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Title: Clinical phenotypes based on clinical prognostic factors in patients with secondary hip osteoarthritis: preliminary findings from prospective cohort study

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ABSTRACT

Objectives

Recently, several clinical prognostic factors for hip osteoarthritis (OA) progression such as spinal malalignment, reduced spinal mobility, and excessive daily cumulative hip loading have been identified. This study aimed to identify clinical phenotypes based on clinical prognostic factors in patients with secondary hip OA using data from prospective cohort studies and to define the clinical features of each phenotype.

Methods

Fifty patients participated. Two-step cluster analysis was performed to identify the phenotypes using the following potential prognostic factors for hip OA progression: spinal inclination in standing, thoracolumbar spine mobility, daily cumulative hip moment, and minimum joint space width (JSW) at baseline. Comprehensive basic and clinical features (age, body mass index, hip pain, Harris hip score, JSW, radiographic hip morphology, hip impairments, spinal alignment and mobility, and gait-related variables) and ratio of progressors in 12 months were compared among the phenotypes using bootstrap method (unadjusted and adjusted for age).

Results

Three phenotypes were identified and each phenotype was characterized as follows ($P < 0.05$): phenotype 1 (30%), relatively young age and higher daily cumulative hip loading; phenotype 2 (42.0%), relatively older age, reduced JSW, and less spinal mobility; and phenotype 3 (28.0%), changed thoracic spine alignment and less spinal (especially in the thoracic spine) mobility. The ratio of progressors among the phenotypes was not statistically significantly different. These characteristics remained after adjustment for age.

Conclusion

Three phenotypes with similar progression risk were identified. This finding will help in designing treatment tailored to each phenotype for hip OA progression prevention.

Keywords: Hip osteoarthritis, Progression, Phenotype, Gait, Spine

Key-points

- Three phenotypes with similar progression risk were identified based on clinical prognostic factors.
- Phenotype 1 was characterized by young age and higher daily cumulative hip loading.
- Phenotype 2 was relatively old age and had reduced JSW and less spinal mobility.
- Phenotype 3 had changed thoracic spine alignment and less thoracic spine mobility.

Introduction

As osteoarthritis (OA) is a heterogeneous disease characterized by multiple-tissue failure and various clinical features [1], subgrouping of patients with OA will improve the understanding of the disease, and treatment tailored to phenotypes could enhance therapeutic efficacy [2]. In patients with knee OA, various phenotype classifications from different perspectives (e.g., clinical, laboratory, imaging, and etiologic phenotypes) have been proposed [3], whereas information on the classification of patients with hip OA is limited.

Historically, hip OA has been classified as primary and secondary hip OA. However, as many of the primary hip OA have been associated with potential morphological abnormalities, the boundary between the two classifications is becoming less clear [4]. Although a few attempts have been made to classify patients with hip OA based on a genome-wide DNA methylation profile of chondrocytes in hip cartilage [5] and shape of the proximal femur [6], the clinical characteristics of these phenotypes and the association between phenotypes and the predisposition to progression of hip OA have not been examined.

Hip OA is a chronic progressive disease; thus, identifying different phenotypes associated with prognostic factors is essential in the prevention of hip OA progression. Previous studies reported that some phenotypes are characterized by direction of femoral head migration or have a bone remodeling response pattern [7,8], and patients with superolateral migration and atrophic bone response have been considered more prone to hip OA progression [9]. However, phenotype classification associated with clinical and modifiable prognostic factors has not been performed in patients with hip OA, presumably because no such prognostic factors have been found. Recently, our prospective cohort studies have demonstrated that spinal malalignment during standing, reduced thoracolumbar spinal mobility, and excessive daily cumulative hip loading during walking (i.e., daily total amount of external load on the hip joint) are associated with subsequent radiographic progression of hip OA [10,11]. These clinical prognostic factors are modifiable by therapeutic exercise.

The identification of these multiple clinical prognostic factors subsequently raises the following question: Does a certain high-risk patient group have all of these prognostic factors or are there some phenotypes with different prognostic factors? This question could be answered by

exploratory subgrouping of patients based on multiple clinical prognostic factors. For the subgrouping of patients, an epidemiological method based on a priori hypothesis and a statistical (data-driven) method, such as cluster analysis, are commonly applied [3,12]. A statistical method may be better if it is unclear whether the patients could be divided into clusters or if the number of clusters is unknown [13]. Identifying phenotypes based on modifiable clinical prognostic factors and defining the clinical features of each phenotype would help clinicians tailor the treatment for the prevention hip OA progression.

Hence, this study aimed to identify clinical phenotypes based on clinical prognostic factors in patients with mild-to-moderate secondary hip OA using data from prospective cohort studies and to define the clinical features of each of identified phenotype. We hypothesized that no single phenotype has a combination of all clinical prognostic factors; however, there are distinct phenotypes with different clinical prognostic factors and similar progression risk. This data-driven phenotyping may contribute to greater responsiveness to disease-modifying interventions in hip OA with heterogeneous features.

Participants and Methods

Participants

From the non-surgical outpatients in the orthopaedic department of the university hospital, 50 participants were recruited continuously. The inclusion criteria were as follows: patients with secondary hip OA aged ≥20 years; a diagnosis of pre-osteoarthritis (acetabular dysplasia with no other abnormal radiographic findings) or early (slight joint space narrowing [≥2 mm] and abnormal subchondral sclerosis) or advanced-stage (marked joint space narrowing [<2 mm] with or without cysts or sclerosis) hip OA [14]; and ability to walk without any assistive device. The exclusion criteria included the following: patients with a baseline joint space width (JSW) of <0.5 mm; previous hip surgeries; and neurologic, vascular, or other conditions that affect gait or activity of daily living. Only female patients were included in this study because of the substantial gender bias (males, 7.1%), which

is similar to previous reports on secondary hip OA (males, 7.6–9.2%) [15,16]. Moreover, primary hip OA cases are fewer and rare in Asians [4,17]; thus, only secondary hip OA cases were included in this study. In patients with bilateral hip OA, the side with more severe joint space narrowing was included in the analysis. This study used data from the cohort in previous prospective cohort studies [10,11]. Functional status of the patients was assessed using Harris hip score (HHS). The study protocol was approved by the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine. All participants provided written informed consent.

Joint space width and hip morphology

Minimum JSW and hip morphology were assessed using a digital supine anteroposterior radiograph of the pelvis. Radiograph was taken in a standardized manner by skilled radiology technicians and evaluated by a single experienced examiner. The image was reviewed and measured digitally using Centricity Enterprise Web, version 3.0 (GE Health care, Buckinghamshire, England). To assess the degree of cartilage degeneration and the progression of hip OA, JSW was measured at the vertex and medial and lateral sides of the weight-bearing surface, and if there was a minimum JSW position other than the aforementioned three locations, it was also measured as the fourth measurement [10,18]. The minimum value of three or four locations was defined as the minimum JSW [10,18]. JSW was measured at baseline and 12 months thereafter, and patients with >0.5 mm reduction in minimum JSW over 12 months was classified as progressors [19,20]. The intrarater reliability (intraclass correlation [ICC] 1,1) of JSW measurement was 0.99 [10].

For hip morphology, Sharp angle, lateral center edge angle, acetabular head index, and acetabular roof obliquity were measured digitally with the same image and software used in JSW measurement. The ICC (1,1) for hip morphology measurements was 0.95–0.98 [10]. The examiner was blinded to the patients' name and date of radiographic imaging during JSW and hip morphology measurements.

Hip impairments

Hip pain intensity was assessed as the average pain experienced during activities of daily living within the last 3 months using a 100-mm visual analogue scale. Passive range of motion (ROM) of the hip joint was measured in flexion, extension, abduction, adduction, external rotation, and internal rotation [21]. The position of the patients for each ROM test was as follows: flexion, supine with the knee flexed; extension, supine with hip joint positioned at the edge of the treatment table and the contralateral hip flexed to flatten the lumbar spine and stabilize the pelvis; abduction, supine with the contralateral hip positioned at 10° abduction; adduction, supine with contralateral hip slightly flexed; and external and internal rotations, prone with the knee flexed at 90°. The pelvis and contralateral femur were fixed with a stabilization belt during measurement. A single examiner recorded the ROM using a standard two-arm goniometer. The ICC (1,1) for the ROM tests was 0.82–0.99 [22].

Hip muscle strength was recorded in flexion, extension, abduction, adduction, external rotation, and internal rotation [21,23]. Maximal isometric muscle strength was measured using a handheld dynamometer (μ-TAS F-1; Anima Co., Ltd, Tokyo, Japan) by a single examiner. Hip flexion was measured in the sitting position. Hip extension was measured in the supine position with the leg raised straight at 20°. Hip abduction was measured in the supine position, with 0° of abduction/adduction of both hips. Hip external and internal rotations were measured in the prone position with 90° of knee flexion. The pelvis and contralateral femur were fixed with a stabilization belt, and patients were instructed to hold the edge of the table to stabilize their body. After several practice trials, two maximal trials for 3 s each were recorded. The mean of the two trials was used for analysis. The ICC (1,1) for the muscle strength tests was 0.85–0.98 [22].

Spinal alignment and mobility

Spinal alignment and mobility were measured by Spinal Mouse (Idiag AG, Switzerland), which is a reliable and valid device for the measurement of spinal alignment and ROM [24–26]. Spinal alignment in the standing position was assessed for the following: thoracic kyphosis (from T1/2 to T11/12), lumbar lordosis (from T12/L1 to L5/S1), sacral inclination (the angle between the straight line from S1 to S3 and a vertical line), and spinal inclination (the angle between the straight line from T1 to S1 and a vertical line) angles. The mean value of three measurements was used for analysis. The

ICC (1,1) for the spinal alignment measurements was 0.86–0.99 [11].

Spinal mobility of the thoracic spine, lumbar spine, and thoracolumbar spine was measured using Spinal Mouse. Measurements were performed in the sitting position to minimize the appearance of hip symptoms, and the patient was instructed to bend their spine forward and backward as much as possible. The mean value of three measurements was used for analysis. The ICC (1,1) for the spinal mobility measurements was 0.95 [11].

Gait-related variables

Gait analysis was performed using an 8-camera Vicon motion system (Vicon Nexus; Vicon Motion Systems Ltd., Oxford, England) on a 7-m walkway embedded with four force plates (Kistler Japan Co., Ltd., Tokyo, Japan). Raw marker trajectories (200 Hz sampling) were filtered with a fourth-order Butterworth low-pass filter with a 6-Hz cutoff, and ground reaction force (1000 Hz sampling) was filtered with a low-pass filter (20 Hz). Reflective markers were placed over the close-fitting shorts and T-shirt by a single experienced examiner. The marker positions were as follows: bilaterally on the anterior superior iliac spine, posterior superior iliac spine, superior aspect of the greater trochanter, lateral femoral condyle, medial femoral condyle, lateral malleolus, medial malleolus, heel, fifth metatarsal head, and first metatarsal head [22]. After several practice trials, at least three trials at a self-selected speed without any assistive devices were recorded.

Three-dimensional external hip joint moments were calculated using BodyBuilder software (Vicon Motion Systems Ltd., Oxford, England). Joint moment was computed by adding the coordinate data to the ground reaction force data, in which the position of the center of mass, weight portion, and moment of inertia of each segment were used as parameters. External hip joint moment impulse in three planes was calculated for the stance phase. Furthermore, daily cumulative hip moments were calculated by multiplying the hip joint moment impulse in each of the three planes and the mean number of steps per day for affected limb. The number of steps for seven consecutive days was recorded by a pedometer (EX-500, Yamasa Tokei Co., Ltd., Tokyo, Japan) within a month from the day of gait analysis. The patient was instructed to keep the pedometer in their pocket from awakening to bedtime. High accuracy of this method has been verified previously [10].

Statistical analysis

SPSS version 24 (IBM Japan Ltd., Tokyo, Japan) was used for the statistical analysis. Statistical significance was defined as $P < 0.05$.

To classify the patients, a two-step cluster analysis was performed. This analysis is better than the widely used hierarchical or k-means clustering methods especially when all clustering variables are continuous [27,28]. Because this study is exploratory in nature and the number of clusters is unknown, a two-step cluster analysis, which could automatically determine the number of clusters based on a predefined criterion, is suitable for this study. The following suggested clinical prognostic factors for hip OA were included as clustering variables: spinal inclination in standing, thoracolumbar spine mobility, and daily cumulative hip moment (hip abduction/adduction) [10,11]. Additionally, minimum JSW at baseline was included in the clustering variables because it has been considered a factor involved in hip OA progression [9,29]. As the bivariate correlation between the clustering variables were at most 0.43, collinearity was not confirmed [13]. Before the cluster analysis, all clustering variables were standardized using z-scores. In the first step of the two-step cluster analysis, pre-clusters were computed, which are dense regions in the analyzed attribute space. In the second step, hierarchical clustering technique was performed to determine the optimal number of clusters according to the distance measurement. Log-likelihood criterion was used for distance measurement. Akaike's information criterion was also used to identify the optimal number of clusters. Furthermore, the overall goodness-of-fit of clusters was evaluated by Silhouette measure. Silhouette measure <0.20 indicates a poor solution quality; a measure between 0.20 and 0.50, a fair solution; and a measure >0.50, a good solution [13]. As the clustering result may depend on the input order of cases [27], the cluster analysis was performed again after randomly changing the order of cases to check the stability of the clustering [13].

After determining the number of clusters, basic and radiographic characteristics, hip impairments, spinal alignment and mobility, and gait-related variables, including clustering variables, were compared between clusters. Comparison of these variables was performed by Holm-corrected unpaired *t*-test. Unpaired *t*-test was used in this study because of its major advantages over non-

parametric tests, especially for a small sample [30]. To compare the basic and clinical characteristics between clusters with adjustment for age, Holm-corrected unpaired *t*-test adjusted for age using a general linear model was also performed. Furthermore, a generalized linear model was used to examine the association between cluster differences and ratio of progressors (radiographic progression [yes/no] as dependent variable and cluster number as independent variables) with and without adjustment for age.

Furthermore, as each cluster was expected to contain small samples, the bootstrap method, which is a reliable resampling method that does not require normality assumption [31], was employed for the comparison of clinical characteristics and ratio of progressors between clusters. The bootstrap method was conducted with 1000 replicates.

Results

Fifty patients (age, 47.4 ± 10.7 years; body mass index, 22.4 ± 4.1 kg/m^2) participated in this study. On average, the patients had moderate hip pain (visual analogue scale, 42.0 ± 27.5 mm) and showed a relatively good HHS (86.9 ± 9.9 points).

Determination of phenotypes

The two-step cluster algorithm identified three phenotypes based on predefined criteria: phenotype 1 (n = 15, 30.0%), phenotype 2 (n = 21, 42.0%), and phenotype 3 (n = 14, 28.0%). Silhouette measure was 0.5, which represents a cluster quality between fair and good, and was considered acceptable clustering [13]. No change in the number of clusters and the number of patients included in each cluster was observed even if the order of cases was changed.

Comparison of clinical characteristics and hip OA progression between phenotypes

The differences in demographic, clinical, and radiographic characteristics between the three

phenotypes based on bootstrap unpaired t-test with Holm correction are shown in Table 1. Age was statistically significantly different among the three phenotypes. Minimum JSW at baseline in phenotype 2 was smaller than that in phenotypes 1 and 3. Even after adjustment for age, the statistically significant differences remained. HHS was higher in phenotype 1 than in phenotype 2; however, the difference did not remain after adjustment for age.

Hip impairments in each phenotype are shown in Table 2. Hip abduction and internal rotation ROM were smaller in phenotype 2 than in phenotypes 1 and 3, and hip adduction ROM was smaller in phenotype 2 than in phenotype 1. However, these differences in hip ROM between phenotypes did not remain after adjustment for age.

Spinal alignment and mobility of the three phenotypes are summarized in Table 3. For spinal alignment, thoracic kyphosis was smaller in phenotypes 2 and 3 than in phenotype 1, and the difference between phenotypes 1 and 3 remained after adjustment for age. For thoracic spine mobility, the lowest was observed in phenotype 3, followed by phenotypes 2 and 1. Even after adjustment for age, phenotypes 2 and 3 had lower thoracic spine mobility than phenotype 1. Thoracolumbar spine mobility was lower in phenotypes 2 and 3 than in phenotype 1, which remained even after adjustment for age.

Gait-related variables in the three phenotypes are shown in Table 4. Gait speed was slower in phenotype 3 than in phenotype 1; however, the difference was not observed after adjustment for age. Physical activity (steps/day) was higher in phenotype 1 than in phenotypes 2 and 3 after adjustment of age. Excursion in hip abduction/adduction angle during gait was greater in phenotype 1 than in phenotype 2 only when not adjusted for age. Although the hip moment impulse was not statistically significantly different between phenotypes, the daily cumulative hip moment in hip abduction/adduction was higher in phenotype 1 than in phenotype 3 without adjustment for age and was higher in phenotype 1 than in phenotypes 2 and 3 after adjustment for age.

The number of progressors was 5 (33.3%) in phenotype 1, 11 (52.4%) in phenotype 2, and 5 (35.7%) in phenotype 3 (Figure 1); no statistically significant association between phenotype differences and the ratio of progressors with and without adjustment for age was found (Table 5). Based on the differences in clinical characteristics, the three identified phenotypes were labeled as follows: “higher daily cumulative hip loading phenotype,” “cartilage degeneration and less spinal mobility phenotype,” and “changed alignment and less mobility of thoracic spine phenotype.”

Discussion

The main finding of this study was that there are three clinically distinctive phenotypes based on clinical prognostic factors in patients with secondary hip OA. To our knowledge, no previous study has investigated the clinical phenotypes in relation to hip OA progression. Consistent with our hypothesis, these phenotypes have different clinical characteristics but the progression risk (i.e., ratio of progressors) is similar. Patients with knee OA could be divided into two to five phenotypes [3], and the identification of three clinical phenotypes in patients with hip OA would be an appropriate result. The findings will help to design of more effective interventions for prevention of the progression of hip OA depending on the characteristics of each group.

For patients included in phenotype 1 (higher daily cumulative hip loading phenotype), excessive cumulative hip loading during activities of daily living should be monitored to prevent hip OA progression. Clinically relevant characteristics of this phenotype included relatively young age, retained JSW, and maintained high functional levels possibly because of young age. Spinal mobility was greater in phenotype 1 than in the other phenotypes even after adjustment for age. Moreover, phenotype 1 had the highest daily cumulative hip moment in hip abduction/adduction, which was observed even after adjustment for age and thus could be an essential feature of this phenotype. Increased daily cumulative hip loading may be attributed to increased physical activity (i.e., steps/day). Physical stress level is a composite value of magnitude, time (repetition), and direction of stress application, and articular cartilage degeneration could be attributed to excessive stress [32]. Cumulative loading is an index reflecting both the magnitude and time of the loading [10,33]. Given that excessive repetitive loading with a load similar to that during walking could damage cartilage chondrocytes [34] and increased daily cumulative hip loading was identified as a prognostic factor for hip OA progression [10], excessive vigorous activity of young patients may sometimes aggravate articular cartilage degeneration.

Phenotype 2 (cartilage degeneration and less spinal mobility phenotype) had multiple prognostic factors associated with hip OA progression. Age has been identified as a possible prognostic

262 factor for hip OA progression [9]. JSW was clearly reduced in this phenotype compared to other
263 phenotypes, even after adjusting for age. The difference was beyond the clinically and statistically
264 meaningful 0.5 mm [19]. Considering that minimum JSW <2.0 mm at baseline is a predictor of hip
265 OA progression [35] and minimum JSW <2.5 mm is associated with future hip joint replacement [36],
266 a mean minimum JSW value of 1.95 mm in phenotype 2 is associated with the risk of future hip OA
267 progression. Furthermore, although spinal mobility generally decreases with age [37], phenotype 2 is
268 characterized by reduced thoracic and thoracolumbar spine mobility even after adjustment for age.
269 Reduced thoracolumbar spine mobility has been shown to be associated with future hip OA progression
270 [11]. Various activities of daily living, such as sit-to-stand, include both the spine and hip motion; thus,
271 as the mobility of one (e.g., spine) decreases, the required motion of the other (e.g., hip) increases [38],
272 which could in turn result in increased local stress in the joint with increased motion (e.g., hip).
273 Moreover, low HHS and reduced hip ROM are the more assessable clinically relevant characteristics
274 of phenotype 2. However, they seem to be characteristics affected by aging as the difference in HHS
275 and hip ROM between phenotypes was not observed after adjustment for age. Although no difference
276 in the ratio of progressors between phenotypes was noted, phenotype 2 has multiple prognostic factors
277 and may be more susceptible hip OA progression.

278 Phenotype 3 (changed alignment and less mobility of thoracic spine phenotype) is
279 characterized by reduced spine, especially thoracic spine, mobility accompanied by reduced thoracic
280 kyphosis. Change in postural alignment in the sagittal plane is common in patients with hip OA; the
281 whole spine tends to tilt forward with anterior pelvic tilt as hip OA progresses [39,40]. This imbalanced
282 sagittal alignment is likely to be compensated by reduced thoracic kyphosis [40]. Change in thoracic
283 spine alignment is accompanied by muscle tension around the thoracic spine, which may in turn limit
284 the flexible motion of the thoracic spine.

285 The identification of the three phenotypes with different clinical characteristics has
286 implications for phenotype-tailored therapy in clinical practice. OA has been considered a multifaceted
287 and heterogeneous syndrome; thus, to tailor the treatment according to specific phenotypes is essential
288 [2]. For example, relatively young patients included in phenotype 1 may need to receive appropriate
289 information and patient education, especially regarding physical activity and changes in lifestyle, as
290 part of the recommended core non-pharmacological management of hip OA [41,42]. For the relatively

291 older patients in phenotype 2, spinal mobility improvement by mobilization and stretching, which are
292 proven effective even for the elderly individuals [43], may be recommended because aging and
293 cartilage degeneration could not be directly modified by exercise therapy. Additionally, improvement
294 in thoracic spine mobility, thoracic spine alignment, and underlying imbalanced sagittal postural
295 alignment may be suitable for patients in phenotype 3. There is little evidence on the effects of exercise
296 therapy on the prevention of hip OA. Furthermore, there are no reports of phenotype-tailored treatment
297 directed to prevent hip OA progression. The findings of the current study can contribute to the design
298 of treatments dedicated to each phenotype. Further relevant studies, including advantages and cost
299 effectiveness of phenotype-tailored treatment over a one-size-fits-all therapy are warranted.

300 This study has several limitations. The limited sample size might have weakened the
301 robustness of the subgrouping and reduced the statistical power to detect differences in clinical
302 characteristics between the phenotypes. Because we expected this limitation, bootstrap method was
303 applied in this study to provide reliable and more powerful results by approximating the distribution
304 of the population [44]. However, as this study is a preliminary study that investigated the heterogeneity
305 of patients with hip OA, future studies using large samples are needed to validate our findings.
306 Although majority of the patients with secondary hip OA in our country are females [15–17], our
307 sample was limited to female patients with relatively mild-to-moderate secondary hip OA. Therefore,
308 the findings in this study may not be generalizable to other hip OA populations. Moreover, progression
309 risk was assessed as the ratio of progressors in a relatively short-term of 12 months, although the
310 narrowing of the hip JSW over 12 months is meaningful with reported as a risk factor for hastening of
311 THA [45]. Thus, a longer follow-up may result in differences in the progression risk between
312 phenotypes. Finally, the result of the cluster analysis is dependent on the variables used in the
313 subgrouping within a given sample and on the clustering method and criteria used. If new clinical
314 prognostic factors will be found, reclustering should be performed including these factors;
315 consequently, more robust phenotypes would be identified.

316 In conclusion, three clinical phenotypes with a similar progression risk were identified based
317 on modifiable clinical prognostic factors in patients with secondary hip OA. The results of this study
318 suggest that patients with secondary hip OA with a similar progression risk do not necessarily have the
319 same clinical characteristics. In terms of prognostic factors for hip OA, phenotype 1 is characterized

by increased daily cumulative hip loading due to high physical activity level. Phenotype 2 has multiple prognostic factors, such as relatively older age, advanced cartilage degeneration (i.e., reduced minimum JSW), and reduced spinal mobility. Phenotype 3 is characterized by reduced thoracic spine mobility with change in thoracic spine alignment. This clinically and prognostically relevant subgrouping using longitudinal data would help clinicians in selecting a more appropriate treatment for the prevention of hip OA progression.

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Conflict of Interest disclosure statement

There are no conflicts of interest to declare with regard to this study.

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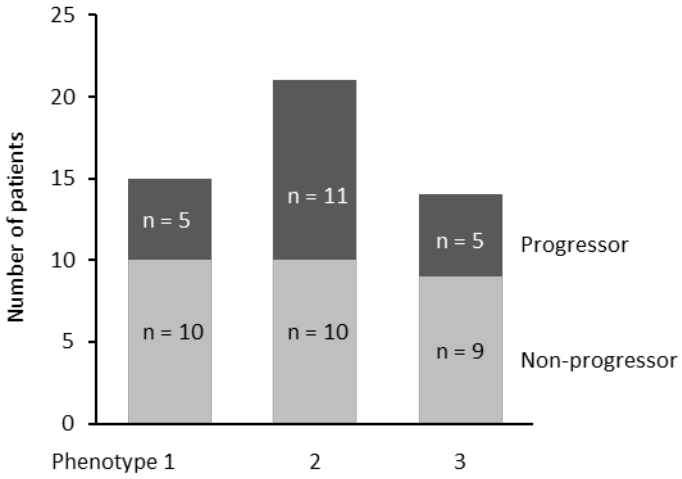

Fig 1. Number of progressors and non-progressors in each phenotype.

Table 1. Demographic and hip morphology characteristics in each phenotype and comparison between phenotypes.

	Phenotype 1 (n = 15)	Phenotype 2 (n = 21)	Phenotype 3 (n = 14)	*P*-value* (95% CI)	*P*-value* adjusted for age (95% CI)
Age, years	36.3 ± 8.0	55.5 ± 7.9	47.2 ± 4.4	**2 > 3 > 1** **1 vs 2: 0.002** (−25.25, −14.40) **2 vs 3: 0.003** (4.10, 12.50) **1 vs 3: 0.003** (−16.37, −6.74)	–
Body mass index, kg/m^2	22.0 ± 3.8	23.4 ± 4.3	21.4 ± 4.0	1 vs 2: 0.736 (−4.00, 1.48) 2 vs 3: 0.561 (−0.88, 4.58) 1 vs 3: 0.705 (−2.27, 3.53)	1 vs 2: 0.517 (−8.54, 3.10) 2 vs 3: 0.216 (0.08, 7.61) 1 vs 3: 0.974 (−3.16, 5.72)
Minimum JSW, mm	4.21 ± 0.85	1.95 ± 0.99	4.46 ± 0.45	**1, 3 > 2** **1 vs 2: 0.002** (1.58, 2.69) **2 vs 3: 0.003** (−2.96, −2.04) 1 vs 3: 0.323 (−0.74, 0.26)	**1, 3 > 2** **1 vs 2: 0.002** (1.51, 3.56) **2 vs 3: 0.003** (−3.24, −2.17) 1 vs 3: 0.381 (−1.04, 0.48)
Pain (VAS), mm	29.9 ± 25.9	52.9 ± 26.5	38.6 ± 25.8	1 vs 2: 0.051 (−38.31, −3.85) 2 vs 3: 0.250 (−3.69, 31.68) 1 vs 3: 0.432 (−27.00, 12.68)	1 vs 2: 0.842 (−49.76, 16.01) 2 vs 3: 0.993 (−9.52, 35.85) 1 vs 3: 0.827 (−36.44, 24.73)
Harris hip score	92.7 ± 5.6	84.7 ± 10.3	84.1 ± 10.8	**1 > 2** **1 vs 2: 0.036** (2.58, 12.73) 2 vs 3: 0.898 (−6.40, 7.97) 1 vs 3: 0.074 (1.31, 15.07)	1 vs 2: 0.186 (−0.88, 18.76) 2 vs 3: 0.961 (−9.17, 7.81) 1 vs 3: 0.240 (−0.35, 15.71)
Hip morphology					
Sharp angle, degrees	44.4 ± 6.1	44.0 ± 5.1	47.1 ± 8.4	1 vs 2: 0.945 (−3.78, 4.08) 2 vs 3: 0.675 (−7.93, 1.39) 1 vs 3: 0.592 (−8.44, 2.10)	1 vs 2: 0.222 (−8.98, 0.66) 2 vs 3: 0.810 (−4.36, 3.75) 1 vs 3: 0.314 (−14.59, 2.04)
CE angle, degrees	24.8 ± 11.1	23.9 ± 12.6	21.4 ± 10.7	1 vs 2: 0.626 (−5.88, 9.82) 2 vs 3: 1.000 (−4.84, 10.50) 1 vs 3: 0.903 (−3.27, 12.25)	1 vs 2: 0.586 (−5.20, 18.81) 2 vs 3: 0.914 (−9.00, 7.63) 1 vs 3: 0.639 (−4.06, 17.72)
AHI, %	76.7 ± 9.9	72.5 ± 11.8	72.9 ± 11.1	1 vs 2: 0.822 (−3.21, 11.57) 2 vs 3: 0.916 (−8.32, 7.70) 1 vs 3: 0.732 (−4.25, 11.31)	1 vs 2: 0.944 (−9.93, 19.19) 2 vs 3: 0.920 (−9.20, 9.13) 1 vs 3: 0.225 (−1.76, 19.51)
ARO, degrees	19.2 ± 9.7	24.4 ± 6.4	22.6 ± 7.3	1 vs 2: 0.099 (−11.27, −0.57) 2 vs 3: 0.462 (−2.55, 6.36) 1 vs 3: 0.458 (−10.83, 2.08)	1 vs 2: 0.624 (−11.26, 5.10) 2 vs 3: 0.705 (−2.57, 8.02) 1 vs 3: 0.691 (−9.32, 5.86)

(Footnotes for Table 1)

Values are mean ± standard deviation. * Holm-adjusted *P*-value with bootstrap method. Bold indicates statistically significant. CI = confidence interval; JSW = joint space width; VAS = visual analogue scale; CE = center edge; AHI = acetabular head index; ARO = acetabular roof obliquity.

527 **Table 2. Hip impairment characteristics in each phenotype and comparison between phenotypes.**

	Phenotype 1 (n = 15)	Phenotype 2 (n = 21)	Phenotype 3 (n = 14)	*P*-value* (95% CI)	*P*-value* adjusted for age (95% CI)
Hip range of motion, degrees					
Flexion	115.5 ± 16.3	109.3 ± 13.5	112.5 ± 14.8	1 vs 2: 0.738 (−4.14, 15.90) 2 vs 3: 1.000 (−13.00, 6.32) 1 vs 3: 0.591 (−7.82, 13.70)	1 vs 2: 0.932 (−10.61, 19.72) 2 vs 3: 0.882 (−15.54, 4.69) 1 vs 3: 0.706 (−20.71, 10.91)
Extension	12.0 ± 4.2	10.8 ± 3.3	12.2 ± 2.8	1 vs 2: 0.387 (−0.45, 4.18) 2 vs 3: 0.388 (−3.47, 0.77) 1 vs 3: 0.874 (−2.95, 2.53)	1 vs 2: 0.799 (−6.00, 4.05) 2 vs 3: 0.951 (−4.15, 1.41) 1 vs 3: 1.000 (−5.21, 3.86)
Abduction	25.9 ± 4.6	19.8 ± 5.6	24.4 ± 5.7	**1, 3 > 2** **1 vs 2: 0.003** (3.22, 9.73) **2 vs 3: 0.046** (−8.63, −1.07) 1 vs 3: 0.414 (−2.12, 5.11)	1 vs 2: 0.308 (−1.45, 8.37) 2 vs 3: 0.057 (−9.20, −1.41) 1 vs 3: 0.660 (−4.29, 7.00)
Adduction	17.5 ± 2.7	13.5 ± 3.9	16.2 ± 3.2	**1 > 2** **1 vs 2: 0.003** (1.80, 6.09) 2 vs 3: 0.038 (−4.82, −0.45) 1 vs 3: 0.274 (−0.98, 3.37)	1 vs 2: 0.752 (−2.04, 6.44) 2 vs 3: 0.891 (−5.45, 1.09) 1 vs 3: 0.762 (−3.01, 2.01)
External rotation	23.3 ± 12.2	24.7 ± 11.6	23.6 ± 12.8	1 vs 2: 1.000 (−8.69, 6.42) 2 vs 3: 1.000 (−7.24, 8.87) 1 vs 3: 0.807 (−8.04, 10.11)	1 vs 2: 1.000 (−12.57, 10.42) 2 vs 3: 0.893 (−9.71, 7.70) 1 vs 3: 1.000 (−15.95, 8.70)
Internal rotation	49.3 ± 15.7	32.7 ± 10.9	45.4 ± 10.9	**1, 3 > 2** **1 vs 2: 0.006** (5.75, 24.83) **2 vs 3: 0.009** (−20.76, −5.89) 1 vs 3: 0.443 (−6.81, 13.08)	1 vs 2: 0.610 (−5.75, 20.49) 2 vs 3: 0.117 (−20.81, −1.34) 1 vs 3: 0.910 (−13.72, 11.14)
Hip muscle strength, Nm/kg					
Flexion	0.93 ± 0.29	0.85 ± 0.27	0.83 ± 0.19	1 vs 2: 0.732 (−0.10, 0.28) 2 vs 3: 0.777 (−0.13, 0.16) 1 vs 3: 0.780 (−0.06, 0.30)	1 vs 2: 0.334 (−0.06, 0.53) 2 vs 3: 0.573 (−0.28, 0.12) 1 vs 3: 0.402 (−0.03, 0.36)

Extension	1.59 ± 0.64	1.44 ± 0.51	1.35 ± 0.60	1 vs 2: 0.742 (−0.18, 0.60) 2 vs 3: 0.627 (−0.28, 0.49) 1 vs 3: 0.777 (−0.18, 0.77)	1 vs 2: 0.708 (−0.12, 0.90) 2 vs 3: 0.818 (−0.61, 0.21) 1 vs 3: 0.600 (−0.39, 0.74)
Abduction	0.80 ± 0.20	0.74 ± 0.21	0.73 ± 0.24	1 vs 2: 1.000 (−0.07, 0.19) 2 vs 3: 0.833 (−0.14, 0.16) 1 vs 3: 0.674 (−0.09, 0.25)	1 vs 2: 0.849 (−0.09, 0.35) 2 vs 3: 0.750 (−0.23, 0.07) 1 vs 3: 0.891 (−0.25, 0.20)
External rotation	0.37 ± 0.12	0.37 ± 0.13	0.34 ± 0.13	1 vs 2: 0.978 (−0.08, 0.08) 2 vs 3: 1.000 (−0.06, 0.11) 1 vs 3: 1.000 (−0.07, 0.12)	1 vs 2: 0.474 (−0.03, 0.18) 2 vs 3: 0.544 (−0.13, 0.06) 1 vs 3: 0.582 (−0.04, 0.13)
Internal rotation	0.37 ± 0.16	0.30 ± 0.10	0.32 ± 0.10	1 vs 2: 0.528 (−0.02, 0.17) 2 vs 3: 0.595 (−0.09, 0.04) 1 vs 3: 0.700 (−0.04, 0.15)	1 vs 2: 0.148 (−0.01, 0.26) 2 vs 3: 0.228 (−0.14, 0.01) 1 vs 3: 0.373 (−0.08, 0.20)

(Footnotes for Table 2)

Values are mean ± standard deviation. * Holm-adjusted *P*-value with bootstrap method. Bold indicates statistically significant. CI = confidence interval.

Table 3. Spinal alignment and mobility characteristics in each phenotype and comparison between phenotypes.

	Phenotype 1 (n = 15)	Phenotype 2 (n = 21)	Phenotype 3 (n = 14)	*P*-value* (95% CI)	*P*-value* adjusted for age (95% CI)
Spinal alignment, degrees					
Thoracic kyphosis (+: kyphosis)	48.0 ± 7.4	41.3 ± 9.9	38.9 ± 9.3	**1 > 2, 3** **1 vs 2: 0.028** (1.56, 12.93) 2 vs 3: 0.444 (−4.58, 8.44) **1 vs 3: 0.015** (2.46, 15.80)	**1 > 3** 1 vs 2: 0.633 (−6.12, 8.87) 2 vs 3: 0.258 (−1.18, 13.33) **1 vs 3: 0.033** (3.51, 18.64)
Lumbar lordosis (+: lordosis)	35.8 ± 8.1	29.1 ± 11.6	26.6 ± 9.7	1 vs 2: 0.080 (0.70, 14.13) 2 vs 3: 0.514 (−4.68, 9.85) 1 vs 3: 0.057 (3.28, 17.44)	1 vs 2: 0.546 (−7.07, 13.41) 2 vs 3: 0.140 (−0.13, 14.32) 1 vs 3: 0.090 (3.56, 22.44)
Sacral inclination (+: anterior)	16.1 ± 5.9	14.9 ± 7.4	13.0 ± 7.9	1 vs 2: 0.611 (−3.13, 5.45) 2 vs 3: 0.972 (−2.99, 7.51) 1 vs 3: 0.810 (−1.88, 8.53)	1 vs 2: 0.616 (−6.81, 10.70) 2 vs 3: 0.480 (−2.04, 10.07) 1 vs 3: 0.624 (−2.20, 13.28)
Spinal inclination (+: anterior)	1.0 ± 2.4	2.0 ± 3.0	2.0 ± 2.2	1 vs 2: 0.588 (−2.91, 0.91) 2 vs 3: 1.000 (−1.91, 1.91) 1 vs 3: 0.753 (−2.74, 0.74)	1 vs 2: 0.631 (−3.07, 3.33) 2 vs 3: 1.000 (−2.68, 1.50) 1 vs 3: 0.948 (−3.94, 1.40)
Spinal mobility, degrees					
Thoracic spine	38.5 ± 10.0	28.6 ± 11.1	21.4 ± 7.7	**1 > 2 > 3** **1 vs 2: 0.026** (2.24, 16.40) **2 vs 3: 0.023** (1.09, 13.00) **1 vs 3: 0.003** (10.24, 23.09)	**1 > 2, 3** **1 vs 2: 0.008** (6.83, 26.15) 2 vs 3: 0.473 (−5.26, 9.11) **1 vs 3: 0.006** (9.95, 28.58)
Lumbar spine	56.5 ± 12.5	46.0 ± 10.1	45.9 ± 13.1	1 vs 2: 0.081 (2.56, 18.71) 2 vs 3: 0.985 (−8.05, 8.02) 1 vs 3: 0.094 (1.56, 20.48)	1 vs 2: 0.432 (−2.50, 22.38) 2 vs 3: 0.981 (−7.87, 6.67) 1 vs 3: 0.390 (−4.98, 26.77)
Thoracolumbar spine	95.0 ± 13.3	74.6 ± 13.8	67.3 ± 14.8	**1 > 2, 3** **1 vs 2: 0.003** (11.72, 29.62) 2 vs 3: 0.151 (−2.39, 17.76) **1 vs 3: 0.002** (17.28, 38.82)	**1 > 2, 3** **1 vs 2: 0.003** (15.46, 36.84) 2 vs 3: 0.618 (−10.82, 11.72) **1 vs 3: 0.002** (17.19, 46.77)

(Footnotes for Table 3)

Values are mean ± standard deviation. * Holm-adjusted *P*-value with bootstrap method. Bold indicates statistically significant. CI = confidence interval.

572 **Table 4. Gait-related characteristics in each phenotype and comparison between phenotypes.**

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	Phenotype 1 (n = 15)	Phenotype 2 (n = 21)	Phenotype 3 (n = 14)	*P*-value* (95% CI)	*P*-value* adjusted for age (95% CI)
Gait speed, meters/seconds	1.20 ± 0.16	1.16 ± 0.16	1.03 ± 0.14	**1 > 3** 1 vs 2: 0.508 (−0.07, 0.14) 2 vs 3: 0.052 (0.03, 0.23) **1 vs 3: 0.021** (0.06, 0.28)	1 vs 2: 0.855 (−0.13, 0.22) 2 vs 3: 0.201 (−0.02, 0.24) 1 vs 3: 0.208 (−0.01, 0.28)
Steps/day	7,491 ± 2,211	6,061 ± 2.583	6,440 ± 2.757	1 vs 2: 0.270 (−0.27, 3.00) 2 vs 3: 0.660 (−2.31, 1.25) 1 vs 3: 0.602 (−0.95, 2.88)	**1 > 2, 3** **1 vs 2: 0.040** (−0.05, 5.00) 2 vs 3: 0.382 (−3.32, 1.44) **1 vs 3: 0.039** (0.52, 4.43)
Hip range of motion during gait, degrees					
Hip flexion/extension	37.5 ± 5.0	35.7 ± 6.0	38.0 ± 4.7	1 vs 2: 0.632 (−1.65, 5.28) 2 vs 3: 0.633 (−5.75, 1.51) 1 vs 3: 0.782 (−4.20, 3.00)	1 vs 2: 0.474 (−9.99, 1.87) 2 vs 3: 0.656 (−5.24, 3.39) 1 vs 3: 0.660 (−8.12, 1.81)
Hip abduction/adduction	15.6 ± 3.7	12.1 ± 3.3	13.3 ± 2.5	**1 > 2** **1 vs 2: 0.033** (1.26, 5.87) 2 vs 3: 0.220 (−3.10, 0.70) 1 vs 3: 0.124 (0.00, 4.38)	1 vs 2: 0.348 (−0.80, 5.51) 2 vs 3: 0.362 (−3.83, 1.09) 1 vs 3: 0.363 (−0.45, 5.36)
Hip external/internal rotation	20.7 ± 4.2	19.2 ± 6.5	19.2 ± 3.1	1 vs 2: 0.812 (−2.18, 5.17) 2 vs 3: 0.990 (−3.11, 3.12) 1 vs 3: 0.759 (−1.27, 3.93)	1 vs 2: 0.639 (−8.71, 5.67) 2 vs 3: 1.000 (−5.75, 1.51) 1 vs 3: 0.195 (−0.31, 5.73)
Hip moment impulse, Nm•seconds					
Hip flexion/extension	8.8 ± 2.1	8.4 ± 3.8	8.1 ± 1.3	1 vs 2: 0.858 (−1.88, 1.75) 2 vs 3: 1.000 (−1.20, 2.39) 1 vs 3: 1.000 (−0.80, 1.85)	1 vs 2: 0.895 (−4.85, 3.87) 2 vs 3: 1.000 (−1.72, 4.51) 1 vs 3: 0.516 (−0.41, 3.95)
Hip abduction/adduction	24.7 ± 8.6	22.8 ± 7.6	20.4 ± 5.1	1 vs 2: 0.382 (−2.95, 8.28) 2 vs 3: 0.534 (−1.46, 6.97) 1 vs 3: 0.264 (−1.00, 10.39)	1 vs 2: 0.693 (−10.51, 14.20) 2 vs 3: 0.304 (−0.95, 11.65) 1 vs 3: 0.342 (−1.43, 16.02)

Hip external/internal rotation	2.8 ± 1.2	2.4 ± 0.6	2.4 ± 0.5	1 vs 2: 0.352 (−0.18, 1.21) 2 vs 3: 0.771 (−0.28, 0.43) 1 vs 3: 0.465 (−0.17, 1.25)	1 vs 2: 0.674 (−1.05, 1.82) 2 vs 3: 0.288 (−0.04, 0.78) 1 vs 3: 0.470 (−0.51, 2.15)
Daily Cumulative hip moment, kNm•seconds					
Hip flexion/extension	33.0 ± 15.3	24.4 ± 11.8	26.5 ± 12.7	1 vs 2: 0.408 (−0.16, 1.81) 2 vs 3: 0.618 (−1.09, 0.60) 1 vs 3: 0.594 (−0.45, 1.64)	1 vs 2: 0.106 (0.02, 3.50) 2 vs 3: 0.393 (−1.60, 0.68) 1 vs 3: 0.111 (0.53, 3.28)
Hip abduction/adduction	105.4 ± 56.9	63.3 ± 26.6	58.5 ± 16.9	**1 > 3** 1 vs 2: 0.066 (1.41, 7.40) 2 vs 3: 0.532 (−1.01, 2.01) **1 vs 3: 0.048** (2.06, 7.90)	**1 > 2, 3** **1 vs 2: 0.015** (3.13, 12.40) 2 vs 3: 0.697 (−1.57, 2.67) **1 vs 3: 0.024** (3.98, 11.71)
Hip external/internal rotation	11.2 ± 8.2	7.0 ± 3.0	7.5 ± 3.3	1 vs 2: 0.369 (0.03, 0.93) 2 vs 3: 0.637 (−0.29, 0.15) 1 vs 3: 0.354 (−0.04, 0.87)	1 vs 2: 0.392 (−0.10, 1.74) 2 vs 3: 0.697 (−0.33, 0.26) 1 vs 3: 0.372 (0.01, 1.69)

(Footnotes for Table 4)

Values are mean ± standard deviation. * Holm-adjusted *P*-value with bootstrap method. Bold indicates statistically significant. CI = confidence interval.

Table 5. Generalized linear model analysis with bootstrap method for the association between phenotypes and progression risk.

Variable (phenotype)	Association between phenotypes and ratio of progressors				Association adjusted for Age			
	β	SE	95% CI	*P*-value	β	SE	95% CI	*P*-value
Phenotype 1 vs 2	−0.79	1.98	−2.77, 0.58	0.257	−1.03	1.79	−4.30, 1.34	0.348
Phenotype 2 vs 3	−0.68	1.41	−2.40, 0.73	0.336	−0.79	1.93	−3.04, 0.94	0.307
Phenotype 1 vs 3	−0.11	2.65	−2.03, 1.74	0.876	−0.24	2.60	−2.88, 1.71	0.795

(Footnotes for Table 5)

SE = standard error; CI = confidence interval.