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The Genetics of Generalized Osteoarthritis (GOGO) study: study design and evaluation of osteoarthritis phenotypes[1]

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Summary

Purpose: The primary goal of the Genetics of Generalized Osteoarthritis (GOGO) study is to identify chromosomal regions associated with increased susceptibility to generalized osteoarthritis (OA). Here we describe the study design and phenotype of the 2728 participants from the 1145 families recruited for this study.

Methods: GOGO is an investigator-initiated collaboration involving seven clinical academic sites and sponsored by GlaxoSmithKline. Family ascertainment was carried out between 1999 and 2002. A qualifying family required self-reported Caucasian ethnicity and at least two affected siblings with clinical hand OA. We hypothesized that this clinical phenotype would facilitate identification of participants with multijoint radiographic OA (rOA) in and beyond the hand. The "gold standard" case definition, however, was based on rOA (Kellgren–Lawrence grade $\geq$2) involving $\geq$3 hand joints distributed bilaterally and including at least one distal interphalangeal joint, with two of the three involved joints within a joint group (distal interphalangeal, proximal interphalangeal, or carpometacarpal). Radiographs of hips, knees and spine were also obtained. Additional siblings and living parents from qualifying families, both affected and unaffected, were invited to participate.

Results: A total of 2706 participants had complete clinical and radiological examination data. Of these, 2569 participants met clinical examination criteria for affected status; while 1963 (73%) participants met the prespecified radiographic criteria for affected status. This corresponded to a total of 707 families with at least two affected siblings that met the hand rOA criteria. Of those individuals with rOA of the hand, the frequency of rOA at other sites was highest for the knee (51%) and spine (54%), and less common for the hip (25%). Concordance rates among hand affected siblings were greatest for spine (36%) followed by knee (31%) and hip (9%); a total of 53% of the affected sib pairs were concordant for specific patterns of generalized rOA involving the hand and large joints (knees, hips or spine).

Conclusions: GOGO represents a large multicenter collection of families with multiple joint OA that have been characterized both clinically and radiographically. The GOGO study will employ a comprehensive strategy for genetic screening based upon both qualitative and quantitative radiographic trait analyses, circulating biomarkers in a quantitative trait-based analysis, fine mapping, and candidate gene analysis. This sample should provide sufficient power to detect linkage to OA associated genes.

Key words: Generalized osteoarthritis, Genetics, Hand, Hip, Knee, Spine.

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Introduction

Osteoarthritis (OA) is the most common joint disease in man, especially in aging populations, and is expected to be the fourth leading cause of disability by the year 2020[1–3]. Since 1941, a genetic component to OA has been recognized[4]. Available evidence suggests that genetic factors play a major role in OA, although the roles of specific genes involved remain to be clarified. The genetic associations that have been elucidated most clearly include two loci on chromosome 2q[5,6] and one on chromosome 9q[7]. One of these is explained by polymorphisms within the FRZB gene, which regulates skeletal development and bone mass and is associated with a four-fold increased unadjusted odds of hip OA in women[5]. A second report of OA associations is related to polymorphisms in the interleukin-1 gene cluster that either increase or reduce the odds of knee OA four- to five-fold in a United Kingdom (UK) population, dependent upon the specific gene polymorphism[6]. A third OA association, conferring a 1.7- to 2.6-fold increased odds of knee or hip OA in Japanese individuals, is related to polymorphisms in asporin[7], a small leucine-rich extracellular matrix protein[8] that regulates tumor growth factor β (TGFβ)-mediated expression of cartilage extracellular matrix genes. Potentially, many other OA susceptibility loci remain to be discovered.

Heritability estimates for OA at the major joint sites of hands, hips, knees and spine, range from 39 to 74%[9]. The heritability estimate for the sum of affected joints at each of these sites has been reported to be 78%[10], suggesting significant genetic susceptibility for multijoint or "generalized" OA. The purpose of the Genetics of Generalized Osteoarthritis (GOGO) study is to identify regions in the human genome related to generalized OA affecting the hands and other commonly affected joints (knees, hips and spine).

No standardized definition of OA exists for the purposes of genetic studies. This is reflected in the different ascertainment strategies of previous studies (reviewed by Jordan *et al.*[11]) that have included the following: hand OA by physical examination or radiograph; hip and knee OA by radiograph or history of joint replacement; and spine OA by radiograph or magnetic resonance imaging (MRI). Participants in the GOGO study were screened on the basis of clinical hand OA but the gold standard diagnostic criteria were the presence of radiographic OA (rOA).

We evaluated the utility of the clinical hand exam for detecting radiographic disease in a subset of the total cohort ascertained up until 2001, prior to the enrollment of all families. We found that bony enlargement by clinical hand exam identified radiographic hand OA [Kellgren–Lawrence (KL) grade $\geq$2] with high sensitivity (79%), reasonable specificity (52%), and a positive predictive value (PPV) of 71%[12]. Bony enlargement of single distal interphalangeal joints (DIPs) 2, 3 or 5, or the first interphalangeal (IP) joint yielded the highest PPV for radiographic disease. For the GOGO study, we therefore required bony enlargement of at least one DIP as part of the screening criteria. We further hypothesized that the GOGO hand OA phenotype would facilitate identification of participants with multijoint rOA in and beyond the hand. This report describes the GOGO study design and phenotypic characteristics of the participating individuals and families. We found that this screening strategy yielded a large cohort with rOA of the hand, and a majority with rOA beyond the hand.

Methods

ASCERTAINMENT STRATEGY

GOGO is a collaborative study involving seven academic sites, five in the United States (US) and two in the UK. GlaxoSmithKline provided medical genetics expertise, coordination, and funding. Phenotype discussions and family ascertainment were initiated at two sites in the US in 1999 (Duke University and the University of North Carolina at Chapel Hill). The results of this pilot project were reviewed, and the ascertainment strategy finalized, in 2000. Upon obtaining all the site-based Institutional Review Board approvals, recruitment began at all sites in 2000 and was completed in 2002. Written informed consent was obtained for each participant in GOGO. Participants were recruited primarily from Rheumatology clinics, hospital databases of OA patients, pre-existing OA cohorts, and from the community, by advertisements and word of mouth. A qualifying family consisted of at least two siblings with self-reported Caucasian ethnicity who fulfilled clinical GOGO hand OA criteria (bony enlargement of $\geq$3 joints distributed bilaterally, including bony enlargement of at least one DIP joint, and no more than three swollen metacarpophalangeal joints as defined below). In a family, the first individual that met clinical GOGO hand OA criteria was designated the proband and was invited to participate along with at least one clinically affected sibling. Once the sibling pair was positively identified as being clinically affected, the nuclear family was invited to participate, together with potential affected or unaffected siblings beyond the required two affecteds. Living parents of the affected sibling pair were also invited to participate. For the purposes of family based association studies, unaffected status was assigned to any participant who did not meet GOGO gold standard criteria for radiographic hand OA. Near study initiation, we evaluated the proportion of positive agreement (P_{pos}) and negative agreement (P_{neg})[13], and the PPV of the hand examination among examiners. Thirty patients underwent clinical hand examinations by each of the GOGO study personnel to assess bony enlargement, first carpometacarpal (CMC-1) squaring and clinical impression regarding the presence or absence of GOGO hand criteria. GOGO personnel were blinded to the radiographic hand OA status of the patients. Results were discussed and examinations were repeated in random order the following day. The P_{pos} among examiners was 75%, and P_{neg} was 58%. The PPV was described previously[12].

RADIOGRAPHIC PROCEDURES

Women of childbearing potential were required to undergo a pregnancy test prior to radiography.

Hands: A posteroanterior (PA) radiograph of each hand was performed with the beam centered on the third metacarpalphalangeal (MCP) joint.

Knees: A fixed-flexion PA knee radiograph was taken with the SynaFlex™ X-ray positioning frame (Synarc, San Francisco, CA)[14]. With this platform, the feet were externally rotated 10°, the knees and thighs touched the vertical platform anteriorly, and the X-ray beam was angulated 10° caudally. Skyline views of both patellae were taken with the participant in the seated position, knees bent, and the beam angled from the feet toward the knees.

Hips: An anteroposterior view of the pelvis was performed with the participant supine and feet internally rotated 10°.

Spine: A lateral view of the lumbar spine (L_1–L_5) was performed with the participant recumbent, with left side down. Lumbar spine radiographs were obtained at the US sites

only (due to differences in research ethics approval systems between the US and UK).

RADIOGRAPHIC GRADING

The phenotypic analyses reported herein were based on KL criteria[15] or grading of individual features using a photographic standard atlas[16] that included joint space narrowing, osteophytes, and other joint specific features such as cysts, sclerosis, erosions, and chondrocalcinosis. In addition to grading the DIPs, proximal interphalangeal (PIPs) and first CMCs, the MCP joints were also graded. KL grades, and osteophyte and joint space narrowing grades were assigned to the MCPs using the PIP and DIP pictures in standard atlases' templates[15,16]. Minimal interbone distances were measured manually using a 7× comparator (Cone Instruments) with a graduated reticule to the nearest 0.1 mm, for the hip and the medial and lateral compartments of the knee. Lumbar spine radiographs were scored for the presence and severity of vertebral osteophyte according to a standard atlas[16], and disc narrowing (on a 0–3 scale based on the radiologists expert opinion), and the presence or absence of end plate sclerosis, vacuum disc phenomenon, facet joint OA, compression fracture, platyspondyly and Scheuermann disease. Radiographs were screened for evidence of abnormalities due to rheumatoid arthritis (RA), gout, psoriasis, or hemochromatosis. Individuals with chondrocalcinosis or erosive OA were not excluded. A single experienced bone and joint radiologist (JBR) interpreted all radiographs (approximately 19,096), representing 106,392 joints. Inter-rater reliability (assessed with another trained radiologist) and intra-rater reliability were high for the radiologist's reading of KL grades of the knee and hip (weighted kappa 0.859 inter-rater and 0.886 intra-rater reliability) as described previously[17].

Although many definitions of OA can, and are being evaluated in this study, for the purposes of these descriptive analyses, the following criteria were used to define OA at the various joint sites: knee rOA was defined as KL grade $\geq$2 in at least one knee or a verified history of joint replacement for OA; patellofemoral joint (PFJ) OA was defined as any osteophyte $\geq$grade 2; hip rOA was defined as KL grade $\geq$2, or minimal joint space width $\leq$2.5 mm, or the combination of joint space narrowing grade $\geq$2 and any osteophyte of grade $\geq$1, or a verified history of joint replacement for OA; lumbar spine OA was defined as an osteophyte grade $\geq$1 (above or below the disc space) and disc narrowing $\geq$1 at the same vertebral level.

GOGO GOLD STANDARD CRITERIA

The GOGO criteria for determining affection status were:

(1a) hand rOA of a minimum of three joints involving DIPs, PIPs, or CMC-1 joints with two of the three joints involved within the same joint group (for the purpose of definition, the first IP joint was considered to belong to the PIP group);
(1b) hand rOA of at least one DIP of digits 2–5;
(1c) hand rOA bilaterally distributed; and
(1d) no more than three swollen MCP joints by clinical examination (as defined in the Dictionary of the Rheumatic Diseases[18]).

Participants were excluded on the basis of a clinical diagnosis of systemic lupus erythematosus, a history or radiographic evidence of RA, or psoriatic arthritis, or radiographic and serological evidence of hemochromatosis. Radiographs were screened for gout but this did not represent an exclusionary criterion unless a gout flare had occurred in the previous 3 years or hand radiographs demonstrated changes consistent with gout. Radiologic features that were used to rule in RA in the hands included bilateral, symmetric disease, primarily involving the MCPs more severely than the PIPs and DIPs. Radiocarpal and intercarpal involvement were also regarded as suggestive of RA. Other features included joint narrowing with little or no sclerosis, periarticular osteopenia, marginal articular erosions, characteristic malalignment at the wrist or MCP joints and a lack of osteophytosis. In the knees, features of RA included bilateral and symmetric involvement with diffuse narrowing of all compartments but with a relative lack of osteophytosis. Subchondral eburnation did not exclude RA in the knees. In the hips, features included global narrowing of the joint, again with little or no osteophytosis. Erosions of the femoral neck were sought. As in the knee, subchondral eburnation did not exclude RA. For gout in the hands, features included focal soft tissue swelling, juxtaarticular erosions, preservation of joint width and bone density and an asymmetric distribution. No specific distribution of disease was expected for gout, therefore IP, MCP and wrist joints were all inspected for gout. The evaluation for psoriatic arthritis included assessment of erosions (at the margins of joints or within joints), joint narrowing or widening (depending on the position of erosions), bilateral but not necessarily symmetric distribution of joint abnormalities, soft tissue swelling (either fusiform or focal), and ill-defined periosteal new bone production. Again as with gout, these features were evaluated for all joint sites of the hands including the wrists. The X-ray features that suggested hemochromatosis in the hand were exuberant osteophytes arising from the volar and radial surfaces of the second and third metacarpal heads and prominent joint space narrowing of these joints. Participants with this pattern on X-ray underwent measurement of fasting transferrin saturation (iron/total iron binding capacity ratio) and if >55%, the individual and family were excluded. No subjects met these serological criteria for exclusion.

COLLECTION OF FAMILY AND RISK FACTOR DATA

The family history interview yielded a four-generation pedigree documenting musculoskeletal history within 3° of relationship of the proband. Data were entered into an electronic database using Cyrillic software (Oxfordshire, UK). Data were also collected on general medical history, history of musculoskeletal injury, joint surgery and joint replacement, smoking history, physical activity, occupational history, estrogen use (women only), and OA symptoms using the Western Ontario and McMaster Universities (WOMAC) OA index[19] (collected at six of the seven sites). Anthropometric data collected included height, weight, and arm span. We also collected data on the age of onset at which joint symptoms began at each joint site. As reported previously[20], hypermobility was assessed using the Beighton score[21]. Trabecular and cortical bone density data were acquired. Trabecular bone mineral density (BMD) was measured at the calcaneus using a Norland Apollo™ DEXA at six of the investigative sites. To obtain estimates of cortical bone density, the endosteal and periosteal radii of the second metacarpal of the dominant hand were measured according to the method of Spencer[22]. Pinch and grip strength and the AUStralian CANadian Osteoarthritis Hand Index (AUSCAN)[23–25] were measured at two investigative sites[26], and hand thermography was performed at one investigative site[27].

SAMPLE PROCESSING AND STORAGE

On the day of participant assessment, 28 ml of whole blood (5 ml for sera and 23 ml for plasma and future DNA extraction), and 2 ml of unspun urine were collected. Samples were stored at −80°C until shipment to a central repository at GlaxoSmithKline. For all participants, blood spots were collected on filter cards (Schleicher & Schuell, Keene, NH) as an additional source of DNA and for later verification of genotyping or sample identity if needed[28].

SAMPLE SIZE AND POWER CONSIDERATIONS

A sample size of a minimum of 700 sib pairs, encompassing half the families, was chosen to provide adequate power to detect genes of moderate to large effect in the initial genome screen for linkage. Allowing for heterogeneity, it was estimated that there was 80% power to detect genes with a sibling recurrence risk ratio (RRR) of at least 1.5 in a homogeneous sample comprising 50% of the families, or a sibling RRR of at least 2.0 in a homogeneous sample composed of 20% of the families. These RRRs represent either genes of small effect or genes of moderate to large effect operating in a smaller subset of families. Thus the GOGO study was designed to provide adequate power to detect genes of small to moderate effect, especially in the total sample.

STATISTICAL ANALYSIS

Descriptive statistics per person and family were performed; we present no *P*-values due to the correlated nature of the data. BMI was separated into four categories ranging from normal to severely obese[29]. Categories of affected status were defined by the radiological criteria. Concordance was defined as two siblings with matching involvement for a particular pattern of OA. Discordance for hand OA was defined as lacking GOGO hand rOA criteria while having clinical OA by examination. Self-reported age of onset was evaluated for occurrence of OA at each joint site. Some participants had stated ages of OA onset that were below age 30 (between 1.3% and 2.4% depending on the specific joint with the exception of spine which was 10.7%). Any self-reported ages of onset within the first decade of life were deemed highly improbable to be OA in our samples derived from the US and UK. Therefore, it was assumed that all such values below 10 were intended to represent the number of years prior to the initial study visit rather than an age of onset. This subset represented between 0.25% and 0.64% of all participants; the effect of this imputation was to increase the age of onset $\leq$0.4 years.

Results

PATTERNS OF HAND OA

A total of 2728 participants from 1145 families were enrolled (65% through the five US sites and 35% through the two UK sites) (Table I). The median family size was two with a maximum of nine siblings ascertained in any one family. In addition, one or two parents (6%) of the 66 families participated. A total of 2706 participants had complete clinical and radiological examination criteria. Of these, 2569 participants (95% of cohort) were affected by clinical hand OA criteria and 1963 (73%) met the hand rOA criteria. Clinical and radiographic determinations of affected status were discordant in 750 participants (Table II). Rarely was a participant affected radiographically without meeting clinical criteria of affection status (3% of all participants). More commonly, discordant individuals met clinical hand OA criteria but did not meet the hand rOA criteria (25% of all participants). Overall the sensitivity of the clinical criteria was 96% (range among the seven sites 93−97%), specificity was 9% (4−34%) and positive predictive value was 74% (59−90%). Unaffecteds for the hand rOA criteria were younger (mean of 59 years vs 69 years), more likely to be male (27% vs 20%), but qualitatively similar with respect to BMI (mean 29 kg/m^2) (Table III).

A total of 707 families had at least two siblings that met the hand rOA criteria. The number of sibling pairs (based on Forthofer[30]: $[n(n-1)/2]$ sib pairs for n siblings) equaled 1936 with 1130 effective sibling pairs in which both siblings had rOA of the hand. The majority (80.4%) of the overall samples was females, overall mean age was 66 years, with 34.5% obese (BMI $\geq$ 30.0 kg/m^2), and 72.3% either overweight, obese, or severely obese (BMI $\geq$ 25.0 kg/m^2) (Table IV).

The most frequent hand rOA phenotypes in the affected participants are shown in Table V: these were DIP/PIP/CMC-1 (34.6%), followed by DIP/PIP/MCP/CMC-1 (28.9%) and DIP/PIP (28.6%). The various hand OA phenotypes involved, on average, 12 affected hand joints per

Table I
Sites participating in the GOGO study network and number of families identified

Principal investigators	Institution	Location	No. of families	No. of individuals	No of hand rOA affected individuals	No of hand rOA affected sib pairs
Virginia B Kraus	Duke University	Durham, NC	209	535	412	275
Joanne M Jordan	University of North Carolina	Chapel Hill, NC	201	527	390	242
Michael Doherty	University of Nottingham	Nottingham, UK	203	494	412	270
Anthony G Wilson	University of Sheffield	Sheffield, UK	209	462	291	153
Marc C Hochberg	University of Maryland	Baltimore, MD	124	291	191	83
Roland Moskowitz and Michele Hooper	Case Western Reserve University	Cleveland, OH	134	279	184	79
Richard Loeser	Rush Medical College	Chicago, IL	65	140	83	28
			1145	2728	1963	1130

Table II
Comparison of affected status by criteria used: radiographic vs clinical for all GOGO participants with complete radiographic information (N = 2706)

Affected by clinical GOGO criteria	Affected by GOGO radiographic hand criteria		
	Yes	No	Totals
Yes	1891 (70%)	678 (25%)	2569 (95%)
No	72 (3%)	65 (2%)	137 (5%)
Total	1963 (73%)	743 (27%)	2706* (100%)

Radiographic affected was defined as a minimum of three joints with KL ≥2 OA, distributed bilaterally, involving DIP, PIP, or first CMC joints with two of the three joints involved within the same joint group (first IP joint considered a PIP); and involvement of at least one DIP of digits 2–5. Clinically affected was defined as bony enlargement of a minimum of three joints, distributed bilaterally, involving DIP, PIP, or first CMC joints with two of the three joints involved within the same joint group (first IP joint considered a PIP group); and involvement of at least one DIP of digits 2–5; and fewer than three swollen MCP joints.

*Complete clinical and radiographic data were unavailable for 22 of the 2728 participants, therefore this table is based upon the $N = 2706$ for whom complete data were available.

individual and therefore, many more than the minimum three joint hand rOA involvement required by the GOGO criteria. The distribution of the number of affected joints for each pattern of hand rOA is shown in Fig. 1. The overall frequency of MCP rOA was 36.2%. First CMC disease almost always occurred in combination with DIP/PIP involvement and rarely with DIP disease alone (0.5%) or DIP/MCP disease (0.2%). The self-reported mean ages of onset of these various hand rOA phenotypes were not qualitatively different by joint groups involved (Table V).

Frequencies of large joint involvement

The majority of individuals who met hand rOA criteria also had large joint involvement. The frequencies of large joint rOA in individuals who met rOA hand criteria ($n = 1963$) were highest for the knee (51%, with 8% on the basis of tibiofemoral joint replacement), and intervertebral disc disease of the spine (54%), and lowest for the hip (25%, with 6% on the basis of hip joint replacement). A total of 61% of participants had knee or hip OA, while 16% had both hip and knee OA. Although one site in the UK recruited some GOGO participants from a preexisting knee OA cohort, the overall frequencies of the combined phenotypes were similar in the US and UK (Fig. 2). The availability of lumbar spine radiographs in the US participants revealed that half of the "hand only" affecteds, and a full two-thirds of the "hand/knee" affecteds, had more complex phenotypes that included spine OA. The self-reported mean ages of onset (SD) for hip and knee were qualitatively slightly greater than those of the hand while spine was similar to hand: left hip – 59.4 (10.6); right hip – 59.5 (10.5); left knee – 58.1 (11.2); right knee – 58.2 (11.2); and the lower back in the US subjects – 54.7 (12.2) years.

A total of 319 participants (16%) had radiographic PFJ rOA and all but 39 of these participants also had rOA of the tibiofemoral joint. Thus, PFJ rOA occurred in the setting of tibiofemoral rOA in an overwhelming majority (88%) and rarely in isolation. A majority (87%) of affected sib pairs were concordant for specific patterns of multijoint rOA: 60% were concordant for hand only, 31% for knee, 9% for hip, and 36% for knee or hip, and in the US, the figure for knee, hip or spine was 53%.

Table III
Demographics of the affected based on radiographic criteria for hand vs unaffecteds in the GOGO study population

	Affected ($N = 1963$)	Unaffected ($N = 743$)
Age – mean years (SD)	69 (9)	59 (9)
Range (years)	39–105	25–86
Gender – male	20%	27%
Body mass index (kg/m^2)		
Mean (SD)	29 (6)	29 (7)
% Overweight (25.0–29.9)	38	33
% Obese (≥30–34.9)	21	24
% Morbidly obese (≥35)	13	18
% Overweight or obese	72	75

Radiographic criteria for affected status are given in Table II.

Table IV
Demographics of the subset of participants that met the radiographic criteria for hand affected status in the GOGO study population

	Females ($N = 1578$, 80.4%)	Males ($N = 385$, 19.6%)	All hand rOA participants ($N = 1963$)
Age – mean years (SD)	69 (9)	69 (8)	69 (9)
Range (years)	44–95	39–105	39–105
Body mass index (kg/m^2)			
Mean (SD)	29 (6)	29 (5)	29 (6)
% Overweight (25.0–29.9)	35	48	38
% Obese (≥30–34.9)	21	24	21
% Morbidly obese (≥35)	14	9	13
% Overweight or obese	70	81	72

Radiographic criteria for affected status are given in Table II.

Discussion

The GOGO study is the largest family based linkage study of OA in the world. A major strength of the study is

Table V
Frequencies of affected individuals and age of onset by joint group presentation

Joint group	Affected (%) ($N = 1963$)	Median, no. of hand joints involved	Age of onset (years, SD)
DIP only	1 (0.1%)	3	48.0
DIP, MCP, CMC-1 only	4 (0.2%)	4	55.3 (7.1)
DIP, CMC-1 only	9 (0.5%)	3	55.6 (11.3)
DIP, PIP, MCP only	139 (7.1%)	11	56.3 (11.7)
DIP, PIP only	562 (28.6%)	7	54.1 (10.3)
DIP, PIP, MCP, CMC-1	568 (28.9%)	17	56.3 (11.8)
DIP, PIP, CMC-1 only	680 (34.6%)	10	54.8 (11.6)

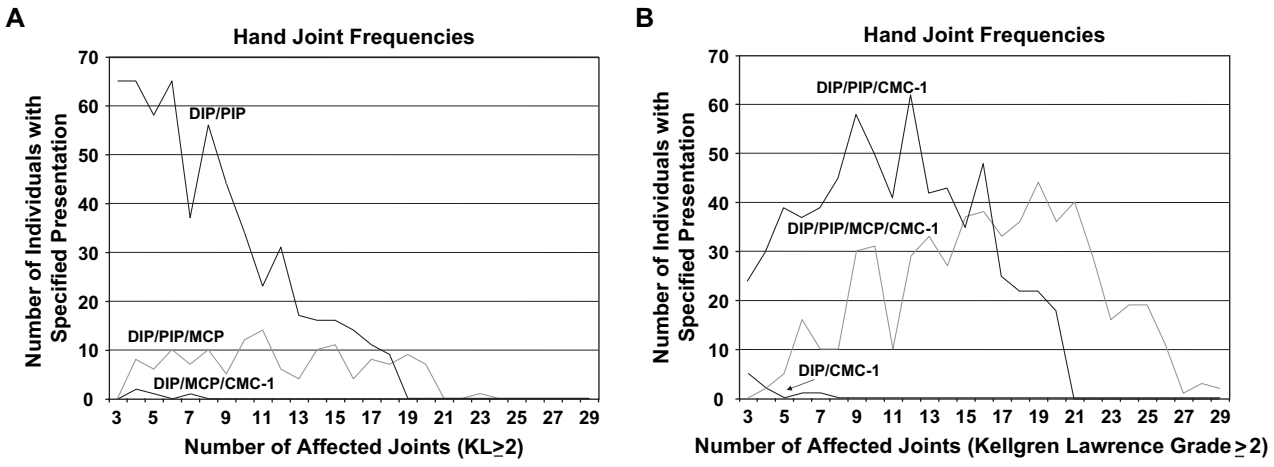

Fig. 1. The number of individuals with specified patterns of hand rOA. The patterns of hand rOA are shown for the 1963 participants meeting GOGO gold standard hand rOA criteria. (A) Number of joints involved for the patterns DIP/PIP, DIP/PIP/MCP, and DIP/MCP/CMC-1; (B) numbers of joints involved for the patterns DIP/PIP/CMC-1, DIP/PIP/MCP/CMC-1, and DIP/CMC-1. One participant had only DIP involvement with three total affected joints (not shown).

the availability of extensive radiographic phenotyping of subjects. In addition, the study has produced a repository of biospecimens for future proteomics and biomarker work to complement the genetic analysis. We used the presence of nodal OA characterized by bony enlargement of hand joints as the screening procedure to determine eligibility for entry into the study. Bony enlargement of the hand joints is strongly familial and has long been considered a marker of OA[4]. This clinical screening strategy yielded 62% of families with at least one affected sib pair with hand rOA.

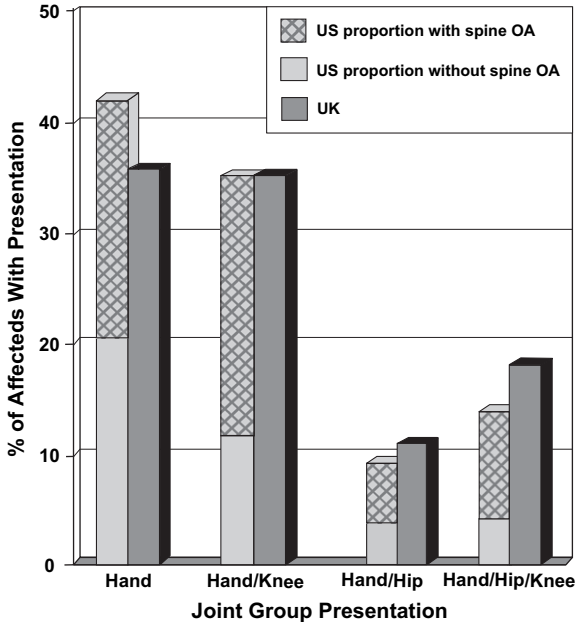

Fig. 2. Frequency of multiple joint involvement with OA. The frequencies of rOA at various sites, and sites in combination, are shown for the US in light gray, and for the UK in dark gray for the 1963 participants meeting GOGO gold standard hand rOA criteria. The groups represented are mutually exclusive. The frequencies of one joint site (hand only), two sites (hand/knee and hand/hip) or three sites (hand/knee/hip) are shown. The frequency of spine OA in combination with the aforementioned phenotypes is indicated by the stippled bars. Because the US sites were the only ones to perform lumbar spine radiography, these stippled bars, representing spine OA frequencies, are only found above the bars representing US frequencies.

We reviewed selected literature that presented population-based estimates of OA prevalence. A study from Zoetermeer in the Netherlands was especially informative because it provided prevalence rates for radiographically defined OA of the hand, knee, hip and spine[31]. For hand, using the DIP as the marker, 10% of males and 7% of females in the Dutch study had radiographically confirmed OA before age 45. In GOGO, 16% of the population had early onset hand rOA prior to age 45. In addition, first CMC disease almost always occurred in combination with DIP/PIP involvement as noted previously by Hirsch *et al.*[32]. With regard to the patterns of rOA in this cohort, MCP rOA was common (36%) despite a lack of evidence for hemochromatosis on the basis of serological screening. This prevalence is quite comparable to the reported prevalence of MCP OA in the Caucasian Framingham cohort that ranged from 29% (women) to 33% (men)[33].

Although few studies account for spine OA, it was very common in our cohort, occurring in more than half of all hand rOA affected individuals. A similar high frequency aggregation of hand and spine OA, up to 59%, has been reported for a Dutch cohort of 191 sibling pairs in which hand, spine, knee and hip radiographs were all obtained[34]. Overall, the GOGO screening strategy yielded a large number of individuals with rOA joint involvement in and beyond the hand.

A total of 25% of participants (678) met clinical hand OA criteria but did not have sufficient radiographic evidence to meet the hand rOA criteria. Due to the lack of standardized hand OA definitions, we relied on the expert opinion of the GOGO principal investigators to derive the relatively stringent hand rOA criteria. The wealth of phenotypic radiographic information provided on these participants will nevertheless be informative for quantitative trait analyses that account for total numbers of joints involved and the severity of joint involvement. Other genetic studies of OA have successfully utilized sum scores of affected joints for quantifying and defining OA[35]. Quantitative trait analysis is a powerful strategy capitalizing on all the phenotypic information provided by each

participant, and does not require *a priori* definitions of OA. This strategy will be utilized in the future as part of a comprehensive analysis of the GOGO data.

It is clear that OA is etiologically heterogeneous. The extensive radiographic phenotyping in the GOGO study yielded families with distinct patterns of OA involvement with high concordance rates. We do not expect the same gene (or combination of genes) to be operating in every family. Because multiple family members were ascertained when available, this screening strategy yielded a total of 1130 sibling pairs with rOA of the hand, providing great power to detect linkage to genes associated with various patterns of OA. This approach incorporates a detailed study of genetic factors and gene–environment interactions that may eventually assist in identifying targeted preventive strategies, promote a better understanding of basic disease mechanisms, and facilitate development of more effective treatments for OA.

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