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Confirmation of two major polyarticular osteoarthritis (POA) phenotypes – differentiation on the basis of joint topography

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Summary

Objectives: Previous studies of patients with primary hand and ankle osteoarthritis (OA) have suggested the presence of two major polyarticular OA (POA) phenotypes, designated Type 1 and Type 2. The former, characterised by sentinel distal interphalangeal (IP) (DIP) or proximal IP (PIP) joint OA resembles generalised OA (GOA), whereas the latter characterised by sentinel metacarpophalangeal (MCP)2,3 OA, resembles the arthropathy associated with hereditary haemochromatosis (HH). The aim of this study was to validate these putative phenotypes and to further investigate their clinical and genetic characteristics.

Methods: Newly referred patients had X-rays if pre-determined clinical criteria for OA in hand and other joints were met. Subjects were assigned to the putative Type 1 POA (T1POA) or Type 2 POA (T2POA) phenotypes if radiological criteria were satisfied. Human haemochromatosis (*HFE*) gene mutations were determined in buffy-coat DNA by polymerase chain reaction amplification, followed by restriction enzyme cleavage and analysis on a 3% agarose gel. The significance of differences was determined by Chi-square test or by Fisher's exact test.

Results: Sixty-seven patients fulfilled criteria for inclusion in this study; 39 (6M, 33F) for T1POA and 28 (18M, 10F) for T2POA. A statistically significant difference in gender was observed (64% male in the T2POA subset, $P < 0.0001$). Heberden's nodes (HNs) were found in 34 of the 39 Type 1 subjects, but in only nine of the 28 Type 2 subjects ($P < 0.0001$). *HFE* gene mutations were found in nine of the 39 Type 1 subjects (23%), whereas 21 of the 28 Type 2 subjects had a single *HFE* gene mutation (75%, $P < 0.0001$).

Conclusions: These findings confirm the hitherto hypothetical proposition of a T1POA phenotype conforming to nodal GOA (NGOA) and a T2POA phenotype closely resembling the arthropathy described in haemochromatosis (HH).

Key words: Polyarticular osteoathritis, Hemochromatosis, Phenotype, HFE gene, Metacarpophalangeal joint.

Abbreviations: POA Polyarticular osteoarthritis, HH Hereditary haemochromatosis, HNs Heberden's nodes, HFE Human haemochromatosis gene, C282Y Tyrosine substitution for cysteine at amino acid position 282 in the HFE protein, H63D Aspartic acid substitution for histidine at amino acid position 63 in the HFE protein, NGOA Nodal generalised osteoarthritis, T1POA phenotype Type 1 polyarticular osteoarthritis phenotype, T2POA phenotype Type 2 polyarticular osteoarthritis phenotype, DIP joint Distal interphalangeal joint, PIP joint Proximal interphalangeal joint, MCP2,3 Index and middle finger metacarpophalangeal joints, STT joint Scaphoid–trapezium–trapezoid joint, RC joint Radio-carpal joint, TMT joint Tarso-metatarsal joint, MTP1 joint Great toe metatarsophalangeal joint, KL criteria Kellgren and Lawrence criteria.

Osteoarthritis (OA) is the commonest disease of the joints. It was estimated to affect 1.62 million Australians or 7.7% of the total population of Australia in 2007[1]. These rates are similar to those reported elsewhere. Multiple joint involvement or polyarticular OA (POA) is common. Kellgren and Moore reported a form of POA designated generalised OA (GOA) in 1952. Others including Lawrence, Spector and Campion, Cooper *et al.* and Hirsch *et al.* have observed clustering of frequently affected joints in support of the notion of POA subsets[2–6]. Heberden's nodes (HNs), which are often observed in subjects with POA, which has led to the proposition that these lesions may represent a clinical marker for at least one form of POA[7]. Moreover, the frequent finding of HNs in POA has given rise to the notion of nodal GOA (NGOA)[8].

In 2006 one of the authors (GC) postulated two major POA phenotypes, one of which is characterised by sentinel interphalangeal (IP) joint involvement conforming to the GOA subset and the other, a hitherto unrecognised yet common POA subset, characterised by sentinel OA in the index and/or middle finger metacarpophalangeal (MCP) (MCP2,3) joints, closely resembling the arthropathy attributed to hereditary haemochromatosis (HH)[9–11]. HH is a common disorder

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which usually arises due to mutations in the HFE or human haemochromatosis gene found on chromosome 6. The two most common and only clinically relevant mutations in the *HFE* gene are the C282Y and H63D mutations which are found in one in seven and one in three Caucasians, respectively (allele frequency one in 14 and one in six, respectively)[12]. In an earlier study, a high frequency of HFE gene mutations was noted in subjects with MCP2,3 POA (62% were heterozygous for either C282Y or H63D) in contrast to the IP joint OA group where the frequency of HFE gene mutations was appreciably lower (18% heterozygous for either C282Y or H63D), but similar to that in an ethnically and geographically comparable Western Australian population cohort[12] derived from the Southwest town of Busselton.

In clinical practice it was observed that in subjects with NGOA, knee joint OA, especially medial compartment knee OA was common. Likewise in the same group OA was often observed in the great toe MTP (MTP1) joint. Accordingly it was postulated that IP [multiple distal IP (DIP), multiple proximal IP (PIP) or combinations of both] joint POA accompanied by symmetrical OA in either both knee (medial compartment) or both MTP1 joints may provide a robust definition for the NGOA or Type 1 POA (T1POA) phenotype. Furthermore, in light of the finding that subjects with HH and arthropathy often exhibit OA in somewhat atypical joints such as the radio-carpal (RC), elbow, ankle and tarso-metatarsal (TMT) joints and since in these joints preliminary data suggested higher than background population frequencies of HFE gene mutations for most of these joint groups[12], it was hypothesised that involvement of one or more of these atypical joints in addition to two or more of the MCP2,3 joints may robustly define a second major POA phenotype designated Type 2 POA or T2POA. Moreover, it was predicted that if indeed the T1POA and T2POA subsets were phenotypically different, they would have other defining clinical characteristics and also potentially different genetic characteristics, including different frequencies of HFE gene mutations. The existence of these two hypothetical POA phenotypes was a pre-specified hypothesis and that they would differ not only in terms of joint topography, but also in respect to clinical and genetic characteristics (HFE genotype) was also predicted. The aim of this study was to test this hypothesis.

Methods

The design and ethical implications of this project were reviewed and approved by the Ethics and Human Rights Committee of the South Metropolitan Area Health Service in Perth, Western Australia. From 01/07/04 to 30/06/07, newly referred subjects ($n = 4749$) with musculoskeletal symptoms were screened for clinical evidence of POA by a single investigator (GC). All patients referred by rural and metropolitan community-based general practitioners for clinical assessment were considered eligible for the study. No patients were referred because haemochromatosis was suspected and no new cases of haemochromatosis were identified during the study. Subjects with co-existent arthropathies such as rheumatoid arthritis, ankylosing spondylitis, psoriatic and enteropathic arthropathies, auto-immune connective tissue diseases and crystal arthropathies were excluded. Clinical screening criteria were used to identify patients with POA (Table I). Where the screening criteria for potential assignment to T1POA or T2POA on the basis of the defined joint topography were met, patients were invited to consent to X-rays of the clinically abnormal joints and the collection of blood for iron studies and HFE genotyping. X-rays were assessed by an experienced radiologist with a special interest in musculoskeletal disorders and by a rheumatologist with a special interest in OA. X-rays were assessed blind (without knowledge of the clinical characteristics of the patients or the investigation results). The joints under study (finger DIPs, thumb IPs, finger PIPs, finger and thumb MCPs, *carpometacarpal1*(CMC1) joints and the scaphoid–trapezium–trapezoid or STT joints and knee joints) were graded on a 0–4 scale by the ordinal criteria of Kellgren and Lawrence (KL)[14]. For the RC, elbow, hip, ankle and TMT joints, where no valid KL criteria are available, patients were required to have either unequivocal osteophytes or unequivocal joint space narrowing. Where there was a difference of 1 grade, the opinion of the radiologist was accepted. Where there was a difference of 2 or more grades the difference was resolved by combined review of the radiographs and consensus agreement. To assess the overall severity of POA, in the hand, the KL grade for all of the joints specified was summed to produce a severity score. Subjects who met screening criteria for clinical evidence of OA in pre-specified joints other than those in the hands (see Table I) had X-rays of the involved joints and the respective contralateral joint(s). Subjects were assigned to one or other of the two POA subtypes if the following qualifying clinical and radiographic criteria were met. Patients were assigned to the T1POA phenotype if they had radiological evidence of OA in at least two DIP or PIP joints and in either both knees (medial compartment) or both great toe MTP joints. Subjects assigned to this phenotype were not permitted to have radiological evidence of OA in any of the finger MCP joints. Patients were assigned to the T2POA phenotype if they had radiological evidence of OA in at least two of the four MCP2,3 joints and in at least one of the RC, elbow, hip, ankle, or TMT joints. Other joint involvement such as in the PIP and/or DIP joints of the same or other rays in the hand was permitted. Examples of the two phenotypes are shown in Fig. 1. Serum iron, serum transferrin, calculated transferrin saturation and serum ferritin were measured. No patient met the pre-specified transferrin saturation exclusion criterion of greater than 48%. *HFE* gene mutations were determined in buffy-coat DNA by polymerase chain reaction (PCR) amplification using published primers (12), followed by restriction enzyme cleavage and analysis on a 3% agarose gel. Subjects were assessed for C282Y using the unique *Rsa*I digestion site. H63D was determined using the unique *Mbo*I digestion site. Subjects were divided into (1) wild types, (2) C282Y/wild-type heterozygotes, (3) compound C282Y/H63D heterozygotes, (4) C282Y homozygotes and (5) H63D homozygotes. Statistical evaluation was performed utilising unpaired two-tailed Student's *t* test for continuous data and for categorical data the significance of differences was determined by Chi-square test where the expected cell frequency was greater than 5, otherwise by Fisher's exact test. *P* values < 0.05 were considered to be statistically significant.

Table I
Clinical criteria used to determine whether radiological examination were indicated

Joint	Clinical criteria to qualify for X-ray
RC	Extension $<45°$ or flexion $< 45°$
Elbow	Extension deficit of $10°$ or more or flexion $< 120°$
Hip	Flexion $< 100°$ or int. rot. $<20°$
Knee	Extension deficit of $10°$ or more or flexion $< 120°$
Ankle	Plantarflexion $< 20°$
TMTs	Hard tissue swelling or palpable osteophytes, pain with passive inversion or eversion or tenderness with squeeze compression of the TMT joints
MTP1 joints	Hard tissue swelling or palpable osteophytes or passive extension $< 60°$

Results

Sixty-seven subjects met the pre-defined clinical and radiographic criteria for assignment to one or other subset. Thirty-nine were assigned to the T1POA subset (33 F, 6M) and 28 to the T2POA subset (10F, 18M), as can be seen in Table II. The ages of the subjects in these two respective subsets were 66.6 ± 8.6 yrs (mean $\pm$ SD) for T1POA and 70.6 ± 8.4 yrs for T2POA (Table II). Although there was a strong trend towards older subjects in the T2POA subset, the difference was not statistically significant ($P = 0.0633$). A striking difference in gender ratio was observed (85% F in T1POA compared to 36% F in T2POA, $P < 0.0001$, Table II). This accords with the predominance of females in NGOA as reported by Kellgren and Moore[2]. The predominance of males in the T2POA subset is similar to the male predominance observed in the arthropathy which accompanies HH. The frequency of HNs was appreciably higher in T1POA ($P < 0.0001$, Table II). Moreover the mean number of HNs per patient was significantly higher in the T1POA subset ($P < 0.0001$, Table II). Body mass indices were not determined

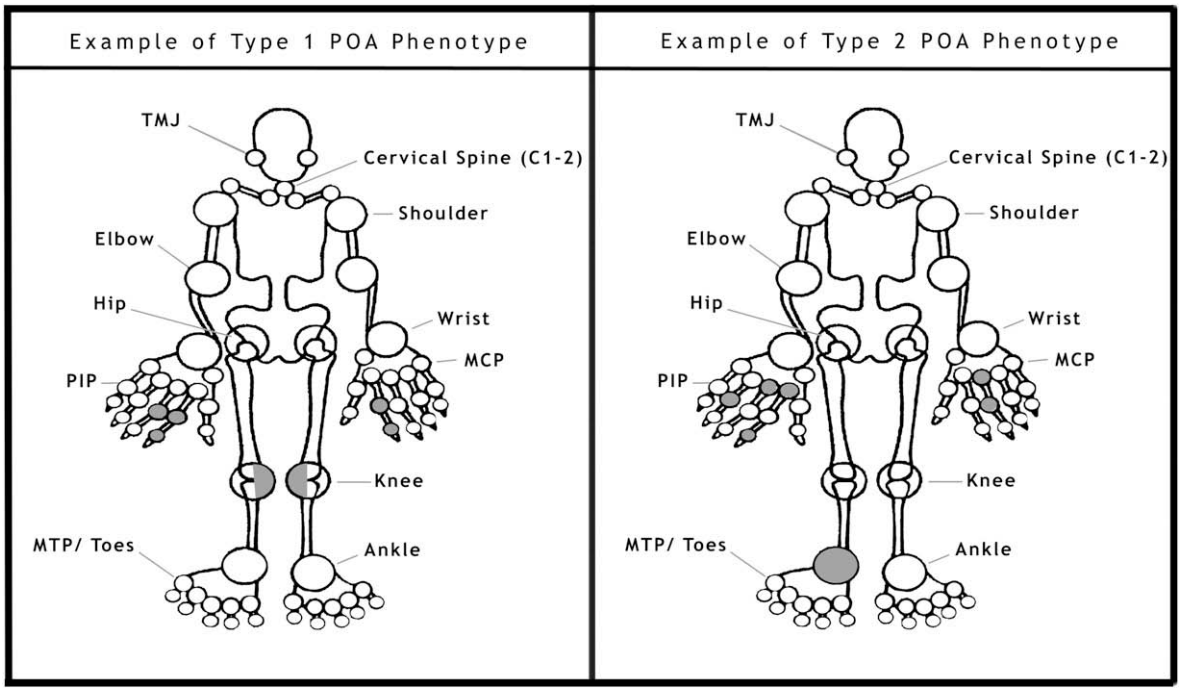

Fig. 1. Examples of the T1POA and T2POA phenotypes.

for the subjects assigned to the two POA subsets. No difference in serum iron or transferrin saturation was observed, but a trend towards higher serum ferritin concentrations was noted in T2POA (157 ± 125 for T2POA vs 119 ± 90 for T1POA, $P = 0.1065$, NS Table II). Two of the 39 (5.2%) in the T1POA group had an elevated serum ferritin compared to four of the 28 (14.3%) in the T2POA group (not significant, $P = 0.2269$, Fisher's exact test). A marked difference in the frequency of HFE gene mutations was noted (Table II). For the purpose of aggregate analysis, homozygotes for H63D were added to compound heterozygotes and non-compound heterozygotes for either C282Y or H63D. There was one H63D homozygote and two H63D/C282Y compound heterozygotes in the T1POA subset, whereas no H63D homozygotes or compound heterozygotes were observed in the T2POA subset. C282Y homozygotes were not observed in either subset. Nine of the 39 T1POA subjects had at least one HFE gene mutation (23%) compared to 21 of the 28 T2POA subjects (75%, $P < 0.0001$). The findings in the T1POA subset are similar to those observed in an ethnically and geographically age matched population cohort from the town of Busselton in Western Australia where 38% of the sample population ($n = 3011$) were either homozygous, heterozygous or compound heterozygous for C282Y or H63D[12]. The frequency of HFE gene mutations in the T1POA subset was also very similar to that observed for IP joint OA in our previous study (18%)[13]. The allele frequency for H63D was found to be one in 20 for the Type 1 phenotype and one in four for the Type 2 phenotype whereas the allele frequency for C282Y was found to be one in 40 for the Type 1 phenotype and one in eight for the Type 2 phenotype. The strong association of HFE gene mutations with T2POA is consistent with earlier observations in MCP2,3 OA alone (62% of subjects had HFE gene mutations however these patients were required to have only one or more of the four MCP2,3 joints affected)[13]. This finding nevertheless reinforces the previous results[13]. In this study, the strength of the association was numerically higher, but the two groups are not strictly comparable, since to qualify for T2POA in the current study, subjects were required to have OA in more than one of the four MCP2,3 joints and also in at least one other specified joint. This more rigorous definition for the T2POA subset may account for the difference. The frequency of other joint involvement in the two subsets was compared for some joints which were not pre-specified and where adequate data were fortuitously available (Table IV). A slightly higher frequency of CMC1 OA was observed in T1POA and a slightly higher frequency of STT OA in T2POA, but these differences were not statistically significant and as can be seen from Table III, the severity scores for these joints differed minimally.

The overall severity of the OA as determined by KL grading was compared for the two phenotypic subsets (Table III). A trend towards more severe OA was observed in the T2POA subset, due to the added contribution of the MCP joints, there being a similar degree of OA in the other component joint groups. The difference was not statistically significant. Ligamentous chondrocalcinosis was observed in two

Table II
Demographic and other data for the putative T1POA and T2POA OA phenotypes

	T1POA ($n = 39$)	T2POA ($n = 28$)	Statistical significance, *P*
Gender	6M/33F	18M/10F	<0.0001
Age (mean ± SD)	66.6 (8.6)	70.6 (8.4)	0.0633 (NS)
Frequency of HNs	34	12	0.0002
Number of HNs (mean ± SD)	4.92 (2.63)	1.86 (2.72)	<0.0001
Serum ferritin mean (± SD in mcg/L)	119 (90)	157 (125)	0.1605 (NS)
Number of subjects with elevated serum ferritin (%)	2 (5.2)	4 (14.3)	0.2269
HFE gene mutations	9	21	<0.0001

of the 28 T2POA subjects. None of the T2POA or T1POA subjects had chondrocalcinosis in the articular cartilage.

Discussion

This study was designed to validate earlier observations, test new hypotheses and predictions and to refine and inform an evolving model of POA, which conceptualises at least two major POA subsets or phenotypes, designated Type 1 POA or T1POA and Type 2 POA or T2POA. The strengths and weaknesses of this study require comment. The strengths of the study include (1) the prospective recruitment of OA subjects referred from the community by family medicine physicians or general practitioners, (2) the use of a single clinical observer who consistently utilised pre-specified methods of clinical assessment, (3) the verification of OA by radiological assessment and (4) the opportunity to capture data concerning OA in other joints not pre-specified and not readily amenable to clinical evaluation. Weaknesses include (1) data omissions due to design flaws and oversights, in particular the lack of data concerning occupation and the extent and duration of hard manual labouring activity, (2) the absence of X-ray data for joints which did not meet the strict clinical criteria for X-ray examination and importantly, (3) the relatively small number of patients, which in turn limits statistical power. Clearly, the single geographic location limits generalisability and in particular makes it difficult to exclude a locally inflated T2POA frequency, possibly due to a founder effect.

Nonetheless, the available data strongly support the likelihood that in Western Australian Caucasians, there are at least two numerically frequent POA subsets, one of which conforms closely to the putative generalised form of OA or NGOA (proposed T1POA) and the other to a haemochromatosis − like arthropathy (proposed T2POA).

The role of occupational and biomechanical factors in the development of OA in the MCP joints and in other joints included in the putative T2POA phenotype also needs to be considered. In a number of studies, OA in the MCP joints and especially MCP1−3 has been found to be more frequent in men involved in some form of hard manual labouring work, such as agriculture[15–17]. OA in the hip joint is also much more common in people involved in long-term farming work[18,19]. It is postulated that on a particular genetic background, which may include mutations in the *HFE* gene or alternatively other genes involved in the regulation of iron metabolism, occupational/biomechanical factors may contribute to the aetio-pathogenesis of the T2POA form of OA. It would be interesting to examine whether there are differences in the occupations of subjects with T1POA and T2POA. It may also be informative to investigate whether occupational factors contribute to the development and pattern of arthropathy in HH and if these effects are similar to or differ from those observed in the proposed T1POA and T2POA phenotypes.

Table III
Table depicting the summative KL grades for selected joint groups and the significance of observed differences between the putative T1POA and T2POA phenotypes

	T1POA	T2POA	Significance, *P*
DIPs	5.00 (6.15)	6.33 (6.85)	0.5100 (NS)
PIPs	9.45 (7.28)	7.47 (6.06)	0.3666 (NS)
PIPs + DIPs	14.45 (11.50)	13.80 (12.62)	0.8637 (NS)
MCPs	1.03 (1.54)	9.00 (6.57)	<0.0001
CMC1s	2.65 (2.35)	3.50 (2.98)	0.3045 (NS)
STTs	1.23 (2.25)	1.57 (1.28)	0.5952

Table IV
Frequency of joint involvement in the T1POA and T2POA OA phenotypes, frequency of chondrocalcinosis in ligaments and cartilage and radiological severity scores

	T1POA ($n=39$)	T2POA ($n=28$)	Statistical significance
CMC1	22	14	NS
STT	5	8	NS
RC	0	2*	Inappropriate
Elbow	0	4*	Inappropriate
Hip	6	7*	Inappropriate
Knee	10*	11	Inappropriate
TMTs	2	7*	Inappropriate
MTP1s	32*	15	Inappropriate
Chondrocalcinosis (ligamentous)	0	2	$P=0.1710$ (NS)
Chondrocalcinosis (articular cartilage)	0	0	NS
Radiological severity score for 32 hand joints, mean ± SD	22.7 (14.2)	31.4 (23.3)	$P=0.1022$ (NS)

*Denotes that this joint was a criterion for assignment to the T1POA or T2POA category, respectively, and in these cases statistical comparisons were deemed inappropriate due to selection bias.

The significance of the observed strong association between HFE gene mutations and the T2POA phenotype is unclear. Whether HFE mutations are just passenger gene mutations, possibly in linkage dysequilibrium with other single or multiple potentially more critical gene defects in T2POA will require further study. Alternatively, the possibility that the HFE gene mutations themselves may be aetiologically/mechanistically important warrants consideration and further investigation. A trend towards higher serum ferritin concentrations, albeit still within the accepted normal range, was observed in the T2POA subset, (Table II). This may simply be due to the gender ratio, as higher serum ferritin concentrations would be expected in the T2POA subset since they are gender dependent (higher in males) and there is a predominance of males in this group. Whether the higher frequency of HFE gene mutations in the T2POA subset is responsible for the trend towards higher serum ferritin concentrations is unclear, but this seems unlikely as significantly higher serum ferritin concentrations have not been observed in people heterozygous for HFE gene mutations in blood donor and other studies[20,21]. It is possible that in T2POA, HFE gene mutations may predispose to a mild, but possibly important degree of localised iron overload in the joints, which may in turn predispose to chondral or other structural joint damage. Some support for this possibility has been found in synovial fluid studies. Our preliminary data suggest that ferritin concentrations are increased in synovial fluid from OA subjects with HFE gene mutations[22]. Yet another possibility is that people with HFE gene mutations engaged in work or recreational activities that result in regular microtrauma and low grade bleeding into the joint cavity, may be at increased risk for joint damage. The observation that haemophiliacs who possess HFE gene mutations develop more severe arthropathy lends credence to this proposition[23].

Alizadeh *et al.* have reported an association between MCP arthropathy and homozygosity, but not heterozygosity for H63D in a large suburban Dutch population cohort[24]. None of our T2POA subjects was homozygous for H63D, but it is possible that this HFE genotype confers an increased risk for MCP2,3. OA and possibly also for the extended T2POA phenotype. It is of interest that in the

HEIRS study, male H63D homozygotes were reported to have an increased risk for arthritis overall[20]. Further population and other studies will be required to investigate whether homozygosity for C282Y or H63D in the absence of systemic iron overload are risk factors for OA in the MCP2,3 joints or for T2POA.

The similarity between the arthropathy observed in the T2POA subjects and that found in HH is striking[25–31]. Our observations in this and previous studies, taken together with other published data[31–33], raise the intriguing possibility that it may not be necessary to be homozygous, but rather simply heterozygous for HFE gene mutations in order to be at risk for the development of an arthropathy which is topographically, clinically and radiologically very similar to that observed in HH.

Conflicts of interest

The authors have no conflict of interest relevant to the contents of the manuscript.

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