HFE Gene Mutations Are Associated with Osteoarthritis in the Index or Middle Finger Metacarpophalangeal Joints

GRAEME J. CARROLL

ABSTRACT. ***Objective***. To test the hypothesis that possession of either C282Y or H63D mutations in the HFE gene is associated with primary osteoarthritis (OA) in joints commonly affected in hemochromatotic arthropathy.

Methods. HFE genotyping was performed in 87 patients with radiologically proven OA in 3 joint regions: index or middle finger metacarpophalangeal joints (MCP2,3; n = 52), elbow joints (n = 8), ankle, intertarsal or tarsometatarsal joints (ankle/IT/TMT; n = 27); and in 56 patients with radiologically proven OA in finger interphalangeal (IP) joints, but not MCP2,3 joints (IP OA control group). HFE mutation frequencies in these groups were also compared to those in a similar population (Busselton population control group).

Results. A statistically significant association between HFE mutations and OA was observed for the MCP2,3 joints (p = 0.0001) and the ankle/IT/TMT joint group (p = 0.002) as well as for the 3 joint regions collectively (p = 0.0001), but not for the elbow joints (p = 0.062). Comparison with the Busselton population controls showed similar statistically significant associations, except for the elbow and ankle/IT/TMT groups, where similar trends were observed.

Conclusion. HFE gene mutations are associated with OA in the MCP2,3 joints. These mutations may be markers for a polyarticular OA phenotype. (J Rheumatol 2006;33:741–3)

Key Indexing Terms:
OSTEOARTHRITIS HEMOCHROMATOSIS HFE GENE MUTATIONS IRON METABOLISM

Arthritis occurs in up to 81% of patients with hereditary hemochromatosis (HH)[1,2]. Whether the arthropathy associated with HH is due to the mutated HFE gene or other factor(s) is unknown. Published studies and personal observations suggest that the joints targeted in hemochromatotic arthropathy, for example the index and middle finger metacarpophalangeal (MCP2,3), elbow, ankle, intertarsal (IT), and tarsometatarsal (TMT) joints, differ from those commonly affected in nodal generalized osteoarthritis (OA), in which the distal interphalangeal (DIP), proximal interphalangeal (PIP), medial femorotibial, and great toe metatarsophalangeal joints tend to be preferentially involved. Further, the clinical and radiological similarities between hemochromatotic arthropathy and "non-traumatic primary" OA in the same joints are striking and suggest a common origin.

From the University Department of Medicine, University of Western Australia; Department of Rheumatology, Fremantle Hospital; and ArthroCare Pty. Ltd., Perth, Western Australia.

G.J. Carroll, MD, FRACP, Honorary Research Fellow, University Department of Medicine, University of Western Australia, Consultant Rheumatologist, Department of Rheumatology, Fremantle Hospital; Medical Director, ArthroCare Pty. Ltd.

Address reprint requests to Dr. G.J. Carroll, ArthroCare, PO Box 6, Mount Lawley, Western Australia 6929. E-mail: md@arthrocare.com.au

Accepted for publication November 25, 2005.

MATERIALS AND METHODS

To test the hypothesis that mutations in the HFE gene predispose to primary OA in joints preferentially affected in HH, consecutive patients presenting to a single rheumatologist with apparent primary OA in one or more of the following joint regions: MCP2,3 joints (region 1), elbow joints (region 2), or the ankles and IT or TMT joints (region 3), were assessed over a period of 28 months.

Patients were selected for study if they were symptomatic for OA (joint pain), had at least one sign of OA (bony swelling, reduced range of movement or crepitus), and had radiological evidence of OA [at least grade 2 by Kellgren and Lawrence (KL) criteria[3]] in at least one joint in any of the 3 joint regions. Radiological diagnosis of OA was provided by the reporting radiologist. Radiographs were all reviewed by the author. KL grading was performed prior to the acquisition of iron studies and HFE genotyping. As there are no KL criteria for regions 2 and 3, patients were considered to have satisfied radiological criteria for definite OA in these joints if they had both osteophytes and joint space narrowing. Patients with clinical or radiological evidence of coexistent arthropathies were excluded. Consecutive patients with DIP and/or PIP OA who had at least grade 2 radiological OA by KL criteria but no MCP2,3 OA clinically or radiologically and no clinically apparent OA in any of the other 2 regions under study were chosen as controls (IP OA control group). A previously studied cohort from Busselton, a town in South-West Western Australia, was used as a population control group.

Serum iron, transferrin, and ferritin concentrations were determined after selection in all participants. HFE genotyping was also performed after selection. Restriction fragment length polymorphism studies were performed after amplification of DNA by polymerase chain reaction. Homozygotes were excluded from the analysis. Data were tested for statistical significance by Fisher's exact test. As 3 joint regions were selected for study a priori, a p value of 0.0167 was determined to be the appropriate cutoff for statistical significance (Bonferroni correction).

RESULTS

Fifty-six patients met the clinical and radiological criteria for the IP OA control group. Fifty-two patients satisfied the clinical and KL radiological criteria for OA in the MCP2,3 joints. Thirty-five satisfied the clinical and surrogate radiological criteria for the elbows (n = 8) and ankles/IT/TMT joints (n = 27).

The results are shown in Table 1.

No patient in the study or control group was found to have clinical signs of HH or laboratory evidence of iron overload (transferrin saturation > 48%, upper limit of normal in the local reference laboratory). Chondrocalcinosis was present in 3 of the 52 patients with MCP2,3 OA, all of whom were heterozygous for C282Y. Chondrocalcinosis was not observed in any of the other joint regions.

A statistically significant association was observed between the presence of either C282Y or H63D and OA in the MCP2,3 joints (p = 0.0001) and the ankle/IT/TMT joint group (p = 0.002), but not in the elbow joints, where a similar trend was apparent (p = 0.062). Similar statistically significant results were apparent when the MCP2,3 joint group was compared to the Busselton population control group (p = 0.0002), but not when the ankle/IT/TMT joint group was compared with the Busselton population controls (p = 0.070), although again a similar trend was apparent.

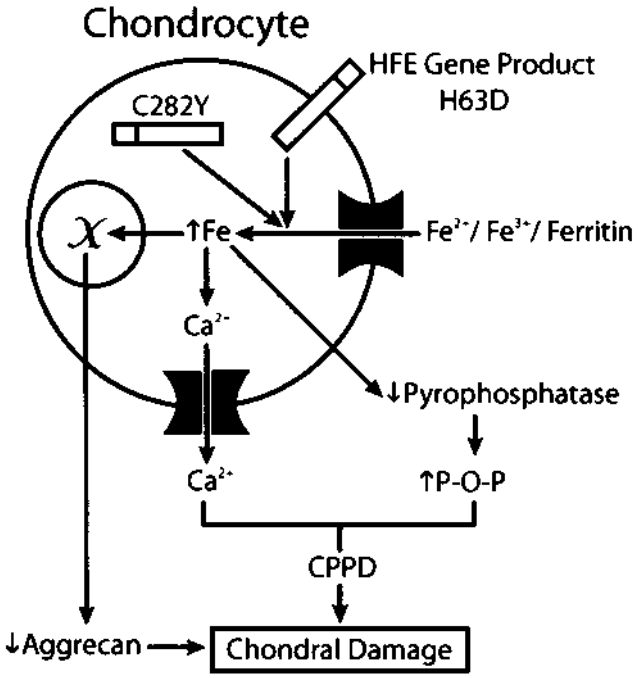

Figure 1. Model for chondral damage in C282Y and H63D heterozygotes.

DISCUSSION

These findings support the hypothesis that HFE gene mutations are associated with primary OA in joints putatively targeted in hemochromatosis. The strengths of this study include (1) the community based design, which is more likely to reflect OA in the population at large; (2) uniform clinical assessment due to the involvement of a single rheumatologist and the application of predetermined diagnostic criteria; and (3) the availability of HFE genotype data derived from a large sample in a geographically and ethnically comparable population.

Significant weaknesses include (1) the lack of ideal control groups; (2) the relatively small number of subjects recruited, which increases the probability of Type 1 and Type 2 statistical errors; and (3) the lack of independent assessment and grading of radiographs by an experienced skeletal radiologist.

In a study of radiological OA of the hand, some of which was incidental, Ross, *et al* found 12.5% of 176 patients were heterozygous for C282Y, compared to 7.8% in population

Table 1. Demographic data and HFE genotype of subjects, according to the 3 target joint regions under study, independently and collectively.

Region	n (female, %)	Median Age, yrs (range)	C282Y	H63D	Heterozygous for Either Mutation, %	Statistical Significance (IP OA control group)	Statistical Significance (Busselton control group)
Busselton population control group	3011 (50)	52 (20–79)	359	711	36		
Finger IP joints, but not MCP2, 3 joints (IP OA control group)	56 (81)	65 (48–88)	2*	8	18		p = 0.007
Index and/or middle finger MCP joints	52 (62)	70 (50–86)	10	22	62	p = 0.0001	p = 0.0002
Elbow joints	8 (25)	65 (51–83)	4	0	50	p = 0.062	p = 0.273
Ankle, IT or TMT joints	27 (65)	70 (35–87)	4	10	52	p = 0.002	p = 0.070
All 3 target joint groups	87 (62)	67 (35–87)	18	32	57	p = 0.0001	p = 0.0001

* p = 0.058 versus Busselton population control group. Joints: IP: interphalangeal; MCP: metacarpophalangeal; IT: intertarsal; TMT tarsometatarsal.

controls[4]. Bulaj, *et al* found a similar prevalence of radiologically confirmed MCP arthropathy (about 10%) in HH probands and in their clinically unselected homozygous relatives[5]. In contrast, Beutler, *et al*[6] and Waalen, *et al*[7], in well powered but predominantly questionnaire-based studies, were unable to show an association between HFE mutations and self-reported OA.

The pathogenesis of hemochromatotic arthropathy is poorly understood. It is possible that HFE mutations are simply passenger mutations and that the observed arthropathy in HH and OA in the regions studied is due to tight gene linkage. Alternatively, the HFE gene may be mechanistically important. In both disorders, chondral damage may be due to mutated HFE protein-mediated dysregulation of iron metabolism in chondrocytes, which may in turn result in failure to maintain the molecular integrity of the cartilage matrix (Figure 1). This model challenges our conceptual understanding of primary OA and provides impetus to study the relationship between chondrocyte iron and macromolecule metabolism. Further basic science and clinical and population studies are required to investigate the relationship between HFE mutations, chondrocyte iron metabolism, and diverse forms of OA.

ACKNOWLEDGMENT

The author is indebted to Dr. Valerie Burke (Department of Medicine, University of Western Australia) for statistical advice and to Associate Professor Virginia Kraus (Duke University, USA) and Dr. Peter Hollingsworth (PathCentre, Western Australia) for helpful discussions.

REFERENCES

1. Schumacher HR. Hemochromatosis and arthritis. Arthritis Rheum 1964;7:41-50.
2. Schumacher HR, Straka PC, Krikker MA, Dudley AT. The arthropathy of hemochromatosis. Recent studies. Ann NY Acad Sci 1988;526:224-33.
3. Kellgren JH. Atlas of standard radiographs. In: Jeffrey MR, Ball J, editors. The epidemiology of chronic rheumatism. Oxford: Blackwell Scientific Publications; 1963:1-9.
4. Ross JM, Kowalchuk RM, Shaulinsky J, Ross L, Ryan D, Phatak PD. Association of heterozygous hemochromatosis C282Y gene mutation with hand osteoarthritis. J Rheumatol 2003;30:121-5.
5. Bulaj ZJ, Ajioka RS, Phillips JD, et al. Disease-related conditions in relatives of patients with hemochromatosis. N Engl J Med 2000;343:1529-35.
6. Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T. Penetrance of 845G – A (C282Y) HFE hereditary haemochromatosis mutations in the USA. Lancet 2002;359:211-8.
7. Waalen J, Felitti V, Gelbart T, Ho NJ, Beutler E. Prevalence of hemochromatosis symptoms among individuals with mutations in the HFE gene. Mayo Clin Proc 2002;77:522-30.