Heritability of Cartilage Oligomeric Matrix Protein and General Joint Hypermobility: the CARRIAGE Family Study

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INTRODUCTION

Cartilage oligomeric matrix protein (COMP), a homopentameric extracellular matrix glycoprotein, is synthesized in cartilage as well as in tendon and ligament. Joint hypermobility due to ligamentous laxity is one of the clinical heritable traits in some osteochondrodystrophies, which are associated with profoundly low serum COMP due to COMP mutations. In our previous study, we found that general joint hypermobility was associated with decreased Osteoarthritis (OA) risk and lower serum COMP levels; however, the precise mechanism of this association remains unclear. The aim of this investigation was to estimate the heritability of serum levels of COMP and joint hypermobility in a large extended family.

METHODS

Study Population

The CARRIAGE (CARolinas Region Interaction of Aging Genes and Environment) family study is a prospective family-based longitudinal study of the interactions between aging, genetic susceptibility, and environment. The family is one of the most extensively pedigreed existing families in the United States comprising nine generations originating from one founder born in the 1700s. After excluding rheumatoid arthritis (n=2) and individuals younger than 25 years of age (n=5), a total of 271 participants were included in this study on the basis of physician-performed examinations for joint hypermobility and blood available for serum COMP analysis. Informed consent was obtained from all participants and the study was conducted with the approval of the Duke Institutional Review Board.

Beighton Criteria for Hypermobility

Hypermobility was determined according to the criteria established by Beighton et al. Patients were graded on a 0-9 point scale based on their ability to achieve the following: (a) passive dorsiflexion of the fifth finger ≥90°; (b) passive apposition of the thumb to the forearm; (c) hyperextension of the elbow ≥10°; (d) hyperextension of the knee ≥10°; and (e) ability to rest the palms flat on the floor with straight knees. Patients were considered as exhibiting hypermobility if they scored 4 or more out of 9 points.

Serum COMP Analysis

Serum was isolated, aliquoted and stored within 4 hours of blood collection at -80°C until biomarker analyses were performed. Duplicate serum COMP levels were performed and analyses were repeated as necessary for samples with a > 15% coefficient of variation (CV). COMP was measured by an in-house ELISA method as previously described, using monoclonal antibodies 17C10 (epitope in the EGF-like domain) and 16F12 (epitope in the NH2-terminal domain) against human COMP. The minimum detection limit is 120 ng/ml. Intra-assay and inter-assay CVs were < 5.8% and 8.7%, respectively.

Statistical analyses

Generalized Estimating Equations (GEE) were used to control for the dependency due to familial clustering of family members (SAS version 9.1, SAS Institute, Cary, NC). We classified individuals into eight clusters based on their relationship to eight members descended from the founder of the CARRIAGE family. The SOLAR (Sequential Oligogenic Linkage Analysis Routines) package was used to estimate maximum heritabilities of quantitative traits. The genetic model was assumed to be additive polygenic components. The analyses were logarithmically transformed to avoid excessive skewness and kurtosis. Heritability is presented as the residual heritability, that is, variance after accounting for covariates (age and gender), which could be attributed to the additive genetic effects. A p value of <0.05 was considered statistically significant.

RESULTS

Joint hypermobility (Beighton score ≥4) was present in 12.9% of the examined family participants and had a female predominance. Mean (SD) in serum COMP decreased significantly with increasing hypermobility by Beighton score: 7.48±0.42 for Beighton score 0; 7.37±0.42 for Beighton score 1-3; 7.29±0.43 for Beighton score≥4 (p=0.034 adjusted for age). When familial clusters were taken into account by the GEE analysis, the inverse association between hypermobility (using Beighton score as a continuous covariate) and serum COMP level remained highly significant (p=0.0035 age-adjusted). The estimates of the heritability for serum COMP and Beighton scores are depicted in Table 1.

Table 1. Heritability estimates for serum COMP and Beighton scores

<table>
<thead>
<tr>
<th></th>
<th>Phenotype</th>
<th>COMP</th>
<th>Beighton scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Residual Heritability (%)</td>
<td>43.2</td>
<td>35.1</td>
</tr>
<tr>
<td></td>
<td>(p-value)</td>
<td>(0.001)*</td>
<td>(&lt;0.05)*</td>
</tr>
<tr>
<td>Age (p-value)</td>
<td>0.6291357e-10*</td>
<td>0.3950335</td>
<td></td>
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<tr>
<td>Sex (p-value)</td>
<td>0.0091972*</td>
<td>0.0058804*</td>
<td></td>
</tr>
</tbody>
</table>

* p value <0.05

DISCUSSION

We found evidence of substantial heritability for serum COMP levels as well as joint hypermobility based on Beighton scores. Our finding agrees with the previous study showing an estimated 40% heritability for COMP in a UK female twin cohort. Our study also shows joint hypermobility is highly heritable in this extended family. The level of heritability of these two traits (between 35-44%) indicates that both joint hypermobility and serum COMP are reasonable phenotypes for further quantitative trait linkage analysis. Further studies to identify gene loci influencing these two associated traits are necessary.

REFERENCES