



Twin Studies on Urinary Pepsinogen A Phenotypes and Serum Pepsinogen A Levels

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Abstract. Urinary pepsinogen A (PGA or PG I) phenotypes and serum PGA levels were studied in MZ and DZ twins and their parents. In 45 out of 48 MZ twin pairs PGA patterns were completely identical, while 3 MZ twin pairs showed minor differences in the relative intensity of the Pg5 isozymogen. This suggests that the intensity of this isozymogen may be influenced by nongenetic factors. There was little difference in the interclass correlations of serum PGA levels between MZ and DZ twins, indicating a large contribution of common environmental factors to serum PGA levels. This is in contrast with previous studies.

Key words: Pepsinogen, Uropepsinogen, Twins, Genetics

INTRODUCTION

The peptic activity of gastric juice, also termed acid protease activity, is essential for the digestion of nutrition proteins, but it is also suspected of playing a role in the etiology of peptic ulcer disease. A major contribution to this activity is made by the pepsinogens, which are activated to pepsin in the stomach by acid produced by the parietal cells.

Pepsinogen can be separated in seven fractions on agar gel electrophoresis [6]. Fractions 1-5 (Pgl-5; PGA or PG I) are immunologically different from fractions 6 and 7 (Pg6-7; PGC or PG II). PGA is synthesized in the gastric corpus and fundus, and is present in serum and urine. PGC is synthesized in the mucosa of the whole stomach and proximal

duodenum and is present in serum and semen, but not in urine.

Pepsinogen A shows genetic heterogeneity which has been studied since the late sixties by several groups [1-8,12]. It is now known that the system is determined by a multigene family located on the long arm of chromosome 11, close to the centromere [1,8-10,15]. Our clinical studies showed a strong association between urinary and gastric mucosal PGA patterns with high intensity of Pg5 and premalignant or malignant conditions of the stomach [11,13]. It is not clear, however, whether this association is caused by genetic predisposition of individuals with certain PGA phenotypes to gastric disease, or by changes in the PGA phenotype, secondary to changes in the gastric mucosa. More specifically, we wanted to know whether the intensity of Pg5 is strictly genetically determined or influenced by environmental factors. Therefore we studied urinary PGA patterns of MZ twins and their parents.

Serum PGA levels are partly genetically determined [5,11]. We studied serum PGA levels in MZ and DZ twins to assess the contributions of genetic and environmental factors to these levels.

SUBJECTS AND METHODS

This study was part of a larger project in which cardiovascular risk factors are studied. Addresses of twins, 14-18 years of age, living in the Amsterdam, were obtained from the population registry of the City Council. A total of 20 MZ and 20 DZ twins and their parents were studied. In addition, urinary PGA phenotypes of 28 MZ twins from a pilot study were included.

Zygoty was determined by analysing the following genetic polymorphisms: ABO, MNS, P, Rhesus, Lutheran, Kell, Duffy, Kidd, GM, AM and KM at the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam.

PGA phenotyping was performed by electrophoresis of urine samples in a vertical discontinuous polyacrylamide gel, followed by staining for acid protease activity according to Taggart et al [8] with modifications according to Frants et al [1].

Serum PGA levels were determined by an enzyme linked immunosorbent assay (ELISA) according to Pals et al [3].

RESULTS AND DISCUSSION

Urinary PGA Phenotypes

The electrophoretic patterns of urinary PGA were studied in 48 MZ twin pairs. Identical patterns were found in all but three twin pairs. The differences within the three discordant pairs concerned the intensity of Pg5, the slowest isozymogen in the electrophoretic pattern. Table 1 shows the frequency of PGA phenotypes and the differences in the patterns found in the twin pairs.

We conclude from these data that the urinary pepsinogen pattern is strongly genetically determined. However, the relative intensity of Pg5 may be affected by nongenetic factors. We have not yet followed the twins with different patterns for a longer period of time, but some observations with individuals from our own laboratory and families that

Table 1 - Frequency of PGA phenotypes and differences in urinary PGA patterns in MZ twins

Concordant MZ twin pairs (N =45):

AA	AB	AC	BB	CD	BD	DD	BC	AB>BB	BC>AA	AB>BC	BD>AA	AB>AA	CD>AA	CD+5S
12	13	2	1	2	11	1	1	1	2	2	4	1	1	1

Discordant MZ twin pairs (N =3):

AB > BC and AB	AB > BD and AB
2	1

have been studied repeatedly, suggest that the slight intensity differences, as were observed between the three MZ twin pairs, may be due to an intraindividual variation of the patterns. We first of all tested some environmental factors which might influence Pg5, such as a large amount of vitamin C in the diet (low urinary pH) or stress before an important examination. Large amounts of vitamin C in the diet had no effect on the PGA pattern. There were some indications that stress might influence the PGA pattern, but the number of subjects studied was small. In a previous study a high frequency of intense Pg5 was found in a nonselected hospital population (7.4%) compared with healthy blood donors (2.4%) [4].

Serum PGA Levels

Fasting blood serum PGA levels were measured in 18 MZ and 19 DZ twins and their parents. Table 2 shows the sex and generation dependent means and standard deviations

Table 2 - Descriptive statistics of serum pepsinogen A levels ($\mu\text{g/l}$) in twins and their parents

	Fathers	Mothers	Sons	Daughters
N	38	36	30	44
Mean	70.4	48.3	48.4	39.3
Standard deviation	29.2	17.1	13.9	9.5
Skewness	0.06	0.27	0.48	- 0.12
Curtosis	0.54	0.74	0.88	0.46

of the data. There is no significant skewness or curtosis in these data within the groups. The absence of skewness is probably due to the homogeneous age of the groups. Removal of skewness by square root transformation [3,5] was not necessary.

Table 3 shows the intraclass correlation for the serum PGA values. Differences between MZ and DZ twins are negligible. Serum PGA levels are higher in fathers than in mothers of twins, which is in agreement with our previous findings that serum PGA levels are higher in males than in females and rise with increasing age [3]. A significant correlation was observed between fathers and children. From the twin data we conclude that

Table 3 - Intraclass correlation between serum pepsinogen A levels in MZ and DZ twins and their parents. Data were standardized with means zero and unit variance in each sex-by-generation group

Group	No. of pairs	Intraclass correlation	P
MZ twins	18	0.50	< 0.012
DZ twins	19	0.45	< 0.023
Father + mother	36	0.20	< 0.115
Father + first born	36	0.29	< 0.036
Father + second born	36	0.52	< 0.000
Mother + first born	36	0.00	< 0.400
Mother + second born	36	0.19	< 0.126

common environmental factors play an important role in determining the serum PGA level. This could also be the explanation for the correlation between parents and children. The weak genetic contribution to serum PGA levels is in contrast with previous studies [5,11]. Rotter et al [5] claimed that there is a strong genetic contribution to serum PGA levels in the general population and calculated a heritability of 0.91, with 0.74 contributed by a dominance component. In a study of 56 MZ and 62 DZ twin pairs, Varis et al [11] calculated a heritability of 0.32 (0.592 after logarithmic transformation). Rotter et al [5] based their conclusions on the study of nuclear families. Comparison with our data is difficult, because the correlations between parents and children were not published. However, Rotter et al [5] remark, that a large environmental effect common to sibs can obscure the possibility finding dominance. The correlation found by Varis et al [10] between MZ (0.368) and DZ (0.210) are lower than in our study. This may be due to the different age of twins: 14-18 years in our study and 28-54 years in their study. All twins in our study still live together. Consequently, common environment may play a more important role than in older twins, usually living apart. In addition, the higher age of the twins in the study of Varis et al [10] may also explain the difference in correlation between MZ and DZ twins. One of the factors influencing the heritability of serum PGA levels at higher age is atrophic gastritis [13]. Atrophic gastritis is partly genetically determined and causes low serum PGA levels. A larger concordance for the presence of atrophic gastritis in MZ compared with DZ twins may therefore result in a higher correlation of serum PGA levels between MZ twins, due to common low serum PGA levels, secondary to atrophic gastritis. This effect is most unlikely to be present in the twins of our study, with ages of 14-18 years.

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