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Clinical and Molecular Spectrum of Nonsyndromic Early-Onset Osteoarthritis

Valentin Ruault,¹ Kevin Yaury,² Aurélie Fabre,¹ Mélanie Fradin,³ Julien Van-Gils,⁴ Chloé Angelini,⁴ Geneviève Baujat,⁵ Patricia Blanchet,¹ Silvestre Cuinat,⁶ Bertrand Isidor,⁶ Christian Jorgensen,⁷ Didier Lacombe,⁴ Sébastien Moutton,⁸ Sylvie Odent,³ Elodie Sanchez,⁹ Sabine Sigaudy,¹⁰ Isabelle Toutou,⁹ Marjolaine Willems,¹ Florence Apparailly,⁹ David Geneviève,⁹ and Mouna Barat-Houari¹

Objective. Osteoarthritis (OA) is the most common joint disease worldwide. The etiology of OA is varied, ranging from multifactorial to environmental to monogenic. In a condition called early-onset OA, OA occurs at an earlier age than is typical in the general population. To our knowledge, there have been no large-scale genetic studies of individuals with early-onset OA. The present study was undertaken to investigate causes of monogenic OA in individuals with nonsyndromic early-onset OA.

Methods. The study probands were 45 patients with nonsyndromic early-onset OA who were referred to our skeletal disease center by skeletal dysplasia experts between 2013 and 2019. Criteria for early-onset OA included radiographic evidence, body mass index ≤ 30 kg/m², age at onset ≤ 50 years, and involvement of ≥ 1 joint site. Molecular analysis was performed with a next-generation sequencing panel.

Results. We identified a genetic variant in 13 probands (29%); the affected gene was *COL2A1* in 11, *ACAN* in 1, and *SLC26A2* in 1. After familial segregation analysis, 20 additional individuals were identified. The mean \pm SD age at onset of joint pain was 19.5 ± 3.9 years (95% confidence interval 3–47). Eighteen of 33 subjects (55%) with nonsyndromic early-onset OA and a genetic variant had had at least 1 joint replacement (mean \pm SD age at first joint replacement 41 ± 4.2 years; mean number of joint replacements 2.6 per individual), and 21 (45%) of the joint replacement surgeries were performed when the patient was <45 years old. Of the 20 patients age >40 years, 17 (85%) had had at least 1 joint replacement.

Conclusion. We confirmed that *COL2A1* is the main monogenic cause of nonsyndromic early-onset OA. However, on the basis of genetic heterogeneity of early-onset OA, we recommend next-generation sequencing for all individuals who undergo joint replacement prior to the age of 45 years. Lifestyle recommendations for prevention should be implemented.

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INTRODUCTION

Osteoarthritis (OA) is the most common degenerative joint disorder worldwide, one of the main sources of morbidity in developed countries, and a major socioeconomic burden for health care systems. It is characterized by joint cartilage damage, subchondral sclerosis, and the formation of osteophytes, leading to severe pain and loss of joint function. Treatment is symptomatic and in cases of severe OA, usually includes joint replacement surgery.

Unlike secondary OA, which is caused by trauma, infection, metabolic disorder, or another disease, primary OA is considered a complex multifactorial disease according to previous epidemiologic and molecular data (1). The estimated heritability of OA (i.e., the portion of phenotypic variance that is of genetic origin) is ~50% (2). Although the common forms of OA are multifactorial, rare early-onset forms of OA are dominantly inherited Mendelian diseases. At least 13 genes have been reported to be involved in nonsyndromic forms of early-onset OA: *ACAN*, *COL2A1*, *COL9A3*, *COL11A2*, *COMP*, *MATN3*, *PRG4*, *RIPK2*, *SMAD3*, *TNFRSF11B*, *TRAPPC2*, *TRPV4*, and *TUFT1* (MIM ID *155760, +120140, *120270, *120290, *600310, *602109, *604283, *603455, *603109, *602643, *300202, *605427, *600087, respectively) (3–13).

To our knowledge, no study to date has provided a large-scale genetic overview of nonsyndromic early-onset OA or clinical follow-up of early-onset OA patients with a known molecular characterization. Therefore, we investigated the clinical and molecular spectrum of nonsyndromic early-onset OA in a cohort of French individuals referred for molecular analysis.

PATIENTS AND METHODS

Participants. We studied probands with nonsyndromic early-onset OA who were referred, in 2013–2019, to the Montpellier University Hospital Skeletal Disease Center by geneticist experts in skeletal dysplasia from 8 French hospitals. The referring physicians had determined that affected individuals had early-onset OA without chondrodysplasia. Inclusion criteria for primary early-onset OA were based on those described by Aury-Landas et al (8): no known condition suggesting that OA was secondary as opposed to primary, body mass index (BMI) ≤ 30 kg/m² before the first symptoms of OA, radiologically confirmed OA, and age at OA onset ≤ 50 years (Supplementary Table 1, on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41387/abstract>).

We systematically requested skeletal radiographs of affected joints, as well as extensive skeletal surveys that had been reviewed by bone dysplasia experts during dedicated bone dysplasia meetings. To exclude syndromic early-onset OA, we specifically checked for reported palatal or subtle cleft, ocular, and hearing features in all individuals. We collected data regarding age at first experience of joint pain and first joint replacement surgery, BMI, metabolic disease, profession, and sports participation.

Genetic testing. We used the Agilent online SureDesign tool (<https://earray.chem.agilent.com/suredesign/>) for designing the panel, targeting 49 genes associated with congenital skeletal disorders including OA (Supplementary Table 2, <http://onlinelibrary.wiley.com/doi/10.1002/art.41387/abstract>). Using genomic DNA from all probands, we prepared Illumina multiplexed paired-end libraries with the SureSelectQXT Target Enrichment system, according to the protocol recommended by the manufacturer (Agilent). We then indexed, pooled, and sequenced captured libraries using a NextSeq 500/550 MidOutput Kit, version 2 (300 cycles), according to standard protocols. We used SeqNext NGS analysis software (JSI) for read alignments, variant calling, and annotation and classified variants in 5 pathogenicity groups according to the American College of Medical Genetics 2015 guidelines, then performed confirmation analysis of all variants of interest using conventional ABI Sanger sequencing restricted to exons of interest. We used GnomAd (<https://gnomad.broadinstitute.org/>) and Varsome (<https://varsome.com/>) to assist in variant classification. Segregation of the genetic variants identified in index cases was performed using Sanger sequencing in all family members (Supplementary Figures 1–13, on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41387/abstract>).

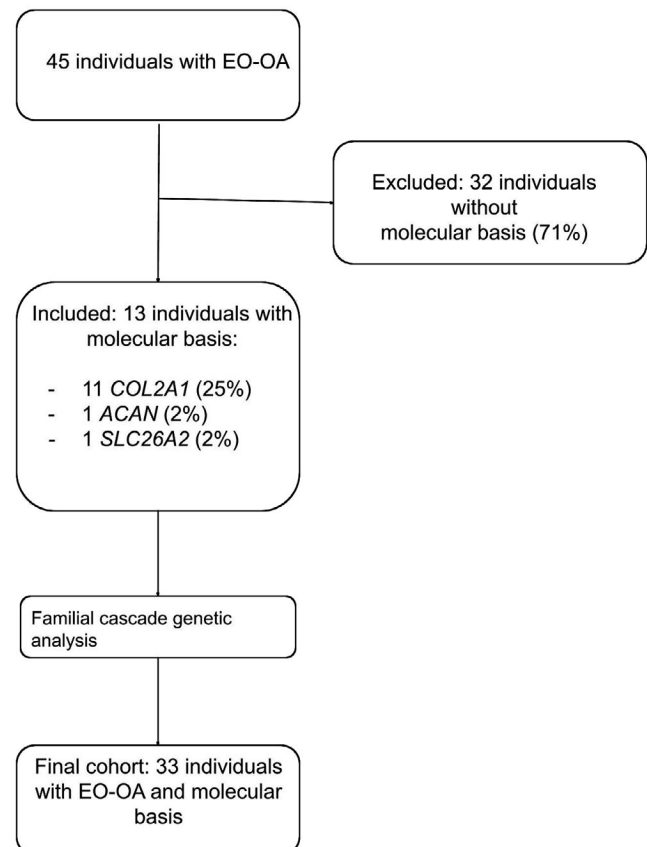


Figure 1. Flow chart showing the disposition of the probands with early-onset osteoarthritis (EO-OA) and the involved genes in those found to have a genetic variant.

Consent and ethics approval. All subjects, parents, or legal guardians provided written informed consent for genetic diagnosis procedures. The study was performed in accordance with the ethical standards of our national research committee and with the Helsinki Declaration. Ethics approval was granted by Montpellier University Hospital Institutional Review Board (IRB-MPT_2020_03_202000373).

RESULTS

Cohort constitution. The 45 probands with early-onset OA were between 3 and 45 years old, with a mean and median age at onset of joint pain of 19.5 years and 16 years, respectively. We found a genetic variant in 13 probands (29%), who were then included in the study cohort. After familial cascade screening, the final cohort consisted of 33 individuals with early-onset OA and a genetic variant (Figure 1).

Clinical findings. Clinical characteristics of the patients in the study cohort are shown in Table 1 and in Supplementary Table 3 (<http://onlinelibrary.wiley.com/doi/10.1002/art.41387/abstract>). Eighteen of the 33 patients (55%) had had at least 1 joint replacement, with the first joint replacement occurring at a mean \pm SD and median age of 41 ± 4.2 years and 42 years, respectively. These 18 individuals had a total of 47 joint replacements (mean 2.6 per person); 21 (45%) of the joint replacement surgeries were per-

formed when the patient was <45 years old. Of the 20 individuals age >40 years at the time of the study, 17 (85%) had had at least 1 joint replacement. The hip was by far the most frequently affected joint: 15 individuals had at least 1 total hip replacement (THR) (Supplementary Figure 14, on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41387/abstract>). None of these individuals had another diagnosis commonly associated with early hip replacement, such as avascular necrosis or Legg-Calvé-Perthes disease.

Although none of the subjects had a BMI of >30 kg/m² at the time they first experienced articular pain, 16% were obese at the last examination (Supplementary Table 3), a proportion not significantly different from the 17.2% obesity rate in the French general population (14). Representative abnormal radiographic findings in individuals from this cohort are shown in Supplementary Figure 15 (<http://onlinelibrary.wiley.com/doi/10.1002/art.41387/abstract>).

Molecular findings. We identified pathogenic or likely pathogenic variants in 13 of the 45 probands (29%). All variant characteristics are shown in Supplementary Table 4 (<http://onlinelibrary.wiley.com/doi/10.1002/art.41387/abstract>).

Eleven (85%) of the patients carried *COL2A1* variants: 6 an arginine-to-cysteine substitution, 4 a glycine substitution, and 1 a frameshift variant that was localized in the chondrocalcin domain and probably altered the stability of the procollagen

Table 1. Clinical data on the patients with nonsyndromic early-onset osteoarthritis and a genetic variant*

| | Male (n = 8) | Female (n = 25) | Total (n = 33) |
|---------------------------------------|------------------------------|----------------------------|--------------------------------|
| Age at last examination, years | 43.0 (13–68) | 40.2 (7–70) | 40.9 (7–70) |
| Height, cm† | 175.1 \pm 0.13 (164.5–181) | 161.1 \pm 0.31 (140–175) | 164.5 \pm 0.27 (140–181) |
| Weight, kg† | 80.1 \pm 1.93 (66–94) | 60.2 \pm 1.07 (41–95) | 65.2 \pm 1.33 (41–95) |
| BMI, kg/m ² | 25.1 (19.5–30.3) | 22.9 (15.3–36) | 23.5 (15.3–36) |
| Age at first articular pain, years | 27 (19–47) | 17.4 (3–45) | 19.5 \pm 3.854 (95% CI 3–47) |
| Location of articular pain, no. (%) | | | |
| Shoulder | 3 (38) | 8 (32) | 11 (33) |
| Elbow | 2 (25) | 4 (16) | 6 (18) |
| Wrist | 3 (38) | 10 (40) | 13 (39) |
| Hand | 4 (50) | 14 (56) | 18 (55) |
| Vertebral column | 6 (75) | 21 (84) | 27 (82) |
| Hip | 6 (75) | 20 (80) | 26 (79) |
| Knee | 4 (50) | 17 (68) | 21 (64) |
| Ankle | 3 (38) | 8 (32) | 11 (33) |
| Foot | – | 3 (12) | 3 (9) |
| Age at first joint replacement, years | | | |
| Shoulder | – | 50.3 (49–51) | 50.3 (49–51) |
| Elbow | – | – | – |
| Wrist | 34 (–) | – | 34 (–) |
| Hand | – | – | – |
| Vertebral column | – | 45 (–) | 45 (–) |
| Hip | 40 (23–54) | 42.8 (30–59) | 42 (23–59) |
| Knee | 45 (40–50) | 42.8 (36–48) | 43.5 (36–50) |
| Ankle | – | 41 (40–42) | 41 (40–42) |
| Foot | – | 35 (–) | 35 (–) |

* Except where indicated otherwise, values are the mean or mean \pm SD (range). BMI = body mass index; 95% CI = 95% confidence interval.

† Data are only for subjects age >18 years.

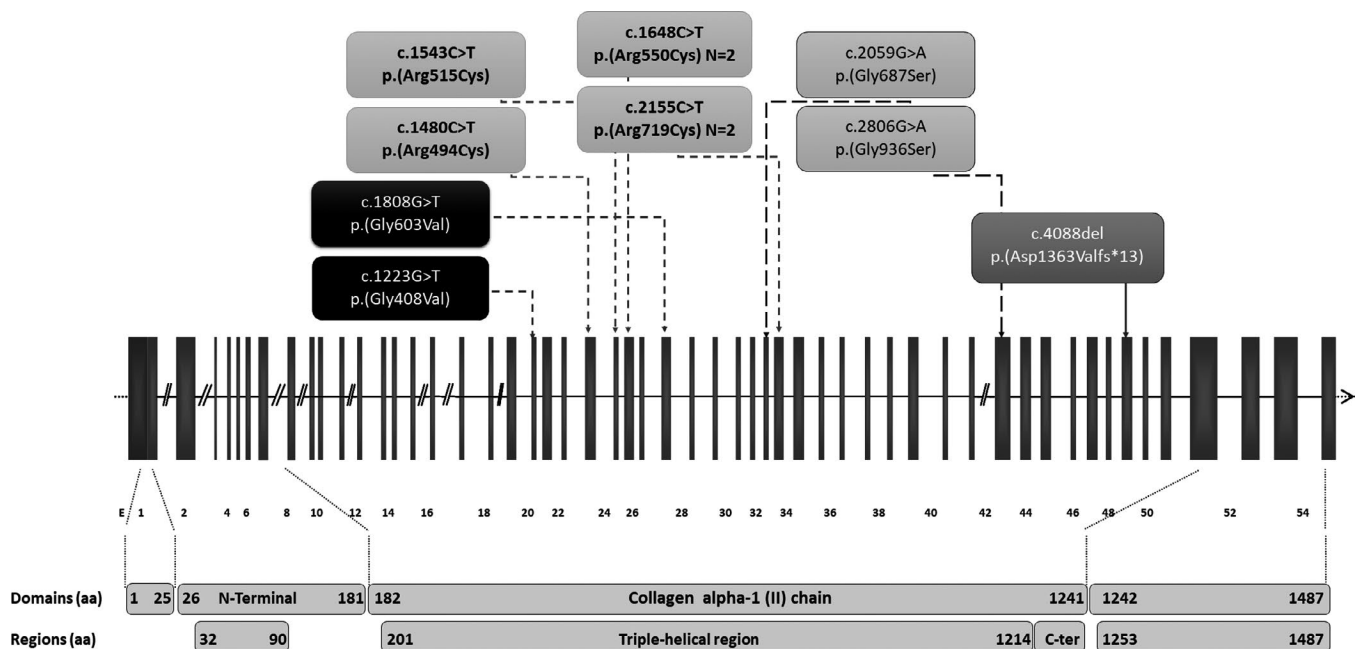


Figure 2. Schematic representation of the *COL2A1* (NM_001844) pathogenic variants identified in the study cohort.

(Figure 2 and Supplementary Figure 16, <http://onlinelibrary.wiley.com/doi/10.1002/art.41387/abstract>). After familial segregation analysis, we included 19 additional individuals carrying a *COL2A1* pathogenic or likely pathogenic variant in this cohort. We also identified a heterozygous pathogenic nonsense variant in *ACAN* (NM_013227; c.2441C>G [p.Ser814*]) in a mother/son dyad and a likely pathogenic homozygous variant in *SLC26A2* (MIM *606718; NM_000112; c.835C>T [p.Arg279Trp]) in 1 subject.

The final cohort consisted of 33 individuals with early-onset OA and a genetic variant (Figure 1). Although dominant-negative variants in *COL2A1* seem to cause a more severe OA phenotype than variants in *ACAN* or *SLC26A2*, we found no significant difference between individuals according to the involved gene or the nature of the genetic variant (Supplementary Tables 4–6, <http://onlinelibrary.wiley.com/doi/10.1002/art.41387/abstract>).

DISCUSSION

Herein we report clinical and genetic data on the largest described cohort with nonsyndromic early-onset OA. Based on clinical exploration of this nonsyndromic early-onset OA cohort, we propose a potential addition to the diagnostic criteria, and lifestyle recommendations. Although height is not included in the diagnostic criteria for primary early-onset OA proposed by Aury-Landas et al (8), it is possible that 3 individuals from our cohort had a syndromic form of early-onset OA, because their height was more than 2 SD below the group mean. Nevertheless, they did not exhibit other signs that would suggest a more generalized skeletal dysplasia (e.g., abnormal vision or hearing, or abnormal findings on skeletal survey). Normal stature could be an additional criterion for nonsyndromic early-onset OA.

OA is the most frequent condition resulting in THR or total knee replacement (TKR) (15). The mean age at the time of THR and TKR in individuals from this series was significantly lower than in the French general population: 42 and 43.5 years, respectively, versus 72.8 and 71 years ($P = 0.007$) (16,17). In the general population, only 3.2% and 1.2% of THRs and TKRs, respectively, have been performed on individuals <45 years old (15), whereas 45% of the subjects in our cohort had undergone joint replacement surgery at age <45 years old ($P = 0.0001$). Furthermore, although joint replacement in the context of primary OA in joints such as the wrist, ankle, or shoulder is rare in the general population, 5 of the 33 subjects in our series (15%) had undergone surgery at these sites.

We suggest that all individuals who meet the early-onset OA criteria published by Aury-Landas et al in 2016 be referred for genetic analysis, as should those who have undergone joint replacement before age 45 years in the context of primary early-onset OA, especially for a joint in which replacement is less common. We also suggest referral of first-degree relatives of individuals with early-onset OA, even if the proband has not had genetic testing.

Identification of risk factors for nonsyndromic early-onset OA, and early recognition of the diagnosis when present, should lead to strict lifestyle interventions to help delay its onset or to delay the need for joint replacement in those in whom it has already occurred. For example, obesity aggravates a vicious circle: pain, sedentary lifestyle, obesity, OA, pain. Regular nontraumatic exercise, dietary modification for weight control, improved workstation ergonomics, and potential career reorientation for those whose jobs involve stress on joints should be strongly recommended to patients.

The gene most frequently involved in nonsyndromic early-onset OA is *COL2A1*, known to cause a wide spectrum of genetic disorders subsumed under the name “*COL2A1*-related

disorders.” In most cases of *COL2A1*-related disorders, individuals have OA (11). Collagens are the major structural components of the extracellular matrix, and type II collagen is the major collagen synthesized by chondrocytes. *COL2A1* protein consists of 3 $\alpha 1$ chains; glycine is the most important amino acid of this triple-helical domain, with a Gly–X–Y repeat motif. As expected, the vast majority of *COL2A1* variants we identified in our early-onset OA series (all but 1) were glycine or arginine substitutions, located in the triple-helical domain of the protein. However, we did not identify either obvious variant hotspots or clear genotype–phenotype correlations; it is possible these might have been found had the study cohort been larger.

The limitations of this study include the need to update the panel with recently published genes such as *TNFRSF11B* (7) (mostly reported in relation to severe forms of Paget’s disease), *RIPK2* (12), and *TUFT1* (reported only once in the literature) (9). To maximize cost-efficiency of the molecular analysis, exome or genome sequencing would be preferred, as they have become the gold standard for sequencing analyses.

In conclusion, the results of this comprehensive study of 45 probands emphasize the high rate of monogenic etiology of early-onset OA (29%). *COL2A1* is by far the most frequently involved gene in early-onset OA (85% of monogenic cases). Among the 33 individuals with a genetic variant, the mean age at first joint replacement surgery was 41 years. The first joint replacement surgery occurred before the age of 45 years in 61% of the subjects. Moreover, 85% of individuals age >40 years had had at least 1 joint replacement. We recommend genetic testing in individuals with early-onset OA, as well as those who undergo joint replacement surgery before the age of 45 years.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Geneviève had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ruault, Yauy, Geneviève, Barat-Houari.

Acquisition of data. Fradin, Van-Gils, Angelini, Baujat, Blanchet, Cuinat, Isidor, Jorgensen, Lacombe, Moutton, Odent, Sigaudy, Willems, Geneviève.

Analysis and interpretation of data. Ruault, Yauy, Fabre, Sanchez, Toutou, Apparailly, Geneviève, Barat-Houari.

ADDITIONAL DISCLOSURES

Author Yauy is an employee of SeqOne.

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