

CONCISE REPORT

Carriers of the aspartylglucosaminuria genetic mutation and chronic arthritis

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Objective: To ascertain whether being a carrier of an autosomal recessive disease, aspartylglucosaminuria (AGU), predisposes to chronic arthritis, as does AGU disease.

Methods: A group of 173 unrelated patients with rheumatoid arthritis (RA) but with no family members with AGU each gave a blood sample for AGU Δ in major mutation DNA analysis. A group of 131 AGU carriers who were parents of patients with AGU completed a questionnaire on joint symptoms and gave a blood sample for rheumatoid factor (RF) analysis. Eight RF positive parents with prolonged joint symptoms had a rheumatological evaluation.

Results: Six patients (1/28) with RA were carriers of the AGU Δ in major mutation, whereas the carrier frequency among Finns in general is 1/50 to 1/85. Three AGU carriers had chronic arthritis (2.3%), and 17 (13%) were RF positive; the respective percentages among Finns in general are 1.4% and 5%.

Conclusion: As for AGU disease, carrier status may also predispose to chronic arthritis.

Aspartylglucosaminuria (AGU; McKusick 208400) is an autosomal recessive disorder of glycoprotein degradation resulting from decreased activity of aspartylglucosaminidase (EC 3.5.1.26). The disease is more common in Finns than in other populations, with 240 identified cases; however, cases have been reported in all populations. A single nucleotide change (AGU Δ in major) in the gene encoding aspartylglucosaminidase results in the amino acid substitution Cys163Ser which is the cause of this condition in almost all Finnish patients.¹ This mutation results in misfolding of the enzyme protein, loss of its enzymatic activity, and rapid degradation in the endoplasmic reticulum. Progressive mental retardation is the main symptom, and life span is usually less than 45 years.² Chronic arthritis is common (7% of female and 4% of male patients) in patients with AGU and is characterised by onset in childhood, seropositivity for rheumatoid factor (RF), and a deforming course.³ Population screening studies on the AGU Δ in major gene in Finland have shown a carrier frequency of 1 case in 50–85.^{4–7} Thus, in a population of 5 million Finns, over 70 000 are estimated to be carriers of AGU.

We screened for AGU Δ in major carriers among patients with chronic arthritis, and studied the occurrence of chronic arthritis in parents of patients with AGU, to ascertain whether AGU Δ in major carrier status also predisposes to chronic arthritis.

PATIENTS AND METHODS

We created two study groups. The first comprised 173 consecutive unrelated patients from the Rheumatism Foundation Hospital laboratory, who had RF positive rheumatoid

arthritis (RA) but no cases of AGU in the family.⁸ These 38 men (age range 31–78, mean 43 years) and 135 women (age range 25–78, mean 37.5 years) received a fact sheet and a consent form, which they signed when agreeing to give a blood sample for the AGU Δ in major mutation DNA test in connection with other laboratory tests.⁹ The patients were informed of the test result and its significance, and of the possibility of genetic counselling. We compared the carrier frequency of our group with the frequencies reported in Finnish population studies.^{4–7} We also combined the samples (a total of 4710 Finns, 74 of whom were AGU Δ in major mutation carriers) in these studies and calculated the prevalence of the AGU Δ in major mutation in the general Finnish population.

Our second study group comprised 131 AGU Δ in major carriers, 59 fathers (age range 25–77, mean 48 years) and 72 mothers (age range 24–70, mean 49 years) of patients with AGU. They participated in a family meeting in April 1999, and consented to give a blood sample for RF analysis (RF-Latex). They also filled in a questionnaire about joint symptoms. Three of these parents already had an inflammatory rheumatic disorder confirmed by a rheumatologist, and their hospital records were analysed. Eight RF positive parents with joint symptoms, who had been previously treated by a general practitioner, had a rheumatological examination (clinical, basic laboratory tests, and radiographs of hands, feet, and sacroiliac joints) at the Rheumatism Foundation Hospital.

The study design was approved by the ethics committee of the Rheumatism Foundation Hospital.

RESULTS

Six of the 173 patients with RA (3.5%; 95% confidence interval (CI) 1.5 to 7.6) were AGU Δ in major carriers (fig 1). Other studies show a prevalence of this mutation among Finns of 1.6% (95% CI 1.2 to 2.0).^{4–7} Thus, the relative risk for a patient with RA to be a carrier of AGU Δ in major was 2.2 (95% CI 0.9 to 5.0; $p=0.054$). The mean age of these six carriers at onset of joint symptoms was 31 years (range 22–50), whereas that of the 167 non-carriers was 39 years (range 16–77); the difference was not significant.

Three of the 131 parents of patients with AGU had chronic arthritis. One 72 year old mother had had RF positive RA for 50 years, and two HLA-B27 positive fathers (45 and 48 years old) had had ankylosing spondylitis for 25 and two years. Further, 17 subjects (13%) were positive for RF, eight of whom had had joint symptoms lasting for more than three months over the preceding three years. These eight had a rheumatological examination, but no additional cases of chronic arthritis were diagnosed.

Abbreviations: AGU, aspartylglucosaminuria; RA, rheumatoid arthritis; RF, rheumatoid factor; CI, confidence interval.

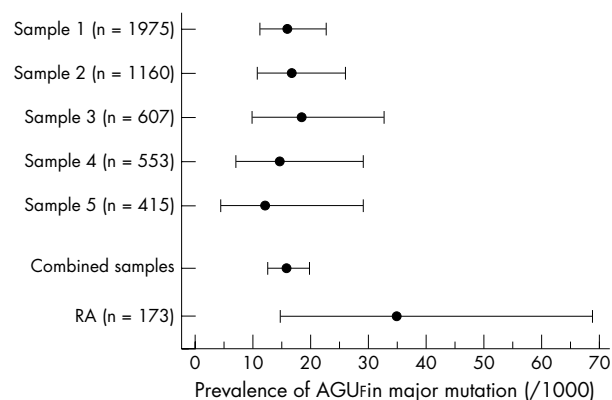


Figure 1 Prevalence, with 95% confidence intervals, of the AGUFin major mutation among Finns. Samples 1–5 (samples 4 and 5 are from the same study) are from earlier studies.^{4–7} RA, Patients with rheumatoid arthritis.

DISCUSSION

The prevailing conception is that carrier status for an autosomal recessive disease has no effect on the carrier's health. Although AGU carriers do not have metabolic problems related to AGU, a predisposition to other health problems as the result of being a carrier may exist.¹⁰

The estimated prevalence of chronic arthritis in Finland is 1.4%, and among patients with AGU it has been found to be 5.5%.^{3–11} The prevalence of RA and ankylosing spondylitis in Finland is 0.8% and 0.15% respectively^{12–13}; one mother with RA is not more than expected, but two of 59 fathers (3.4%) with ankylosing spondylitis is much more than expected. The prevalence of ankylosing spondylitis among patients with AGU has not yet been studied. Of the parents of patients with AGU, 13% were RF positive, whereas the corresponding frequency among Finns in general is 5%.¹⁴ The highest prevalence of RA in Finland at the present time is in people aged 65–74 years,¹¹ and therefore the mean age of our parent group, 48 years, was much lower. As studies of parents of patients with AGU would require over 20 years of follow up, and as the number of parents needs to be higher before it is possible to draw any reliable conclusion, we studied the frequency of the AGUFin major mutation in patients with RF positive RA. It was important to screen the mutation in patients with juvenile RF positive RA, because AGU arthritis is also characterised by early onset, but genetic testing of people under 18 years of age should be avoided for ethical reasons. The carrier frequency of AGUFin major in Finns in general is 1 in 50–85. That our group of patients with RA showed a ratio of 1 in 28 suggests that the AGUFin major gene may be at least weakly associated with chronic arthritis. This finding may prove important in future studies and in discussions of genetic aspects of rheumatic diseases.

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