 transcription factor-binding site.
The TT > GC polymorphism enhances transcription factor binding

The −798/+89 promoter-SEAP construct mutated to contain either the TT or GC allele was transiently transfected in parallel into HEK293 cells, and serum-starved cells were stimulated as described earlier. Serum- and angiotensin II-stimulated reporter activities were significantly higher in the GC compared with the TT constructs (*P = 0.048 and 0.003, respectively, Figure 2B), suggesting an impact of this polymorphism upon transcriptional activity. In electrophoretic mobility shift assay (EMSA) experiments using oligonucleotide probes spanning nt −731 to nt −645 of the GNAQ promoter (EMSA1, Figure 2A), one band was more pronounced in GC compared with TT alleles (Figure 2C, lanes 2 and 7). Competition with 100× molar excess of unlabelled probes abolished two bands (lanes 3 and 8), suggesting that these represent specific transcription factor-binding sites. Because GC boxes within these oligos suggest binding sites for Sp-1, we added an Sp-1 antibody (lanes 4 and 8) or molar excess of...
unlabelled Sp-1 consensus probe (lanes 9 and 10) which abolished these two bands, suggesting authentic Sp-1-binding sites. In contrast, addition of an AP2α antibody or molar excess of an AP2α probe (an AP2α-binding site is adjacent to the GC > TT polymorphism) had no effect (not shown). Indeed, when the non-radioactive DIG-EMSA system was used, the incomplete
supershift obtained using the Sp1 antibody has been observed previously.  

Subsequently, different short oligonucleotides (nt-716/nt-683) with GC and TT alleles were synthesized (Figure 2A), and gel shift experiments were repeated with recombinant human Sp-1 protein. As shown in Figure 2D, one shifted band was identified in the TT construct (lane 2), whereas two bands appeared in the GC construct (lane 7), indicating the loss of one Sp-1-binding site in the TT genotype. Again, addition of an Sp-1 antibody (lanes 3 and 8) or molar excess of unlabelled probes in ascending concentrations (lanes 4–5 and 9–10) suppressed these bands.

Collectively, these data suggest that Sp-1 binds specifically to a sequence that includes the TT GC polymorphism and that Sp-1 binding to the GC probe is more effective than to the TT probe because of an additional Sp-1-binding site.

Table 1  Baseline characteristics of the third Augsburg MONICA/KORA survey by GNAQ genotype

<table>
<thead>
<tr>
<th>Combined</th>
<th>GC/GC</th>
<th>GC/TT</th>
<th>TT/TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>50.4±13.6</td>
<td>49.8±13.5</td>
<td>49.0±13.9</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>133.3±19.3</td>
<td>133.5±20.4</td>
<td>133.9±20.2</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>79.6±11.3</td>
<td>80.9±11.6</td>
<td>81.6±12.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.7±3.9</td>
<td>26.7±4.1</td>
<td>26.4±3.9</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>232.9±42.7</td>
<td>234.6±42.9</td>
<td>230.6±42.6</td>
</tr>
<tr>
<td>Antihypertensive medication, %</td>
<td>16.7</td>
<td>19.5</td>
<td>18.7</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>40.2</td>
<td>45.9</td>
<td>40.0</td>
</tr>
</tbody>
</table>

Values are means ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index. Two-tailed P-values from ANOVA and x² test.
The GC allele increases Gq expression and results in enhanced activation of the Gq pathway

We measured Gq mRNA expression by quantitative real-time PCR using 95 human right atrial specimens. Gq mRNA expression was significantly different between genotypes, the highest expression being associated with GC/GC genotype compared with GC/TT or TT/TT genotypes \((P < 0.0001; \text{Figure 3A})\). Interestingly, using a two-way ANOVA analysis, we found a significant interaction between gender and genotypes \((P = 0.02)\), with a higher difference of Gq mRNA expression in females \((\text{fc: GC/GC vs. TT/TT}; 1.71; \text{n} = 22; P < 0.001)\) compared with males \((\text{fc: GC/GC vs. TT/TT}; 1.27; \text{n} = 73; P < 0.01; \text{Figure 3A})\).

We examined functional consequences of genotype-dependent Gq expression by investigating the intracellular Gq signal transduction pathway in primary human skin fibroblasts from healthy volunteers with different GNAQ genotypes. We determined peak rises of intracellular \(\text{Ca}^{2+}\) \((\left[\text{Ca}^{2+}\right]_{\text{i}}\)) in cells stimulated by bradykinin, which results in Gq activation. \(\text{Bradykinin-stimulated rises in } \left[\text{Ca}^{2+}\right]_{\text{i}} \text{ were strongest in cells from GC/GC carriers (GC/GC, 665 ± 49 nM; GC/TT, 665 ± 101 nM; TT/TT, 550 ± 117 nM; } P = 0.008; \text{Figure 3B})\).

**MONICA/KORA Augsburg survey**

**Echocardiographic substudy**

GNAQ genotypes were determined in 593 men and 611 women participating in the echocardiographic substudy of the third MONICA Augsburg survey. Baseline characteristics are given in Table 1. Because of the significant interaction of gender and genotype regarding Gq expression, we also analysed the data separately for men and women. The genotype distribution of the GNAQ polymorphism did not deviate from Hardy–Weinberg equilibrium, and GC allele frequency was 0.55, which was not significantly different from the allele frequency from our blood donor sample. There was no relevant difference in age, blood pressure, BMI, plasma lipid measures, and hypertension between GNAQ genotypes (Table 1).

Comparing the genotype frequencies of the GNAQ polymorphism in individuals with and without LVH, we found that the GC allele was more common in individuals with LVH than without LVH, this effect being most prominent in women. Logistic regression analysis including age, SBP, BMI, antihypertensive medication, and gender as covariates revealed that the ORs for LVH were 4.07 (95% CI 1.63–10.16; \(P = 0.003\)) for GC/GC vs. TT/TT in the combined group and 5.52 (95% CI 1.69–18.05; \(P = 0.005\)) in women (Table 2). In order to elucidate what drives the genotype association with LV hypertrophy, LVM measurements according to genotypes were compared using multiple linear regression adjusting for relevant covariates \(\text{age, BMI, systolic blood pressure, antihypertensive medication, and gender (combined group)}\). As shown in Table 3, LVM indexed \((\text{LVMi})\) to body surface area \((\text{g/m}^2)\) or height \((\text{g/m})\) was higher in GC than in TT/TT allele carriers, the effect being most prominent in women \((P = 0.017\) and \(P = 0.014\)\) and showing a gene-dose effect. However, neither wall thickness nor LVEDD alone was associated with the genotype on a 5% level.

**Table 2** Odds ratios (95% CI) for left ventricular hypertrophy associated with the GNAQ genotype

<table>
<thead>
<tr>
<th></th>
<th>Combined</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>TT/TT</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>GC/TT</td>
<td>2.90 (1.22–6.88)</td>
<td>0.016</td>
<td>3.98 (1.05–15.00)</td>
</tr>
<tr>
<td>GC/GC</td>
<td>4.07 (1.63–10.16)</td>
<td>0.003</td>
<td>2.22 (0.49–10.05)</td>
</tr>
<tr>
<td>GC allele</td>
<td>3.24 (1.41–7.46)</td>
<td>0.006</td>
<td>3.25 (0.91–11.66)</td>
</tr>
</tbody>
</table>

**Discussion**

We describe a gain-of-function dinucleotide polymorphism of the GNAQ gene promoter and identify it as a genetic risk factor for cardiac hypertrophy, notably in women. Substitution of TT for GC at positions \(-695/-694\) was associated with increased Gq expression and enhanced signal transduction via Gq-coupled receptors which could, however, be influenced by one or several other yet-identified functional single-nucleotide polymorphisms in GNAQ being in strong linkage disequilibrium with GC/\((-695/-694)\)TT. In the third MONICA/KORA Augsburg survey, the association of the GC allele with higher prevalence of cardiac hypertrophy supports the previously hypothesized critical role for Gq signalling in the normal and hypertrophied human heart. However, analysing LV mass as a continuous trait revealed a positive association between the common allele and higher LV mass only in women.

Gq pathways are essential for normal cardiac embryonic development, as combined genome-wide ablation of Gq and its functional analogue G11 results in early embryonic lethality with ventricular hypoplasia. The antibiotic experiment likewise provides the opposing result, as Gq overexpression in the early post-natal period (at a time of robust normal cardiac growth) causes cardiac hypertrophy. Similarities at the molecular, cellular, and functional levels between Gq-mediated signalling and pressure-overload cardiac hypertrophy further suggest that Gq signalling might transduce this pathological response. Inhibition of cardiac Gq signalling with a C-terminal peptide, or cardiac-specific ablation of Gq\(_{11}\), both resulted in normal hearts with attenuated hypertrophic responses to pressure overload. These results support the notion that Gq signalling is essential both for normal
Characterization of the GNAQ promoter

Left ventricular mass measurements in the third MONICA/KORA Augsburg study by the GNAQ genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Combined Men Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVMI, g/m²</td>
</tr>
<tr>
<td>GC/GC</td>
<td>89.1 ± 0.93</td>
</tr>
<tr>
<td>GC/TT</td>
<td>86.8 ± 0.94</td>
</tr>
<tr>
<td>TT/TT</td>
<td>86.8 ± 0.94</td>
</tr>
</tbody>
</table>

Data are least square means ± SE adjusted for age, SBP, BMI, antihypertensive medications, and gender (combined group).

Values from linear regression analyses assuming an additive model. LVMI indicated left ventricular mass indexed to body surface area (g/m²) or height (g/m).

LVMI failure. Blockade of these receptors or inhibition of angiotensin-converting enzyme markedly attenuate hypertrophy and failure and such regimens are now standard therapy for human heart failure. In contrast, recent data suggest that the cardiac α1-adrenergic receptor Gq pathway is necessary for the adaptation to pressure overload, providing additional support for potentially deleterious effects of α1-adrenergic receptor blockade. Furthermore, cardiac Gq overexpression has been shown to protect cardiomyocytes against apoptosis by activating the pro-survival Akt pathway. It was hypothesized that in early stages of cardiovascular disease, there might be equal Gq-dependent signalling down the respective hypertrophic and the anti-apoptotic pathways, resulting in compensatory hypertrophy. Interestingly, our current data show that Gq expression is inducible upon stimulation with angiotensin II, and this effect was strongest in GC alleles. It is therefore conceivable that in the chronic setting of increased workload, as circulating levels of angiotensin II increase and exposure is prolonged, Gq expression and activation of Gq-coupled receptors increase, resulting in pro-apoptotic pathways and finally in heart failure.

Clearly, the Gq polymorphism-associated phenotype is strongest in women. Gender-related differences with respect to LVH have been reported before, whereas the cellular mechanism for such interaction is unclear. Notably, the interaction of hypertrophy with female gender occurs already at the level of Gq mRNA expression. Finally, it has to be mentioned that polymorphisms in receptors, which couple to Gq, could interact with the GC(−695/−694) TT polymorphism. This could be of particular importance in the case of the angiotensin receptor gene which was shown to be associated with cardiac hypertrophy. Therefore, the interaction with GNAQ may result in additional effect concerning LVH. Future studies should discover possible links between these genes, which could help better identify patients at risk for LVH.

Supplementary material

Supplementary material is available at European Heart Journal online.

Conflict of interest: none declared.
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